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DAVID RAKEL

Integrative Medicine

THIRD EDITION

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Integrative Medicine

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THIRD EDITION

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University of Wisconsin School of Medicine and Public Health
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1600 John F. Kennedy Blvd.
Ste 1800
Philadelphia, PA 19103-2899

INTEGRATIVE MEDICINE ISBN: 978-1-4377-1793-8

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Library of Congress Cataloging-in-Publication Data
Integrative medicine / [edited by] David Rakel. – 3rd ed.
p. ; cm.
Includes bibliographical references.
ISBN 978-1-4377-1793-8 (hardcover : alk. paper)
I. Rakel, David.
[DNLM: 1. Integrative Medicine–methods. 2. Complementary Therapies–methods. 3. Preventive Medicine–methods. 4. Primary Health Care–methods. WB 113]
616—dc23 2012009514

Senior Content Strategist: Kate Dimock
Content Development Specialist: Julie Mirra
Publishing Services Manager: Anne Altepeter
Senior Project Manager: Doug Turner
Designer: Steve Stave

Printed in the United States of America
Last digit is the print number: 9 8 7 6 5 4 3 2 1

For my wife, Denise

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Foreword

With the publication of the revised and expanded third edition, *Integrative Medicine* has become an established textbook in this new and rapidly growing field of clinical medicine. As I wrote in the foreword to the second edition:

> David Rakel and I and our growing number of colleagues feel strongly that integrative medicine is the way of the future. Not only is it the kind of medicine that most of our patients want, it is the kind that more and more physicians want to practice, because it restores the core values of the profession that have so eroded in the era of managed care. We also believe that it offers hope for rescuing a health care system on the verge of collapse. The reason is that integrative medicine can save money by bringing lower-cost treatments into the mainstream while preserving outcomes (or even improving them). At some point, we believe, we will be able to drop the word *integrative.* This will just be good medicine.

Most needed now are outcomes studies to document the effectiveness and cost-effectiveness of integrative versus conventional treatments for common health conditions. It is not so easy to design and conduct such studies, which are expensive and require large enough study populations to generate meaningful data. Clinical outcomes studies are not within the mission of the National Institutes of Health, and few researchers are trained to work with the complex and individualized treatments that practitioners of integrative medicine (IM) use. But demonstrating that IM works and saves money is the only way to change policies of reimbursement that are now the main impediment to taking IM mainstream.

The Arizona Center for Integrative Medicine will soon have graduated 1000 physicians from its intensive fellowship training and has been successful in making IM training a required, accredited part of residency training in family medicine. We are now expanding Integrative Medicine in Residency to pediatrics and internal medicine. As more and more clinicians learn IM, there is greater need for reliable, evidence-based treatment guidelines. I believe that *Integrative Medicine* answers that need.

This new edition includes more conditions (some of which are multiple sclerosis, Parkinson disease, insomnia, Lyme disease, polycystic overian syndrome, and erectile dysfunction), as well as discussions of the healing encounter, human energetic therapies, and other topics of relevance to IM practice. As in previous editions, there is strong emphasis on prevention and a visual icon to help readers evaluate evidence for both the benefits and risks of treatments.

David Rakel is committed to keeping this text current and informed by the best available research data. He has made the new edition even better and more useful than the last.

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July 2011

Preface

I am excited to present the third edition of *Integrative Medicine*. This text is focused on empowering the clinician to practice an integrative approach using therapies that address all aspects of health to facilitate healing.

We have worked hard to make this edition more efficient so the clinician can access evidence-based information quickly without having to sift through a lot of text. We have reduced the page count while increasing the density of content. There are 114 chapters with 37 new authors and 12 new chapters that include topics such as Lyme disease, polycystic ovarian syndrome, insomnia, and hormone replacement in men and women.

The text is divided into three parts. Part 1, "Integrative Medicine," is an overview of the field of integrative medicine and focuses on the philosophy of integrative medicine, how to create optimal healing environments, and key ingredients of the healing encounter. Part 2, "Integrative Approach to Disease," is the core of the text and discusses integrative approaches to treating disorders that range from insomnia to diabetes to various forms of cancer. Part 3, "Tools for Your Practice," includes practical, how-to information on common integrative therapeutic interventions.

The text format makes the information easy to find. Each disease-focused chapter concludes with a Therapeutic Review section that summarizes an integrative approach. Evidence-versus-harm icons provide the clinician a quick and efficient way to assess the level of evidence compared with the level of the potential harm for recommended therapies. Potential for harm has been an important missing factor in evidence-based rating scales (see "Using the Evidence-Versus-Harm Grading Icons" following the preface). Each chapter also has a Prevention Prescription, which summarizes key factors that will help prevent the disease being discussed and its recurrence. The text can also be accessed electronically.

Integrative medicine offers a path to improve the value of heatlh care by lowering cost and improving quality as health and healing become our primary objectives. I hope that this text proves to be a useful tool as you partner with your patients to find health within the complexity of life. Thank you for engaging in this work.

David Rakel, MD

Using the Evidence-Versus-Harm Grading Icons

In the busy practice of medicine, being able to access information quickly and efficiently is important for obtaining the highest quality data in the shortest period of time in the effort to enhance care.

The Strength of Recommendation Taxonomy (SORT)[1] rating for evidence has been an excellent step in this direction. The A, B, and C ratings give us a quick and simple way to judge the quality of evidence for a particular intervention. There are limitations to making decisions based only on the evidence. One limitation is the absence of the potential harm of the evidence. Even if the evidence may be grade A, the potential harm of that intervention may negate its effect.

An example is the Randomized Aldactone Evaluation Study (RALES) published in the *New England Journal of Medicine* in 1999.[2] This study showed that spironolactone significantly improved outcomes in patients with severe heart failure. A follow-up article published in the same journal in 2004[3] showed that after the publication of this study, the number of prescriptions written for spironolactone significantly increased in Ontario, Canada, from 34 per 1000 patients in 1994 to 149 per 1000 patients in 2001. Thus the Canadian physicians were practicing evidence-based medicine, and their prescribing habits resonated with this. The follow-up study also noted that despite this evidence-based practice, there was a significant increase in the number of hospital admission and in the death rate related to hyperkalemia when spironolactone and ACE inhibitors were used together. In fact, when the investigators took into account the number of deaths related to hyperkalemia, there was no decrease in the number of admissions or the death rate for congestive heart failure patients after the publication of RALES. The initial benefit of improving outcomes in congestive heart failure with spironolactone seen in the original study was not evident in the application of the evidence in the clinical setting. The potential harm of the evidence was not taken into account, and this drug may have caused more harm than good.

Adding a rating for potential harm will enhance the rating of the evidence for the clinician but is by no means a final guiding rule. Decision making goes beyond the evidence and the harm and is grounded in the much broader insights obtained through relationship-centered care. It is only a tool that we hope will make the clinician's life a little easier in recommending specific therapeutic interventions.

Grading the Evidence

The authors of this text used the SORT criteria for grading the evidence for the therapies that are recommended in the Therapeutic Review sections of the chapters. A simplified summary follows:

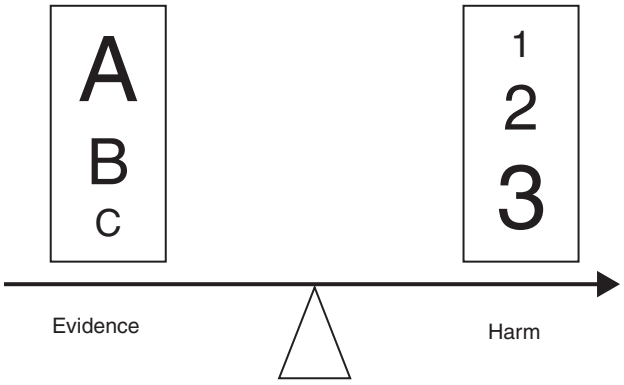
Grade A	Based on consistent, good-quality, patient-oriented evidence (e.g., systematic review or meta-analysis showing benefit, Cochrane Review with clear recommendation, high-quality patient-oriented randomized controlled trial). Example: Acupuncture for nausea and vomiting.
Grade B	Based on inconsistent or limited-quality patient-oriented evidence. Example: Ginger for osteoarthritis.
Grade C	Based on consensus, usual practice, opinion, disease-oriented evidence (e.g., study showing a reduction in blood sugar but no studies in humans to show a benefit to those with diabetes).

Grading the Potential Harm

Unlike grading for evidence, there is no unified, acceptable grading system for harm. In grading the three levels of harm, we used the following grading scale:

Grade 3 (most harm)	This therapy has the potential to result in death or permanent disability. Example: Major surgery under general anesthesia or carcinogenic effects of the botanical *Aristolochia* (birthwort).
Grade 2 (moderate harm)	This therapy has the potential to cause reversible side effects or interact in a negative way with other therapies. Example: Pharmaceutical or neutraceutical side effects.
Grade 1 (least harm)	This therapy poses little, if any, risk of harm. Examples: Eating more vegetables, increasing exercise, elimination diets, encouraging social connection.

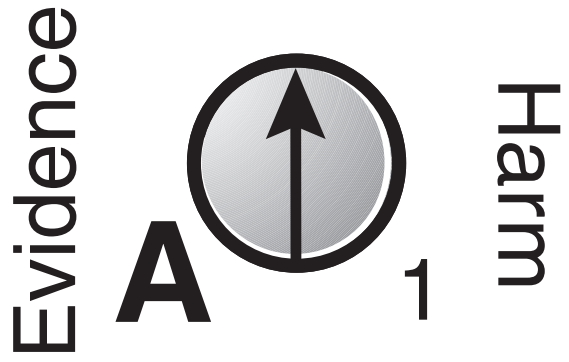
The resulting icons incorporate a weighing of the evidence versus the potential harm. If the evidence is strong (A) with the least potential harm (1), the arrow will point up. If the evidence is weak (C) with the most potential harm (3), the arrow will point down.



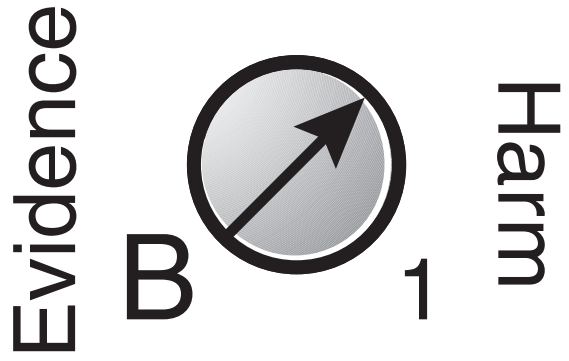
Examples:

Clinical Recommendation

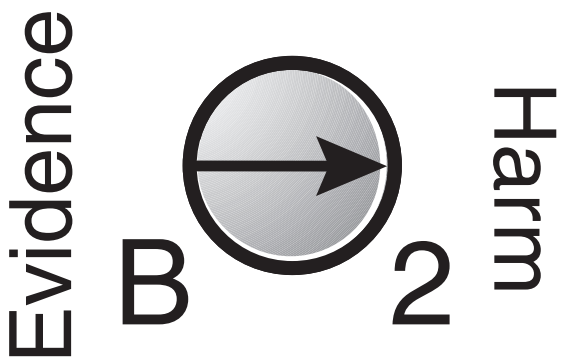
- Exercise for diabetes management (A,1)



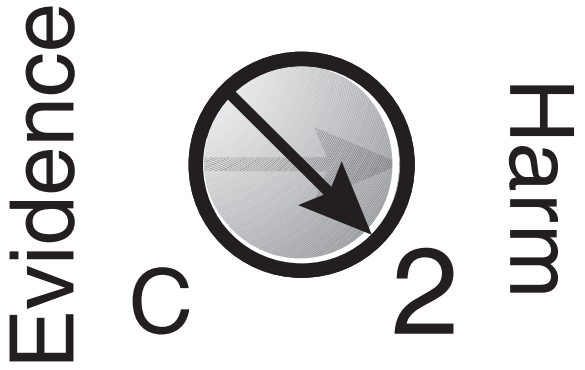
- Hypnosis for irritable bowel syndrome (B,1)



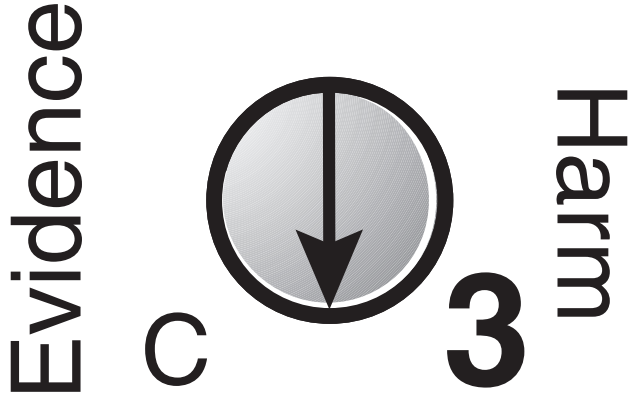
- Zinc supplementation for infectious diarrhea (B,2)



- Astragalus root for infectious hepatitis (C,2)



- *Aristolochia* (birthwort) to support immunity (C,3)



Rating Options	Arrow	Icon
(A,1)	↑	
(A,2) (B,1)	↗	
(A,3) (B,2) (C,1)	→	
(B,3) (C,2)	↘	
(C,3)	↓	

Strengths of Evidence-Versus-Harm Grading

- Gives quick access to the balance of available evidence and potential harm for a given therapy.
- Works best for therapeutic interventions for chronic disease compared with acute or emergency treatments.
- Gives more credibility to therapies that have little potential harm. For example, we know that encouraging social support, reducing stress, and enhancing spiritual connection are beneficial for quality of life and health, but the evidence may not be strong. The potential harm will always be low, giving the benefit a more positive outlook.
- Helps us honor our primary goal, which is to "first, do no harm." This rating scale allows us to include this important fact in medical decision making. This is very important, seeing that adverse drug reactions from medical therapy have been found to be the sixth leading cause of hospital deaths in the United States.[4]

Limitations of Evidence-Versus-Harm Grading

- Is used only for those therapies proved to have a positive benefit. There may be good evidence showing that a therapy does not work. If this was the case, the therapy was not included in the Therapeutic Review.
- Does not reward the potentially life-saving interventions that are risky and have little available evidence showing benefit. For example, there has not been a meta-analysis showing that emergency repair of a dissecting aortic aneurysm has therapeutic benefit. The potential harm of this therapy is high (Grade 3). On the evidence-versus-harm scale, this therapy would have an arrow pointing toward the negative side, but without the therapy the patient would likely die.
- Those therapies that have the most potential for economic gain often have the most evidence. For example, there are more resources to do high-quality research for a potentially profitable pharmaceutical that can be patented than for a whole food or plant that cannot. Therapies such as pharmaceuticals will have a higher quality of evidence in general when compared with botanicals, mind-body therapy, and spiritual connection.
- This rating scale can be reductionistic. It is much easier to complete high-quality research based on our scientific model on a physical process, drug, or supplement. It is harder to show an enhanced quality of life or a reduction in suffering from reducing social isolation, for example.

Summary

This model includes potential harm along with the strength of the evidence. The arrows will give a quick reference for potential benefit when the evidence and harm are weighted against each other. For example, strong (heavy) evidence with little (light) potential harm will result in an arrow pointing up. This will be most helpful for recommendations for chronic disease. Unlike acute life-threatening conditions that often need more aggressive intervention with higher potential risk, chronic disease is often managed using lifestyle choices that will be supported by this model.

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4. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients. *JAMA*. 1998;279:1200–1205.

Acknowledgments

This text would not have been possible without the talents of a passionate group of people. I would like to thank my colleagues at Elsevier—Kate Dimock, Julie Mirra, Doug Turner, and Kate Crowley—for their support, advice, and hard work. I am very appreciative of the more than 100 authors who took time from their personal lives and families to write this text. I am thankful to the faculty and staff at the University of Wisconsin Department of Family Medicine, UW Health Hospitals and Clinics, and the Program in Integrative Medicine for their support and friendship. I am grateful to my colleagues at the Arizona Center for Integrative Medicine, the Consortium of Academic Health Centers for Integrative Medicine (CAHCIM), and the American Board of Integrative Holistic Medicine (ABIHM) for contributing to this text and helping define a new model for health care delivery. It is an honor to be able to work with such a talented and caring group of people. I would also like to thank the students, residents, and fellows from the University of Wisconsin and across the country for all that they have taught me and encouraged me to think about and explore. And finally, I am thankful to my wife, Denise, and children, Justin, Sarah, and Lucas, for their love and presence.

Chapter 1

Philosophy of Integrative Medicine

David Rakel, MD, and Andrew Weil, MD

A Brief History of Integrative Medicine

> When religion was strong and medicine weak, men mistook magic for medicine;
>
> Now, when science is strong and religion weak, men mistake medicine for magic.
>
> *Thomas Szasz, The Second Sin*

The philosophy of integrative medicine is not new. It has been talked about for ages across many disciplines. It has simply been overlooked as the pendulum of accepted medical care swings from one extreme to the other. We are currently experiencing the beginning of a shift toward recognizing the benefits of combining the external, physical, and technologic successes of curing with the internal, nonphysical exploration of healing.

Long before magnetic resonance imaging and computed tomographic scanners existed, Aristotle (384-322 BC) was able simply to experience, observe, and reflect on the human condition. He was one of the first holistic physicians who believed that every person was a combination of both physical and spiritual properties with no separation between mind and body. It was not until the 1600s that a spiritual mathematician became worried that prevailing scientific materialistic thought would reduce the conscious mind to something that could be manipulated and controlled. René Descartes (1596-1650), respecting the great unknown, did his best to separate the mind and the body to protect the spirit from science. He believed that mind and spirit should be the focus of the church, thus leaving science to dissect the physical body. This philosophy led to the "Cartesian split" of mind-body duality.

Shortly afterward, John Locke (1632-1704) and David Hume (1711-1776) influenced the reductionistic movement that shaped our science and medical system. The idea was that if we could reduce natural phenomena to greater simplicity, we could understand the larger whole. So to learn about a clock, all we need to do is study its parts. Reductionism facilitated great discoveries that helped humans gain control over their environment. Despite this progress, physicians had few tools to treat disease effectively. In the early twentieth century, applied science started to transform medicine through the development of medical technologies. In 1910, the Flexner report[1] was written and had a significant impact on the development of allopathic academic institutions. They came to emphasize the triad that prevails today: research, education, and clinical practice. Reductionism and the scientific method produced the knowledge that encouraged the growth of these institutions.

The scientific model led to greater understanding of the pathophysiologic basis of disease and the development of tools to help combat its influence. Subspecialization of medical care facilitated the application of the new information. We now have practitioners who focus on the pieces and a society that appreciates their abilities to fix problems. Unfortunately, this approach does not work well for chronic disease that involves more than just a single part. In fact, all body organs are interconnected, so that simply repairing a part without addressing the underlying causes for its failure provides only temporary relief and a false sense of security.

More Technology, Less Communication

The tremendous success of medical science of the twentieth century was not without cost. Total health care expenditures reached $2.5 trillion in 2009, an amount that was 17.6% of the Gross Domestic Product (GDP) and translates to $8086 per U.S. resident. The health care market grows when more

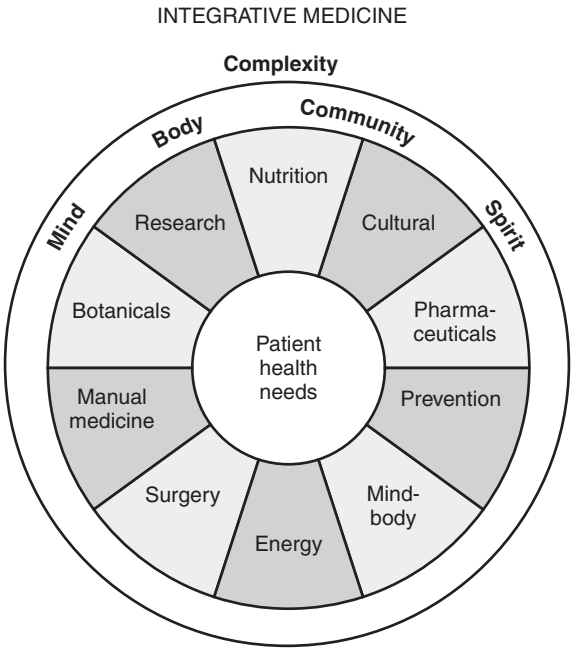
attention is focused on parts that can be treated with drugs or procedures. In just 6 years (2003 to 2009), drug spending in the United States rose 39% from $180 billion to $250 billion.[2] Financial rewards increase when we have more subtypes of disease to which treatments can be matched. The system encourages patients to believe that tools are the answer to their physical woes and discourages them from paying attention to the interplay of mind, community, and spirit. Technology is the golden calf in this scenario. We have become dependent on it, and overuse has widened the barrier of communication between patient and provider. The old tools of the trade—rapport, gestalt, intuition, and laying on of hands—were used less and less as powerful drugs and high-tech interventions became available.

To help curtail costs, managed care and capitation were born. These new models reduced excessive costs and further eroded the patient-provider relationship by placing increased time demands on physicians that did not involve patient care. Physician and patient unrest followed. Physicians are unhappy in part because of loss of autonomy in practicing medicine. Patients are unhappy in part because they believe they are not receiving the attention they need. Most upset are patients with chronic medical conditions whose diseases do not respond well to the treatments of specialized medicine. This comes at a time when the incidence of chronic and degenerative diseases is at an all-time high. Diseases such as heart disease, diabetes, irritable bowel syndrome, chronic fatigue, and chronic pain syndromes are quite common. They require evaluation and treatment of much more than any one organ. The public has started to realize the limitations of Western medicine and wants more attention paid to health and healing of the whole person, especially when someone has no "part" to be fixed.

Public Interest Influences Change

The deterioration of the patient-provider relationship, the overuse of technology, and the inability of the medical system to treat chronic disease adequately has contributed to rising interest in complementary and alternative medicine (CAM). The public has sent its message with their feet and their pocketbooks. In fact, more visits were made to CAM providers in the early 1990s than to all primary care medical physicians, and patients paid for these visits out of pocket, with an estimated expenditure of $13 billion.[3] This trend continued throughout the 1990s; 42% of the public used alternative therapies, and expenditures increased to $27 billion from 1990 to 1997.[4] Patients are also demanding less aggressive forms of therapy, and they are especially leery of the toxicity of pharmaceutical drugs. Adverse drug reactions have become the sixth leading cause of death in hospitalized patients,[5] and in 1994, botanicals were the largest growth area in retail pharmacy.[6] Research shows that people find complementary approaches to be more aligned with "their own values, beliefs, and philosophical orientations toward health and life."[7] The public, before the medical establishment, realized that health and healing involved more than pills and surgery. Less invasive, more traditional treatments such as nutrition, botanicals, manipulation, meditation, massage, and others that were neglected during the explosion of medical science and technology were now being rediscovered with great enthusiasm (Fig. 1-1).

FIGURE 1-1
Integrative medicine pie chart.



Medicine Gets the Message

The popularity of CAM therapies created a need for research in these areas. In 1993, an Office of Alternative Medicine was started within the National Institutes of Health (NIH). The initial budget was $2 million, a fraction of the $80 billion budget of the NIH. The office was later upgraded to the National Center for Complementary and Alternative Medicine (NCCAM), and the amount of money available for scholarly research kept pace with this growth. By 2010, the NCCAM budget grew to $127 million.[8] This allowed for needed research to explore ways in which these areas of medicine could enhance health care delivery. At first, researchers tried to use traditional methods to learn about CAM therapies. These methods were sufficient for studying some areas such as botanicals. The limitations of the reductionistic model became apparent, however, when it was applied to more dynamic systems of healing such as homeopathy, traditional Chinese medicine, and energy medicine. New methods were required to understand the multiple influences involved. Outcome studies with attention to quality of life were initiated. Research grants in "frontier medicine" were created to help learn about fields such as energy medicine, homeopathy, magnet therapy, and therapeutic prayer. Interest grew in learning how to combine the successes of the scientific model with the potential of CAM to improve the delivery of health care.

Academic Centers Respond

In 1997, one of the authors of this chapter, Andrew Weil, started the first fellowship program in integrative medicine at the University of Arizona. This 2-year clinical and research fellowship was created to train physicians in the science of health and healing and to teach more about therapies that

FIGURE 1-2
Adults and children who have used complementary and alternative medicine (CAM): United States, 2007. (From Barnes PM, Block B, Nahin R. *Complementary and Alternative Medicine Use among Adults and Children: United States, 2007*. National health statistics report no. 12. Hyattsville, Md: National Center for Health Statistics; 2008.)

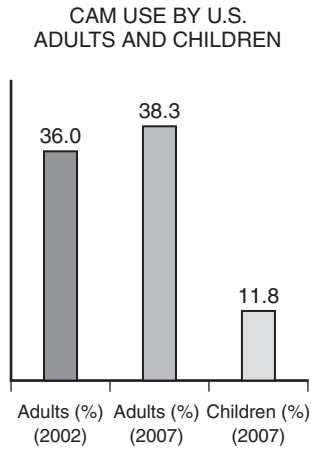
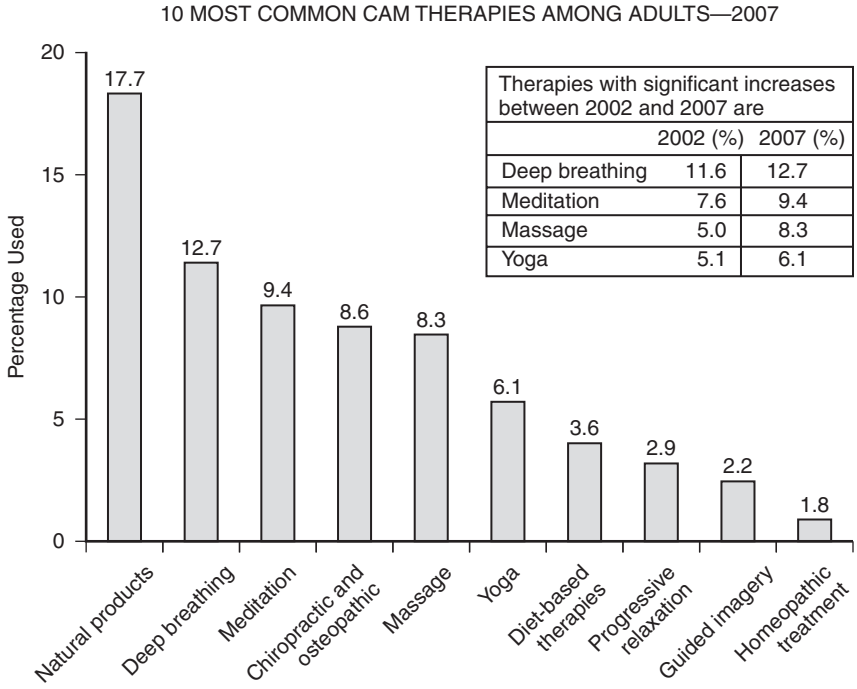


FIGURE 1-3
The 10 most commonly used complementary and alternative medicine (CAM) therapies among adults and a list of the most significant increases in therapies from 2002 to 2007. (From Barnes PM, Block B, Nahin R. *Complementary and Alternative Medicine Use among Adults and Children: United States, 2007*. National health statistics report no. 12. Hyattsville, Md: National Center for Health Statistics; 2008.)



were not part of Western medical practice. Other fellowship programs have been created since this time, as well as projects to incorporate integrative medicine into a 4-year family medicine residency training model. NIH-sponsored R-25 grants have been awarded to medical schools across the country to bring these concepts into medical school curriculums. The Consortium of Academic Health Centers for Integrative Medicine (CAHCIM) now comprises more than 45 medical schools across the United States and Canada, and it brings academic leaders together to transform health care through rigorous scientific studies, new models of clinical care, and innovative educational programs that integrate biomedicine, the complexity of humans, the intrinsic nature of healing, and the rich diversity of therapeutic systems.[9]

Integrative medicine is defined as healing-oriented medicine that takes account of the whole person (body, mind, and spirit), including all aspects of lifestyle. It emphasizes the therapeutic relationship and makes use of all appropriate therapies, both conventional and alternative.

Complementary and Alternative Medicine Use Grows in the United States

Because of the popularity of CAM in the United States, the Institute of Medicine (IOM) published the results of a review of CAM in 2004 to create a better understanding of how it can best be translated into conventional medical practice. The IOM recommended that health profession schools incorporate sufficient information about CAM into the standard curriculum to enable licensed professionals to advise their patients competently about CAM.[10]

Data collected from National Health Interview Survey in 2002 by the Centers for Disease Control and Prevention's National Center for Health Statistics showed that 62% of U.S. adults used CAM within 12 months of being interviewed. When prayer was excluded as a CAM therapy, the percentage dropped to 36%.[11] This survey was repeated in 2007, during which the use of CAM rose slightly from 36% to 38.3%. The 2007 survey included children, in whom it showed 11.8% use of CAM therapy, most commonly for back/neck pain (6.7%) and colds (6.6%) (Fig. 1-2). The 10 most commonly used CAM therapies can be reviewed in Figure 1-3. The use of natural products was the most common at 17.7%. Pain conditions were the most common reason for CAM therapy in adults, and low back pain accounted for the highest CAM use, at 17.1% (Fig. 1-4).[12] A review also showed an increase in use of CAM in those who did not have access to conventional medical care, thus showing the importance of CAM as an option for the uninsured.[13] These data suggest that people value other ways of treating illness and that they want to be empowered to be active participants in their care. They also feel that CAM offers them more opportunity to tell their story and explore a more holistic view of their problem.[14]

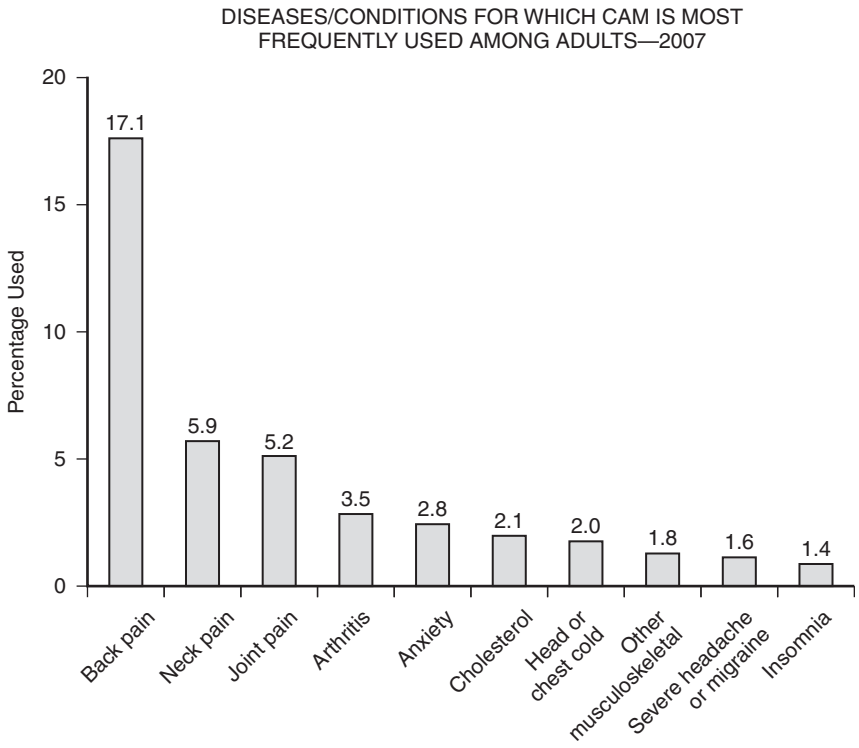
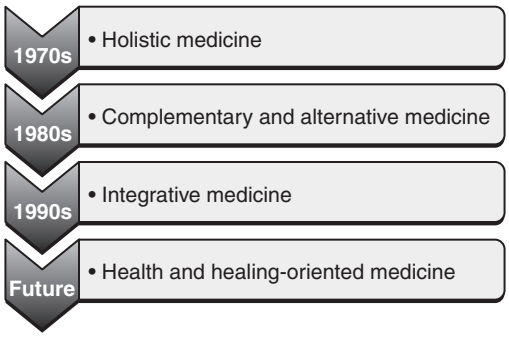


FIGURE 1-4
Diseases and conditions for which complementary and alternative medicine (CAM) is most frequently used in adults. (From Barnes PM, Block B, Nahin R. *Complementary and Alternative Medicine Use among Adults and Children: United States, 2007*. National health statistics report no. 12. Hyattsville, Md: National Center for Health Statistics; 2008.)

Avoiding Complementary and Alternative Medicine Labels

With the growth of good scientific research regarding many CAM therapies, we are realizing that the labels once used to classify these therapies are no longer needed (Fig. 1-5). The use of the terms *complementary* and *alternative* serve only to detract from a therapy by making it sound second class. Therapies that are often labeled under the heading of CAM include nutrition and spirituality. Many would argue that a lack of attention to these important influences on health has resulted in an epidemic of obesity, diabetes, and substance abuse. Stress, which many CAM-labeled mind-body therapies address, was found to be the second leading risk factor for heart disease after smoking in one of the largest studies ever completed across multiple cultures.[15] CAM therapies are hardly of lesser significance than conventional therapies.

FIGURE 1-5
Evolution of titles in the field.



Labeling therapies as CAM also avoids the deeper issues that need to be addressed in health care delivery and promotes further fragmentation of care. Simply adding CAM therapies without changing our health care model is like increasing the number of specialists with no primary care infrastructure, an approach that increases cost and reduces the quality of care.[16] Having multiple providers treating the patient in many different ways prevents what is needed most in the restructuring of health delivery: a medical home that is founded in relationship-centered care.

The term *integrative medicine* stressed the importance of using the evidence to understand how best to integrate CAM therapies into our health care model and allowed us to understand better how they can be used to facilitate health and healing. This evolving understanding helped influence positive change in our health care system.

Changing the Medical Culture

In 2001, the IOM published a report on the overall state of U.S. health care. The IOM concluded that the U.S. health care system was so flawed it could not be fixed and an overhaul was required.[17] In 2006, a report from the American College of Physicians (ACP) stated that

> Primary care, the backbone of the nation's health care system, is at grave risk of collapse due to a dysfunctional financing and delivery system. Immediate and comprehensive reforms are required to replace systems that undermine and undervalue the relationship between patients and their personal physician.[18]

This crisis has led to proposals toward a restructuring of health care that resonate with the philosophy of integrative medicine. The family medicine community has joined

the IOM and the ACP in creating their own proposal on a new model for care that promotes a relationship-centered medical home for the establishment of excellence in health creation in the outpatient setting. Principles of the medical home include the following:[19]

1. Access to care based on an ongoing relationship with a personal primary care clinician who is able to provide first contact and continuous and comprehensive care
2. Care provided by a physician-led team of professionals within the practice who collectively take responsibility for the ongoing needs of patients
3. Care based on a whole-person orientation in which the practice team takes responsibility for either providing care that encompasses all patient needs or arranging for the care to be done by other qualified professionals
4. Care coordinated or integrated across all elements of the complex health care system and the patient's community
5. Care facilitated by the use of office practice systems such as registries, information technology, health information exchange, and other systems to ensure that patients receive the indicated care when and where they need and want it in a culturally and linguistically appropriate manner
6. A reimbursement structure that supports and encourages this model of care

A similar set of goals was stated by the IOM in their proposal for a new health system for the twenty-first century (Table 1-1).

TABLE 1-1. Simple Rules for the Twenty-First Century Health Care System

OLD RULE	NEW RULE
Care is based primarily on visits.	Care is based on continuous healing relationships.
Professional autonomy drives variability.	Care is customized according to patient's needs and values.
Professionals control care.	Patient is the source of control.
Information is a record.	Knowledge is shared, and information flows freely.
Decision making is based on training and experience.	Decision making is evidence based.
"Do no harm" is an individual responsibility.	Safety is a system priority.
Secrecy is necessary.	Transparency is necessary.
The system reacts to needs.	Needs are anticipated.
Cost reduction is sought.	Waste is continuously decreased.
Preference is given to professional roles rather than the system.	Cooperation among clinicians is a priority.

From Institute of Medicine, Committee on Quality of Health Care in America. *Crossing the Quality Chasm: A New Health System for the 21st Century.* Washington, D.C.: National Academy Press; 2001.

In 2009, the Bravewell Collaborative sponsored a summit on Integrative Medicine and the Health of the Public at the Institute of Medicine in Washington, D.C. The goal of this conference was to share the science in the field and the potential for ways in which it can improve the health care of the nation. It succeeded in opening up dialogue among clinicians, administrators, and politicians to bring awareness of how the field could bring balance to a health care system that is weighted heavily toward disease management. A report of the meeting is available online.[20]

The field of integrative medicine was created not to fragment the medical culture further by devising another silo of care but to encourage the incorporation of heath and healing into the larger medical model. The culture of health care delivery is changing to adopt this philosophy, and the integration of nontraditional healing modalities will make this goal more successful.

It is important to see the benefits and limitations of our current allopathic system and realize that science alone will not meet all the complex needs of our patients.[21]

Integrative Medicine

Integrative medicine is healing oriented and emphasizes the centrality of the physician-patient relationship. It focuses on the least invasive, least toxic, and least costly methods to help facilitate health by integrating both allopathic and complementary therapies. These therapies are recommended based on an understanding of the physical, emotional, psychological, and spiritual aspects of the individual (Table 1-2).

The goal of integrative medicine is to facilitate health within complex systems, from the individual to the communities and environment in which all things live.

Health and Healing-Oriented Medicine

"Health" comes from the Old English word *Hal,* which means wholeness, soundness, or spiritual wellness. Health is defined by the World Health Organization (WHO) as "a state of complete physical, mental, and social well-being

TABLE 1-2. Defining Integrative Medicine

- Emphasizes relationship-centered care
- Integrates conventional and complementary methods for treatment and prevention
- Involves removing barriers that may activate the body's innate healing response
- Uses natural, less invasive interventions before costly, invasive ones when possible
- Engages mind, body, spirit, and community to facilitate healing
- Maintains that healing is always possible, even when curing is not

and not merely the absence of disease or infirmity."[22] Cure, on the other hand, refers to doing something (e.g., giving drugs or performing surgery) that alleviates a troublesome condition or disease. Healing does not equal curing. We can cure a condition such as hypertension with a pharmaceutical product without healing the patient. Healing would facilitate changes that reduce stress, improve diet, promote exercise, and increase the person's sense of community. In doing this, we help improve the balance of health of the body that may result in the ability to discontinue a pharmaceutical agent and thereby reduce the need for the cure.

An example of this can be seen in Figure 1-6. Here we have two trees, A and B. Tree A is obviously in a better state of health than tree B. This is likely because of its ability to be in balance with its environment. If a branch breaks on tree A, we can feel comfortable that if we mend the branch, it will likely heal well, or even heal itself. If a branch breaks on tree B and we mend it, the branch not going to heal because the tree is not in a state of health. The point here is that our focus in medicine has been on fixing the branch while neglecting the health of the tree. If we give more attention to helping tree B find health either by removing barriers that are blocking its own ability to heal or by improving areas of deficiency, the branch will heal itself—we will not need to spend as much time and money fixing the parts.

Integrative medicine is about changing the focus in medicine to one of health and healing rather than disease. This involves understanding the influences of mind, spirit, and community, as well as the body. It entails developing insight into the patient's culture, beliefs, and lifestyle that will help the provider understand how best to trigger the necessary changes in behavior that will result in improved health and thus bring more value to health care delivery.

Cure and fix when able, but if we ignore healing, the cure will likely not last or will give way to another disease that may not have a cure.

FIGURE 1-6
Healthy **(A)** and sickly **(B)** trees. It is important to see the benefits and limitation of our current allopathic system and to realize that science alone will not meet all the complex needs of our patients.[21]

Increasing Value Through Integrative Medicine

Achieving high value for patients and incentivizing practitioners to foster health will become the overarching goal of health reimbursement in the future. Value is defined by the health outcomes achieved per dollar spent. It depends on results, not just inputs, and should be measured by the ways we can improve the quality of patients' lives, not by the number of patients seen in a day. This will require a reimbursement model that rewards team-based care that transcends the one-on-one office visit and allows multiple avenues for patient communication and education among an interdisciplinary team of professionals.

Integrative medicine can increase value and lower costs through two of its foundational values: (1) by shifting the emphasis of health care to health promotion, disease prevention, and enhanced resiliency through attention to lifestyle behaviors; and (2) by bringing low-tech, less expensive interventions into the mainstream that preserve or improve health outcomes. This approach requires that these professionals have time to recognize the complexity of someone's life, and it cannot be done without a sound commitment to the practitioner-patient relationship.

Relationship-Centered Care

> It is much more important to know what sort of patient has a disease than what sort of disease a patient has.
>
> *Sir William Osler*

Observing practitioners of various trades such as biomedicine, manual medicine, Chinese medicine, and herbal medicine helps us realize that some practitioners have better results with their chosen trade. Those with more success are able to develop rapport, understanding, and empathy that help them facilitate healing with their therapy. The relationship fosters healing not only by allowing the practitioner to gain insight into the patient's situation but also by building the patient's trust and confidence in the provider. This trust acts as a tool to activate the patient's natural healing response and supports whatever technique the provider uses, whether it is acupuncture, botanicals, pharmaceuticals, or surgery.

The evidence behind the benefits of relationship-centered care is solid, particularly with regard to reducing health care costs. This approach to care has been found to reduce expenditures on diagnostic tests,[23] reduce hospital admissions,[24] and lower total health care costs.[25,26]

Developing a holistic understanding and relationship with patients allows the practitioner to guide them toward health more efficiently. The integrative clinician can point the way toward health while realizing that the patient will have to do the work to get there. This attitude does a great deal to remove pressure and guilt from providers who have been trained to think of themselves as failures when they cannot fix problems. In fact, relationship-centered care is a necessity when dealing with the many chronic conditions that do not have simple cures. Success is now defined as helping the patient find an inner peace that results in a better quality of life, whether the problem can be fixed or not (see Chapter 3, The Healing Encounter).

Prevention

Integrative medicine encourages more time and effort on disease prevention instead of waiting to treat disease once it manifests. Chronic disease now accounts for much of our health care cost and also causes significant morbidity and mortality. The incidence of heart disease, diabetes, and cancer could be significantly reduced through better lifestyle choices. Instead, these diseases are occurring in epidemic proportions. The system needs a reallocation of resources. Unfortunately, this is a large ship to turn. In the meantime, integrative practitioners can use their broad understanding of the patient to make recommendations that will lead to disease prevention and slow or reverse disease progression.

Integration

Integrative medicine involves using the best possible treatments from both CAM and allopathic medicine based on the patient's individual needs and condition. This selection should be based on good science and neither rejects conventional medicine nor uncritically accepts alternative practices. It integrates successes from both worlds and is tailored to the patient's needs, by using the safest, least invasive most cost-effective approach while incorporating a holistic understanding of the individual.

CAM is not synonymous with integrative medicine. CAM is a collection of therapies, many of which have a similar holistic philosophy. Unfortunately, the Western system views these therapies as tools that are simply added on to the current model, one that attempts to understand healing by studying the tools in the tool box. David Reilly said it well in an editorial in *Clinical Evidence:*

> We are the artists hoping to emulate Michelangelo's David only by studying the chisels that made it. Meantime, our statue is alive and struggling to get out of the stone.[27]

Integration involves a larger mission that calls for a restoration of the focus on health and healing based on the provider-patient relationship.

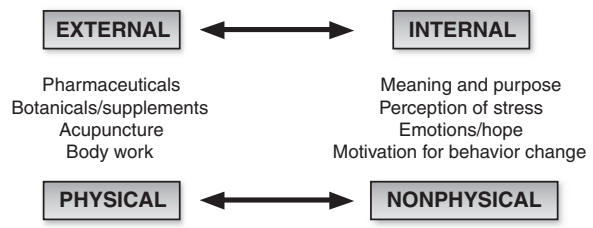
Five Questions to Consider Before Prescribing a Therapy

The integrative medicine practitioner uses relationship-centered care to develop insight into the most effective therapy for the patient's needs. Before prescribing a specific therapy, the practitioner should consider the following five questions:

1. **Does the therapy result in symptom resolution or symptom suppression?**
   Our initial goal should always be the resolution of the symptom, to enable us to use fewer external influences to maintain health. This often requires that we explore the mind and spiritual aspects of a symptom. A symptom is our body asking for some type of change. If we simply suppress the symptom without understanding what it may need to go away, it will likely recur or arise in another part of the body. A good example of this is the use of proton pump inhibitors (omeprazole [Prilosec], lansoprazole [Prevacid], rabeprazole [Aciphex]) for epigastric pain. These are excellent medications to help suppress symptoms or heal ulcers. If we overrely on this technology, however, it prevents us from exploring the symptom further. It may keep us from listening to the patient's story in which the use of metaphor may give us further insight into the mind-body influences on health. A person with epigastric pain may say that his or her job is "eating me up inside." If we do not deal with this stress, the body will not truly heal even though the symptom is suppressed. This can lead to long-term use of a medication that can result in a change of the natural environment of the body. Long-term suppression of acid production can lead to the following: an increased risk of pneumonia[28]; malabsorption of B vitamins, calcium, magnesium, and iron[29]; a higher prevalence of *Clostridium difficile* colitis[30]; and fractures of the hip[31,32] and spine.[33]

   To foster symptom resolution, we need to explore both the external and internal reasons for its expression (Fig. 1-7). An external therapy (medications, acupuncture, surgery, body work) will not have lasting benefit unless it is coupled with an internal exploration of why the symptom is there (emotions, stress, meaning, and purpose). The physical and nonphysical are inseparable, and if we do not address both, it will be difficult for the symptom to resolve. When we have explored both and found no underlying internal source, then it is appropriate to suppress the symptom with our tools to reduce suffering and improve quality of life.

FIGURE 1-7
Dynamic interplay between the physical and nonphysical influences on health and disease.



2. **What is the evidence?**
The scientific model allows us to understand which therapies have the most intrinsic value. Once we have reviewed the evidence, we can combine it with the "art of medicine" to stack the deck further in favor of a positive response. Unfortunately, the amount of evidence we have to rely on is limited. Out of 2404 treatments reviewed in medical care, 15% were found to be beneficial and 47% were not adequately tested.[34]

It is quite expensive to do good research, and the therapies that have the best quality of evidence are often those therapies that have the greatest potential for economic gain. Unfortunately, little economic incentive exists to promote therapies that result in healing in our current health care model. You will not see representatives from the wood and paper industry promoting the use of pencils and paper to support the health benefits of journaling on asthma and rheumatoid arthritis despite the evidence showing benefit.[35] The responsibility falls to the academic institutions and the government to provide funding to research all potential therapies despite their lack of economic rewards.

3. **What is the potential harm?**
It can be dangerous if we look at the evidence only for the potential benefit of a therapy without looking at the evidence for potential harm. In the 1950s, evidence showed that diethylstilbestrol prevented miscarriages, but the potential harm to the unborn fetus was not taken into consideration until after many lives were affected. For supraventricular tachycardia, evidence indicated that flecainide improved the rhythm on the electrocardiogram, but not until later did further research find the drug to increase mortality.[36] The integrative medicine practitioner uses the least harmful, least invasive therapy before using more invasive therapies. It is important that we continue to research not only the potential benefits but also the potential harm of the therapies we prescribe. Because of the potential risk of the external influences on health, we should encourage lifestyle habits with the least potential risk (whole food nutrition, stress reduction, exercise, spiritual connection) so that fewer high-risk interventions are needed, thereby resulting in the least potential risk of harm. For this reason, this text includes an icon that weighs the evidence of benefit against the evidence of harm to help guide the clinician.

4. **What is the cost?**

One of the first duties of the physician is to educate the masses not to take medicine.

Sir William Osler

Despite spending more on health care delivery than any nation in the world by almost 47%, the United States ranks fifteenth in quality when compared with the top 25 industrialized countries according to the 2000 WHO report. Despite this high cost, in 2006 the United States ranked thirty-ninth for infant mortality, forty-third for adult female mortality, forty-second for adult male mortality, and thirty-sixth for life expectancy.[37] Success of the higher-ranked countries comes from a strong primary care infrastructure[38] and healthier lifestyle habits. White and Ernst[39] showed that those primary care providers who provided a range of CAM therapies had a reduced number of referrals and treatment costs. Unfortunately, not all CAM therapists are primary care providers, and the use of CAM without the direction and continuity of these clinicians will only fragment care further and increase costs. The key is to incorporate this integrative philosophy into medical education so that primary care is enhanced and CAM therapies can be used to enable the provider to facilitate health.

CAM therapies are generally low tech and low cost and reduce the need for more expensive interventions. Users of CAM report that their use of prescription drugs and conventional therapies decreases.[40] When CAM was combined with biomedicine, one study showed a reduction of pharmaceutical use by 51.8%, a decrease in outpatient surgeries and procedures use by 43.2%, and a reduction of hospital admissions by 43%.[41]

Much economic incentive exists for physicians in the United States to do the fixing and little for them to do the lifestyle education that would reduce the need for expensive pills and procedures. Ornish et al[42] showed how coronary heart disease can be reversed by incorporating lifestyle changes including nutrition, exercise, stress management, group psychosocial support, and smoking cessation. This is an excellent example of how an integrative approach can result not only in self-healing but also in great savings in morbidity, mortality, and the money needed to treat them. The implementation of integrative medicine has the potential to result in tremendous cost savings, improved efficiency, and quality of care.

5. **Does the therapy match the patient's culture and belief system?**
In our conventional medical system, we have traditionally pulled patients into our paradigm of thought and have told them what they need. This method is often necessary for acute illness, but for chronic conditions that have no "right" answer, we will be more effective if we offer treatment plans that best match patients' belief systems. In this way, we can activate the internal healing response, a process that we know as the placebo effect. Instead of brushing this off as a nuisance, the talented clinician will use it to enhance healing. Becoming able to integrate methods of healing from various cultures will further enable the clinician to match the therapy to the individual. The art of medicine may lie in the clinician's ability to activate this response without deception. We should give patients what they need before we give them what we know. It is nice when we have knowledge about what our patients need, but this often requires collaborative treatments with an integrative team of providers who work toward a common goal of health for the patient.

Reducing Suffering

The secret of the care of the patient is in caring for the patient.

Francis Peabody, MD

Good caring and a weak medicine can give a better outcome than poor caring and a strong medicine.

Unknown

At the core of the delivery of health and healing is our ability to relieve suffering. This is not something that we learn in a book but requires that we explore our own suffering before we can understand how to help others with theirs. We are our own first patient, and part of our continuing education requires a

recurring exploration of our inner self so we can understand what it means to be truly present without judgment.

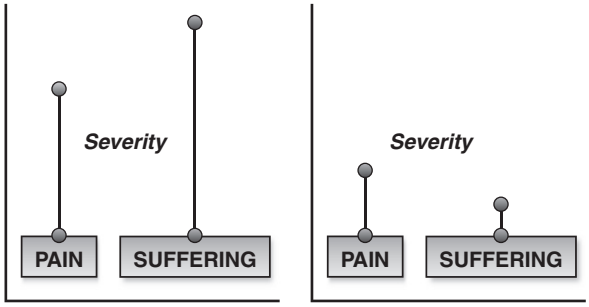
> The integrative medicine practitioner is not afraid to turn toward suffering in the care of another. As each addresses what is real, the authenticity of the truth draws both toward healing.

In learning this, it is helpful to understand how suffering influences the severity of pain and our quality of life. Pain and suffering are intricately connected but are not the same. Pain is a normal bodily reaction; suffering is not. Pain helps protect us against further harm; suffering is an opportunity to learn. Suffering influences how our body perceives pain—"the more I suffer, the more pain I experience" (Fig. 1-8). Our job is to reduce suffering so we can distill the pain to the most physiologic reason for its presence. In treating someone's suffering, we can often make pain more tolerable. In recognizing the severity of suffering, we can often avoid long-term medications that are used to suppress the symptom. It is often through our listening and our presence that we are best able to treat suffering. When no "right" answer or "drug cure" exists, it is our human compassion, connection, and unconditional positive regard that always works, even when our tools do not. This is the most important part of our work and is the reason that we heal in the process of helping others do the same.

The Future

The information age will continue to increase the number of data on the variety of therapies available but will only complicate how we apply them. Informed patients will be looking for competent providers who can help them navigate the myriad therapeutic options, particularly for those conditions for which conventional approaches are not effective. These patients will demand scientifically trained providers who are knowledgeable about the body's innate healing mechanisms and who understand the role of lifestyle factors in creating health, including nutrition and the appropriate use of supplements, herbs, and other forms of treatment from osteopathic manipulation to Chinese and Ayurvedic practices. They will be seeking providers who can understand their unique interplay of mind, body, and spirit to help them better understand what is needed to create their own balance of health. This will require a restructuring of medical training that will involve more research and education on how the body heals and how the process can be facilitated.

FIGURE 1-8
Suffering's effect on the same source of pain. Treating suffering will help reduce the severity of pain and improve the quality of life and should be at the core of our work in integrative medicine.



Conclusion

The philosophy of health based on a balance of mind, body, and spirit is not new or unique to integrative medicine. This understanding has been around since the time of Aristotle. What we call it is not important, but the underlying concepts are. It is time that the pendulum swings back to the middle, where technology is used in the context of healing and physicians acknowledge the complexity of mind and body as a whole. Integrative medicine can provide the balance needed to create the best possible medicine for both the physician and patient. We will know that we are near this balance when we can drop the term integrative. Integrative medicine of today will then simply be the good medicine of the future.

Therapeutic Review

Integrative Medicine

- Emphasizes relationship-centered care
- Develops an understanding of the patient's culture and beliefs to help facilitate the healing response
- Focuses on the unique characteristics of the individual person based on the interaction of mind, body, spirit, and community
- Regards the patient as an active partner who takes personal responsibility for health
- Focuses on prevention and maintenance of health with attention to lifestyle choices, including nutrition, exercise, stress management, and emotional well-being
- Encourages providers to explore their own balance of health that will allow them better to facilitate this change in their patients
- Requires providers to act as educators, role models, and mentors to their patients
- Uses natural, less invasive interventions before costly, invasive ones when possible
- Recognizes that we are part of a larger ecosystem that requires our efforts in sustaining its health so we can continue to be a part of it
- Uses an evidence-based approach from multiple sources of information to integrate the best therapy for the patient, be it conventional or complementary

- Searches for and removes barriers that may be blocking the body's innate healing response
- Sees compassion as always helpful, even when other therapies are not
- Focuses on the research and understanding of the process of health and healing (salutogenesis) and how to reproduce it
- Accepts that health and healing are unique to the individual and may differ for two people with the same disease
- Works collaboratively with the patient and a team of interdisciplinary providers to improve the delivery of care
- Maintains that healing is always possible, even when curing is not
- Agrees that the job of the physician is to cure sometimes, heal often, support always—*Hippocrates*

KEY WEB RESOURCES

Consortium of Academic Health Centers for Integrative Medicine (CAHCIM). http://www.imconsortium.org.	This organization strives to advance the principles and practices of integrative health care within academic institutions. Its members include more than 45 academic health centers in North America.
Bravewell Collaborative. http://www.bravewell.org.	This is a community of leading philanthropists who work together to transform our health care system and improve the health of the U.S. public through the advancement of integrative medicine.The Web site has many resources that help guide the advancement of the field.
American Board of Integrative Holistic Medicine. http://integrativeholisticdoctors.org/.	This board offers continuing medicinal education and credentialing toward becoming a diplomate.
University of Arizona Center for Integrative Medicine. http://integrativemedicine.arizona.edu/.	This center offers education and fellowship training in integrative medicine for physicians, family nurse practitioners, and physician's assistants.
University of Wisconsin Integrative Medicine Program. http://fammed.wisc.edu/integrative.	This program offers patient handouts and educational material for integrative approaches to common medical conditions. It focuses on bringing integrative medicine into primary care delivery models.
National Center for Complementary and Alternative Medicine. http://nccam.nih.gov/.	This branch of the National Institutes of Health focuses on complementary and alternative medicine (CAM) research. It includes literature reviews and education on CAM and common conditions for which CAM is used.

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Chapter 2

Creating Optimal Healing Environments

David Rakel, MD, and Wayne Jonas, MD

Many health practitioners who go into primary care want to both treat and heal, to care for the whole person, to be patient advocates, to apply the best science, and to serve the suffering. In short, we seek to be healers.

However, we often find in medical school and in our practice that the skills needed to be healers and the environment needed to execute those skills are not taught, available, or funded. We know, for example, the factors that increase the risk of disease, but we wait until illness arrives. We understand that relationships, a positive attitude, and behavioral skills form the foundation for compliance and self-care, prevention, and well-being, but we find ourselves without the time to develop them. We see the search for meaning in patients' eyes when they suffer from a serious illness, and yet our science cannot help them find the coherence they seek. For optimal healing to take place, we need to be proactive in creating an environment where these things can happen.

With every medical recommendation is a dynamic environment in which care is delivered. This environment consists of both physical and nonphysical elements. It often includes a synergy among factors that can either promote or hinder the healing process. Our goal is to describe foundational characteristics of an optimal healing environment (OHE) so that any therapy that is prescribed within this space (shown as a container in Fig. 2-1) will be more successful.

Creating an Environment That Enhances the Person's Ability to Heal

A growing amount of research shows how an environment based in positive intention, wholeness, and relationship-centered care can enhance the healing process independent of the treatment used, be it drugs or acupuncture needles.[1,2]

Optimal Healing Environments

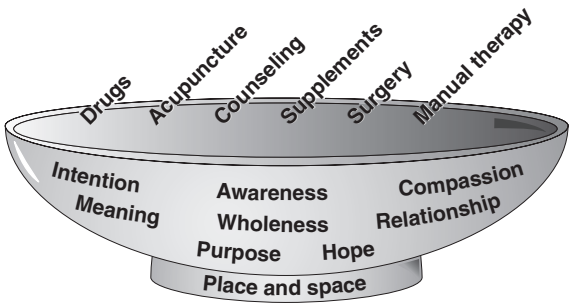
We define an OHE as an environment in which the social, psychological, spiritual, physical, and behavioral components of health care are oriented toward support and stimulation of innate healing capacities and the achievement of wholeness. It is an expansion of Engel's biopsychosocial model, which created a foundation for understanding the dynamic influences of health.[3] These components include at least six domains, in addition to the physical and organizational structures that support them, which are summarized in Table 2-1.[4–28] The six core domains of an OHE are the following:

1. Development of intention and awareness
2. Experience of wholeness
3. Relationship-centered care
4. Health promotion with self-care and lifestyle skills
5. Collaborative treatment
6. Spiritual connection

Intention and Awareness

Intention can have an influence on motivation for change, understanding, and compliance.[9] Being fully present with positive intention for another human is perceived by those we are with and enhances the healing effects of the encounter.[9] It is difficult to connect truly with intention until we have explored our own inner nature. Patient care starts with ourselves. As this connection grows, our ability to sit fully with another suffering human will be enhanced, and appreciation in our work will grow. This growth brings forward foundations in healing that include positive expectation, hope, faith, and unconditional positive regard.[4,29]

FIGURE 2-1
Schematic showing that the therapy we prescribe comes from within a container of influences that can enhance its effectiveness.



Healing can be defined as the dynamic process of recovery, repair, reintegration, and renewal that increases resilience, coherence, and wholeness. Healing is an emergent, transformative process of the whole person—physical, mental, social, spiritual, and environmental. It is a unique personal and communal process and experience that may or may not involve curing.[2]

Wholeness

Health is a result of a dynamic balance of biopsychosocial and spiritual influences. To facilitate healing, it is necessary to develop insight into how these factors are expressed in each unique individual. The holistic model requires that mind, body, emotions, and spirit are explored to understand best how to facilitate positive change so the person can heal most effectively.[11]

Relationship-Centered Care

Relationship is the bond that removes isolation and fear. It enhances insight, understanding, and sense of control. When two people develop trust, significant benefit results by enhancing social connection and by fostering communication, empathy, and compassion. Through relationship, unhealthy emotions are released and optimism and positive expectation are born.[13,15] Patient-oriented, relationship-centered care has been found to improve efficiency of care by reducing the need for medical tests and referrals.[30]

Health Promotion

Empowering the individual to learn how best to take care of himself or herself so both the provider and the patient are active participants in the healing process is a key ingredient. All healing is self-healing, and we, as integrative medicine practitioners, are at our best when we are able to facilitate individuals to care for themselves most successfully. This approach often includes nutrition, physical activity, lifestyle choices, and management of stress and anxiety. These factors can have epigenetic influences on the expression of a healthy phenotype.[18,19] Grounded in relationship and continuity of care, primary care practitioners are in a unique position to influence healthy lifestyle changes before the onset of chronic disease.

Collaborative Treatment

The provider who has developed a relationship and an understanding of the individual's story will then use the most effective tools possible to facilitate health, be they conventional or complementary. This integrative approach begins with less invasive measures before costly invasive ones are needed, when possible. It often involves working with a team of providers who are able to offer practices that help the body heal. It combines the best of technology, when needed, but is grounded in humanism and compassionate care so the least harmful, most effective approach is implemented to influence health.[23–25]

Spiritual Connection

Spirituality is a journey toward, or experience of, connection with sources of ultimate meaning, as defined by each individual. Spirituality includes connection with oneself, with others, with nature, and with a higher power.[31] If we providers can help patients work toward facilitating awareness of these connections, spirituality will enhance a sense of purpose for living, reduce suffering, buffer stress, and optimize self-healing (see Chapter 110, Taking a Spiritual History). Spirituality also is one of the most effective tools in helping change unhealthy behavior (see Chapter 99, Motivational Interviewing Techniques).[32]

Healing Spaces

The six key elements just discussed are enhanced by the physical structure in which they are provided. Nature, color, light, fresh air, music, fine arts, and architecture should be used to create external influences that support the health and well-being of those who enter the space.

Healing Places

Leadership and teamwork are essential to the delivery of OHEs. If employees do not respect and communicate with one another and feel safe to deal with conflict and empowered to contribute toward improvement, these deficiencies will be experienced by patients and will therefore inhibit healing. A culture of healing starts with modeling self-care and core values by the leaders and then flows into the mission, vision, planning, and behavior of health care teams.

Creating an Optimal Healing Environment in the Clinical Setting

How can we bring the components of an OHE into a busy practice? Although transforming a practice into a healing environment may seem like a daunting task, or one with little practical value, experience and evidence indicate that attention to simple and inexpensive details often gradually moves the focus of care from cure only to one filled with healing activity.[33]

The practitioner can develop healing-oriented sessions within the clinical space without having to go through major renovations. The primary care practitioner already has the foundational tools needed to create an OHE. The nonphysical intention is much more important than the physical space. Healing can occur anywhere, whether it is in an $8 million healing center or in an underfunded inner city clinic for the homeless (Table 2-2).

TABLE 2-1. Optimal Healing Environments: Key Components and Skills and Tools to Create Them

COMPONENT	SKILLS	TOOLS
Intention and awareness[4]	Familiarity with cross-cultural medicine and how to maximize therapeutic effect for patients within various cultural and religious traditions[5,6] Awareness of placebo literature and how to help the body self-heal[7,8] Use of intention in one's own practice[9] Personal participation and guidance of others in mindfulness practices	Take a mindfulness course. Take a retreat to define your own spiritual connection and develop awareness, to manage this appropriately with others (see Chapter 98, Recommending Meditation).
Wholeness[10]	Attitude of unconditional acceptance of those seeking care Ability to guide others toward understanding the body's energetic as a mechanism for healing and growth Personal participation in or ability to guide others in personal growth enhancements[10] Philosophy of holism and patient-centered care[11,12] Interviewing practices that focus on all aspects of the patient Ability to create a healing team that has an underlying holistic approach	Study and follow some of the following resources: Engel's biopsychosocial model[3] Ken Wilber's *A Brief History of Everything** Information from the American Holistic Medical Association (AHMA) Regular personal mind-body practices
Healing relationships[13]	Skills in relationship-centered care, empathy, and rapport building[14,15] Understanding how patients relate to their surrounding communities[16] Skill with involving family[17] or other members of the support system in patient care Ability to guide support groups and help patients help each other	Make friends and see how it makes you feel. Look at your medical career as a privilege to be able to make a living taking care of your friends who are also your patients.
Health promotion	Personal experience with living a healthy lifestyle and helping others do the same; skill in helping others take personal responsibility in their care[18,19] Solid background in preventive care and familiarity with principles of nutrition,[20] exercise,[21] stress management,[22] and addictions Ability to educate patients and other providers effectively through information technology, clinic-run education sessions, and so forth	Develop your own health plan. Expand your knowledge base of lifestyle choices and health (nutrition, exercise, mind-body, spiritual connection). Take the American Board of Integrative Holistic Medicine (ABIHM) review course.
Collaborative treatment[23,24]	Skill in integrative approaches to practice[25] Familiarity with the variety of modalities available and when or where they are most useful[26] Understanding the safety of various modalities Ability to draw together and contribute to a diverse group of providers who can work together to create an optimal healing environment Ability to facilitate positive team dynamics and resolve conflicts Knowledge of the treatments available within the community Skill in use of scientific literature, such as Cochrane collaboration (www.cochrane.de) in making evidence-based treatment decisions	Develop relationships with a community of providers whom you trust and with whom you will enjoy working. Obtain therapies first hand from your colleagues. This is a great way to learn about the therapy, the art of the practitioner, and its potential benefits.
Spiritual connection	Incorporation of some of the following questions in your history taking: What gives your life meaning? If life were perfect and resources were limitless, what would it look like for you? How do you want to leave your mark on this world? Who do you want to become?	Become familiar with spiritual assessment tools such as FICA, HOPE, SPIRIT, LET GO (see Chapter 110, Taking a Spiritual History). Explore and define your own spiritual connection. Be careful not to project your beliefs onto others inappropriately.
Healing spaces[27,28]	Skill with using architecture, the arts, sensory stimulation, and ambience to maximize healing Hiring an interior decorator to modify your clinic	Visit spaces that make you feel good and incorporate key elements into your clinical space.

*Wilber K. *A Brief History of Everything.* Halifax, Nova Scotia, Canada: Shambhala; 2001.

TABLE 2-2. Optimal Healing Environment

	Description of Sample Case Study	
OHE INGREDIENTS	**OHE PRESENT**	**OHE ABSENT**
General case description	Mike is a 42-year-old man with low back pain for 8 weeks. He has no history of acute injury, no radicular symptoms, and no improvement despite chiropractic manipulation and over-the-counter NSAIDs.	Mike is a 42-year-old man with low back pain for 8 weeks. He has no history of acute injury, no radicular symptoms, and no improvement despite chiropractic manipulation and over-the-counter NSAIDs.
Relationship-centered care	Mike goes to see Dr. Smith because he knows and trusts her. She helped him through his divorce several years ago.	Mike has no primary care provider. He goes to a local health care clinic close to his home and sees whichever physician is available at the time he visits.
Healing space	Mike likes Dr. Smith's office. It is warm and welcoming and makes him feel at ease, safe, and comfortable.	The clinic is cold and uninviting. You can hear traffic noises from the busy street as you hear the paging system overhead telling the physician that the patient is ready in Room 3.
Self-care	Dr. Smith seems to "walk the talk." Mike sees her jogging around town at lunch, and she never seems "stressed out" like so many other physicians.	Dr. Jones seems rushed and stressed by the demands of all the patients backed up in the waiting room. She appears to be overweight, pale, and fatigued.
Intention and awareness	What Mike likes best about his physician is that she seems totally present when she sees him. He feels like he is the most important thing on her mind during his visits.	Mike feels sorry for the overworked physician and wants to give her information in an efficient manner so that she can do her job quickly. She remains standing, offers little eye contact, and seems distracted by the many demands on her time. Mike feels disconnected.
Holism	Dr. Smith does a full physical examination that shows muscle spasm in the right quadratus lumborum muscle group but no other concerning signs. Mike feels comfortable telling Dr. Smith about the loss of his job a few months back. She educates him about how the body can sympathize and experience symptoms when the mind is under stress.	Dr. Jones focuses on Mike's back pain and asks directed questions related to his discomfort. Time does not allow for questions beyond Mike's physical symptoms. The examination shows muscle spasm in the right quadratus lumborum muscle group, but no other concerning signs are noted.
Collaborative care	Dr. Smith refers Mike for counseling to develop further insight into how his life situation can influence his health. He will also see a massage therapist to loosen up his muscle spasm.	Dr. Jones is concerned about the length of Mike's symptoms without resolution. She orders an MRI scan and refers Mike to an orthopedic surgeon for further evaluation. She educates Mike about the potential benefits of an epidural block.
Lifestyle	Dr. Smith sees that Mike has gained 18 lb in the last year and discusses the need for him to start a gradual exercise program and work on getting back to his ideal body weight. She also recommends a book that discusses the relationship between back pain and stress.	Mike is given a prescription for hydrocodone and a patient education handout on low back pain exercises. He is told that if nothing helps, he may be a candidate for long-term opioid pain management.
Spiritual connection	Dr. Smith knows that Mike has a love of photography and the outdoors. Many of his photographs can be found around town in local shops. She encourages Mike to take this opportunity to direct his career to fulfill those things that he loves to do.	Mike leaves hopeful that the medication will reduce his pain and discomfort.
Compare and Contrast	**OHE Present**	**OHE Absent**
Outcome	Dr. Smith encourages the development of personal insight into how Mike's life situation is influencing his health. He understands what Mike can do to help this situation resolve.	With Dr. Jones' approach, the lack of a holistic view and of relationship-centered care result in a focus on the physical symptom without encouraging the patient's insight.
Goal	The initial goal is symptom resolution.	The initial goal is symptom suppression.

Continued

TABLE 2-2. Optimal Healing Environment—cont'd

Compare and Contrast	OHE Present	OHE Absent
Symptom management	This recruits internal resources to facilitate health and healing.	This relies on external influences for symptom management.
Use of resources	The use of resources is reduced.	The use of resources increases.
Cost	The long-term cost is low.	The long-term cost is high.
"Side effects"	Most side effects are potentially positive (e.g., joy in a new hobby, insight into behavior, increased well-being, and reduced risk factors).	Most side effects are potentially negative (e.g., nausea from hydrocodone, potential drug addiction, and possible surgery).

MRI, magnetic resonance imaging; NSAIDs, nonsteroidal antiinflammatory drugs; OHE, optimal healing environment.

Foundations of a Healing Encounter

To understand the intrinsic value of a therapeutic modality, the scientific model requires that we isolate it from the environment in which it is prescribed. The investigation is also blinded so that the belief systems of the patient and the prescriber do not influence the results. This is important for research but unrealistic when we look at the more complicated environment in which health care is delivered. In fact, the environment in which the prescribed therapy is given may be more effective than the therapy itself.[34]

In the early 1990s, Frank and Frank[35] described four ingredients that were present in a healing encounter:

1. An emotionally charged relationship with a helping person
2. A healing setting (an expected place to go for healing)
3. An explanation for the symptoms that resulted in a sense of control and understanding
4. A ritual, procedure, or plan that involves active participation of both parties that each believes will restore the person to a state of health (a mutual belief followed by an action to overcome the problem)

When one of the chapter authors, David Rakel, was in practice in rural Idaho, he believed that his most successful drug was a selective serotonin reuptake inhibitor. In retrospect, however, the fulfillment of these four criteria may have played the major role in patient improvement. If we look at a case of what happens before we put someone who is depressed on a medication, we can better understand this.

A depressed gentleman whose life is in chaos comes to see you, his physician, with whom he has a relationship based on trust and a holistic understanding of who he is. The patient has come to a healing setting (medical clinic), where he has the expectation that he will receive help. You give him a logical explanation for his symptoms ("a reduction in the level of serotonin") that offers a sense of control and understanding. Both you and the patient agree on a prescribed therapy that you both believe will restore health. You then write down the "answer" on a prescription pad and hand it to him, which then completes the healing ceremony.

When this ritual was performed in a study of St. John's wort, sertraline (Zoloft), and placebo for major depression, it was not the plant or the pill that had the greatest effect, but the ritual (placebo) 8 weeks after initiating therapy.[36] A meta-analysis and review of data submitted to the U.S. Food and Drug Administration for drug treatment of depression also found little difference between the medication and the placebo for mild to moderate depression; both had beneficial effects[37,38] (see Chapter 3, The Healing Encounter).

During the early development of family medicine, this process was known as the art of medicine and was held to be a rare feature of the specialty. With the rise and dominance of pharmaceuticals and evidence-based medicine, it became known as the placebo effect and was not supported in medical care. Subsequently, accumulating evidence on the importance of the healing context and encounter resulted in a reinterpretation as the creation of an OHE.[39] In this chapter, we describe those elements and how they can be systematically brought into clinical practice.

The Practitioner's Influence on Healing

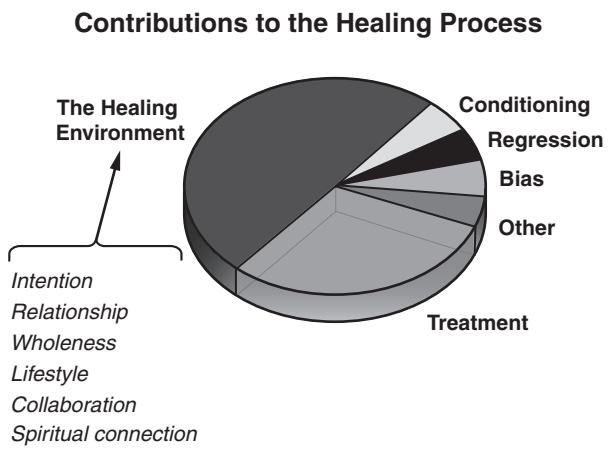
Psychotherapy is a good area to explore the ways in which the therapeutic interaction influences healing because it has few external physical tools such as drugs and surgery. When researchers looked at factors that influenced positive health change in psychotherapy, the factor in the therapist's control that influenced healing the most (30%) was the establishment of a therapeutic relationship in which the patient felt a sense of trust and rapport.[40] A study looking at the "most effective" psychotherapists found that those patients receiving counseling from therapists most talented in developing trusting relationships were much more likely to respond positively to medications than were those patients seeing less effective therapists.[41]

In fact, when psychiatrists rated high in relationship and rapport treated depressed patients with placebo, they had better outcomes than did psychiatrists who were rated lower and who used active drug.[42] Thus, the practitioner, rather than the pill, had the largest impact on outcome.

The quality of the clinician-patient interaction influences outcomes. Studies looking at practitioners' effects on the severity and duration of the common cold and irritable bowel syndrome showed significant enhancement of the therapeutic effect when the treatment was given through an "enhanced" or "augmented" clinical visit in which the clinician took time to create a connection that was perceived as empathetic.[43,44]

In treating one of the most common conditions encountered in primary care—diabetes—high ratings of physician empathy by diabetic patients correlated with better outcomes in diabetes management.[45] The nonspecific healing

FIGURE 2-2
Influences on the healing process.



influences found within the clinical encounter create intention toward health that should be the foundation of the medical home (Fig. 2-2).[46]

> Creating an optimal healing environment will bring more joy to your work. It will allow you to connect with those key elements that attracted you to health care, and in doing so you will find more meaning and purpose.

The Medical Home

The term medical comes from the Latin word *medērī,* which means "to heal." Unfortunately, this word has been shaped by our culture to be perceived as a medicine or an external treatment that is given to the patient. The healing power of the medical home comes from the healing intention of a team of professionals who understand that both inner and outer environments are necessary for health (Table 2-3). One of the most important ingredients is the social connection with a team of people who can support positive lifestyle behaviors while also diagnosing and managing disease. The positive behaviors have been found to have the most significant impact on longevity and the reversal of chronic disease if the disorder is caught early. Behaviors such as avoidance of smoking, weight management, improved nutrition, adequate physical activity, sufficient sleep, and avoidance of substance abuse can reduce the incidence of premature death by 40%[46] and extend life by 14 years.[47] To create this positive change, the medical home environment must empower individuals to do this for themselves. Empowerment requires a self-reflective process that results in a choice to act in a new way. The importance of this approach is exemplified in the care of diabetes, in which 98% of the care is patient directed.[48] Empowerment for behavior change is best facilitated through trusting relationships in which the clinician and the health care team recognize the unique needs of the individual and help create a supportive path toward health. It also honors the unique skills of the team to foster this growth.

Health Teams

New models of care are being defined to improve value and access and reduce cost in the United States. The practitioners of integrative medicine will be leaders in this movement because its philosophy places health creation as its highest priority. Both integrative medicine and conventional medicine will need to create teams of professionals based on the health needs of the community they serve, however, not simply a potpourri of professionals working independently in proximity. For example, if 30% of a community suffers from obesity, metabolic syndrome, and diabetes, the strategic medical home will recruit professionals best suited to address this need. This team may include nutritionists, exercise physiologists, spiritual guides, psychologists, health coaches, and physicians. These team members need adequate communication so that services of each are used when the patient will benefit most. When professionals from varied disciplines come together, shared knowledge allows for insight from different perspectives that can stimulate an "ah ha!" moment in which new ideas allow them to transcend old models of care. When this happens, an interdisciplinary team becomes a transdisciplinary team, and new models of delivery are defined.[49] Multifaceted team-based interventions in primary care are more effective in influencing positive lifestyle behaviors than is isolated specialty care[50–52] (Table 2-4).

TABLE 2-3. Optimal Healing Environments

INNER ENVIRONMENT TO THE OUTER ENVIRONMENT						
Healing intention	Personal wholeness	Healing relationships	Healing organizations	Healthy lifestyles	Integrative collaborative medicine	Healing spaces
Expectation Hope Understanding Belief	Mind Body Spirit Family Community	Compassion Empathy Social support Communication	Leadership Mission Culture Teamwork	Diet Movement Relaxation Addictions	Person oriented Conventional Complementary Culturally appropriate	Nature Light Color Architecture
Enhanced awareness expectancy	Enhanced personal integration	Enhanced caring communication	Enhanced delivery process	Enhanced healthy habits	Enhanced medical care	Enhanced healing structure

Modified from Jones WB, Chez RA. Toward optimal healing environments in health care. *J Altern Complement Med.* 2004;10(suppl 1):51–56.

TABLE 2-4. Defining Disciplinary Teams

TERM	DEFINITION
Multidisciplinary team	**Additive.** "Comprising more than two professionals from different health care disciplines who work with the same patient, set of patients, or clinical condition, but provide care independently of each other" (interdisciplinary team building). For example, a patient may have visits with both a primary care practitioner (PCP) and a physical therapist (PT). Although the PCP may view clinical notes or a report from the PT, the two disciplines usually do not interact.
Interdisciplinary team	**Interactive.** "Dedicated to the ongoing and integrated care of one patient, set of patients, or clinical condition" (interdisciplinary team building). Team members develop collegial relationships with shared goals and joint decision making. They interact, support, as well as question each other's opinions, and negotiate to develop health strategies based on the needs of the individual.
Transdisciplinary team	**Holistic.** Professionals learn from each other and in the process transcend traditional disciplinary boundaries that may result in the emergence of new knowledge. Often, the greater the difference between professions (epistemologic distance, e.g. engineering and humanities), the more likely insight will develop toward the creation of a new way to solve a problem.

From Rakel DP, Jonas W. The patient-centered medical home. In: Rakel R, Rakel D, eds. *Textbook of Family Medicine*. 8th ed. Philadelphia: Saunders; 2011; data from Choi BC, Pak AW. Multidisciplinarity, interdisciplinarity, and transdisciplinarity in health research, services, education and policy: 3. Discipline, inter-discipline distance, and selection of discipline.*Clin Invest Med.* 2008; 31:E41–E48.

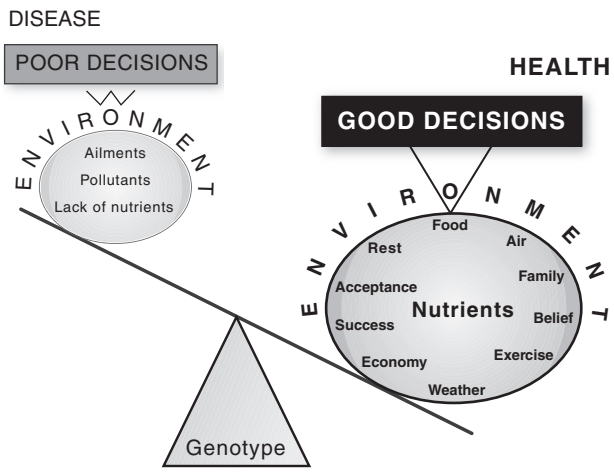
Environment's Influence on Genetic Expression

The goal of an integrative medicine health-oriented team is to work together to create OHEs. Environments can have an influence on the genome of the living beings that live within them. The scientific evidence of this epigenetic influence is exploding and gives power and hope to the individual to make positive lifestyle choices by attending to and changing their environment (Fig 2-3).

Animal studies showed that genetically identical agouti mice bred to develop obesity and diabetes could have this expression suppressed when the mothers were fed methyl-donating foods (genestein) before they gave birth.[53] An Amish community assessed to see whether carriers of the *FTO* obesity gene would become overweight found that carriers who averaged 18,000 steps a day remained at a normal weight. Their lifestyle habits trumped their genetic risk.[54]

Telomers are the protective DNA-protein complexes at the end of the chromosomes that promote stability. Loss in their length has been associated with increased risk of disease and premature mortality. Telomere shortening is counteracted by the enzyme telomerase, and more of this is beneficial. Ornish et al[55,56] looked at telomerase levels in 30 men with prostate cancer. After 3 months of healthy lifestyle changes, including moderate exercise, a low-fat plant-based diet, and social support, the telomerase levels rose,[55] and oncogene expression was inhibited.[56] Exercise alone can increase telomerase activity[57] and brain volume.[58] Stress can decrease telomerase levels,[59] whereas practicing the relaxation response can have a positive influence on genetic expression.[60]Although these behaviors are powerful, they are not the sole dictator of outcomes. The body-mind is complex and mysterious. The clinician should be careful not to instill guilt regarding lifestyle habits when cancer or heart disease is diagnosed. Instead, the clinician should reassure the patient that, even when disease progresses, improved well-being and function are more likely if he or she continues or adopts healthy behaviors.

FIGURE 2-3
Depicted is a balance representing the person's unique genetic constitution and the direction into which his or her decisions will poise the organism's well-being, determined by the presence of nutrients, ailments, or pollutants. A nutrient can be understood as any element that nourishes the body and mind.



Health as a Continuum

The continuum of health starts with ourselves, is supported by others, is influenced by lifestyle choices, and is shaped by our inner and outer environments. This continuum recognizes the importance of the interconnectedness of all things. Health is not found in isolated parts but throughout the whole. Being an integrative medicine practitioner means recognizing the dynamic and complex ecosystem in which we live and working to support its health. In doing so, we occasionally pause to witness the mystery of how nature continuously strives for balance despite the odds we have created for it.

> I would rather live in a world where my life is surrounded by mystery than live in a world so small that my mind could comprehend it.
>
> *Harry Emerson Fosdick*

Several years ago, a primary care clinic in England introduced a spiritual healer into its practice. This was done quietly, without advertisement. Patients who had refractory, chronic illnesses, who were high health care users, and who were taking multiple drugs were offered 12 sessions with the healer. Health care use costs, symptoms, and well-being were measured before and after the study period. Almost all patients got better: health care visits decreased; patients improved in their energy and well-being; and although the diseases were not actually cured, suffering was relieved. Costs were reduced by $2000 per patient per year. Most interesting, however, was the change this approach had on the physicians in the practice. When the investigators examined what the healer did during sessions, the procedures were simple. The healer spent a long time listening intently to the patients and hearing what their concerns were about the illness, linking it up with family events, and challenging patients to perceive their connectivity beyond themselves, to imagine a future that was better and improved. The healer then spent time doing some bioenergy work, holding her hands over the patient in the traditional laying-on-of-hands manner. The physicians in the clinic soon realized that many of these same behaviors were similar to things they had been taught to value in medical school but had not often been able to incorporate into their own practice. These physicians then found themselves spending a few more moments with patients and asking them about social and family issues that earlier they would have glossed over or ignored, getting and giving feedback about the meaning of a person's illness, and listening and responding in a warmer fashion. In other words, the physicians realized that they, too, could become healers in the classic sense of the term.[61]

KEY WEB RESOURCES

Samueli Institute. http://www.siib.org/research/research-home/optimal-healing.html

The Samueli Institute has sponsored research in the development of optimal healing environments. This site contains research papers and resources on the topic.

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References are available online at expertconsult.com.

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Chapter 3

The Healing Encounter

David Rakel, MD, and Luke Fortney, MD

To find health should be the object of the doctor. Anyone can find disease.

T. Still, MD

To write prescriptions is easy, but to come to an understanding of people is hard.

Franz Kafka

What kind of doctor do I need to be for this patient today?

Michael Balint

Medical encounters in the recent past have been dominated by the 15-minute office visit that focuses on a symptom or disease state. This is a pathogenic encounter focusing on the genesis or creation of disease. The healing encounter requires a different goal of salutogenesis that focuses on the creation of health.[1] The clinician's intent is to develop an understanding of what the person needs to self-heal and to help the person find a balance in which he or she can interact smoothly with the environment. This chapter focuses on how the clinician can most efficiently allow this process to unfold. At its deepest beauty, this healing process is not one sided, but one in which both the patient and the clinician are transformed. The result is the most rewarding aspect of the profession.

Salutogenesis (the creation of health) is the opposite of pathogenesis (the creation of suffering or disease). The goal of the healing encounter is to facilitate the creation of health that transcends the physical and results in less suffering and an overall improved quality of life.

Practitioner Versus Pill

The mind often attributes healing to external influences outside of ourselves such as from drugs, herbs, or an acupuncture needle. These specific variables are often the most thoroughly studied and are thought to have the most benefit, partly because they are physical treatments that can be quantified. The gold standard in medical research, the double-blind placebo-controlled trial, focuses on removing the nonspecific variables that can often be more powerful than the pill or procedure being studied. These nonspecific variables include aspects of care that are difficult to quantify. They may include trust, empathy, a sense of control, and compassion, which are key ingredients of the healing encounter. These nonspecific variables have been found to enhance the effects of acupuncture for irritable bowel syndrome,[2] shorten the duration of the common cold,[3] trump antidepressants for mild to moderate depression,[4–6] and improve clinical outcomes in patients with diabetes.[7] The nonspecific effects that have been most thoroughly studied in influencing healing in the clinical encounter can be summarized through the PEECE mnemonic: P, positive prognosis; E, empathy; E, empowerment; C, connection; and E, education.[8] Many of these healing influences are cultivated in the process of mindfulness.

Mindfulness in Your Practice

Mindfulness is a way of being in the present moment, on purpose, non-judgmentally.

Jon Kabat-Zinn[9]

When we sit with a patient, the mind will naturally wander and be distracted. Without intentional redirection of the attention back to the patient, however, we lose the opportunity to understand the person sitting across from us. When we are not present and anchored in the moment, we can slip into

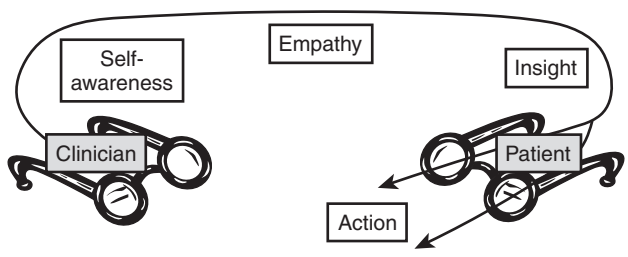
seeing patients not as who they truly are but as we project them to be. Medical training conditions us to label patients with disease. As we become more adept at recognizing the disease states within people, however, our perception of each other changes to honor the label and not the individual.

In an observational study from 1973, eight *sane* people presented to eight different psychiatric hospitals in California with the complaint of, "*I am hearing thuds*." After being admitted, these people behaved in a normal and healthy way. The researchers wanted to see what diagnoses they would be given and how long they would remain in the hospital. All eight were given the diagnosis of schizophrenia in remission, and the average length of stay was 19 days. One of the eight was in the hospital for 52 days.[10] The doctors and nurses were not able to see the *sane* patients for who they really were because of their disease-focused conditioned thinking. Recognizing disease patterns is an important part of a clinician's everyday work. If we are not aware and do not recognize the habitual nature of these snap judgments, however, we risk being stuck in these conditioned perspectives and may not recognize arising moments and situations when it is appropriate to step out of these perspectives. The people who questioned the appropriateness of the eight *sane* patients' admissions to the psychiatric hospital were not the doctors or nurses but their fellow inpatients—those with whom the sane people developed relationships through meals, group therapy, and daily activities. Through close relationships the other inpatients were able to see the individuals as they truly were.

Self-Reflection

The healing encounter requires that the practitioner be aware of and recognize their own mind states that may or may not be helpful. Noticing personal bias can help minimize inappropriate judgments and projections. The mindful clinician will be able to meet patients where they are by recognizing their true needs. We will be more successful in helping others if we are able to recognize our own beliefs and then do our best to see the world through the lenses of our patients and their life perspectives (Fig. 3-1). Primary care clinicians trained in mindfulness report improved mood and sense of personal well-being, which, in turn, has a positive impact on patient care.[11,12] To be of service to a person in need is difficult if the clinician is suffering more than the patient. As the saying goes, "you can't give what you don't have."

FIGURE 3-1
Seeing from the patient's perspective.



There is nothing like a difficult patient to show us ourselves.

William Carlos Williams

Most people do not listen with the intent to understand; they listen with the intent to reply. They're either speaking or preparing to speak. They're filtering everything through their own paradigms, reading their autobiography into other people's lives.

Stephen Covey

A study of psychotherapists in training found that the patients taken care of by those therapists who practiced mindfulness had better outcomes, including greater symptom reduction, than did the patients of therapists who did not practice mindfulness. The personal practice of clinicians may influence the outcomes of the patients in their care.[12]

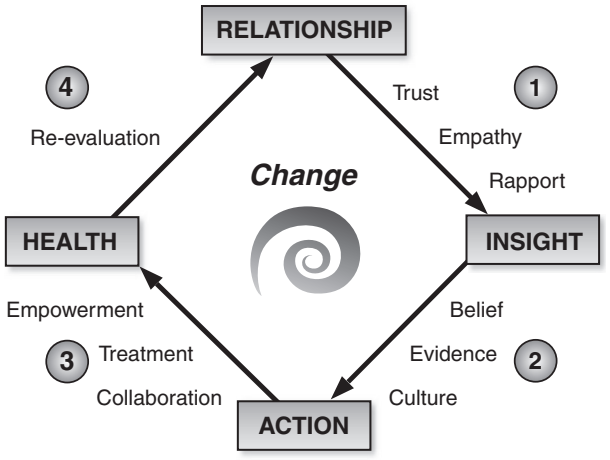
Empathy

Empathy is defined as a cognitive attribute that involves an understanding of experiences, concerns, and perspectives of the patient, combined with the capacity to communicate this understanding.[13] Empathy is a foundational ingredient of the healing encounter. It asks that we initially set aside what we know, feel what patients are communicating, and then communicate this back to them so that they know they were heard. Patients often do not remember what you tell them, but they remember how you made them feel. We feel first through empathy, and then we take action second, based on the information obtained through mindful listening that is combined with medical knowledge and training. We must listen and feel first, however. It is not surprising that empathy significantly declines through medical school and residency as learners focus more on increasing their knowledge at the expense of emotional health and awareness.[14] The combination of this empathetic insight with knowledge best serves the authentic needs of the patient to experience healing. Both are important and necessary.

Insight and Intuition

Insight requires empathy and is the process by which information is gained that allows clinicians to understand how best to serve the health needs of the patient. Intuition is a unique human ability. It is the process of taking a variety of different unrelated bits of information and arriving at a logical conclusion. The more information we have to work with, the more accurate the intuition. If a patient is seen as a disease or an organ system, the clinician will often start with what he or she knows, and the information obtained through listening and feeling will not be incorporated into the patient's care. This is why ongoing relationship-centered care is so important: it can enhance the accuracy of our intuition and insight. A clinician who has known a patient for 10 years is likely to have more accurate insight and intuition based on the many bits of information (analytical and emotional) assimilated over time. This insight results in action that guides the patient most efficiently to health (Fig. 3-2).

FIGURE 3-2
The dynamic process of facilitating health and healing. (From Rakel DP. The healing power of relationship-centered care. In: Rakel DP, Faass N, eds. *Complementary Medicine in Clinical Practice*. Boston: Jones & Bartlett; 2006.)



Functional magnetic resonance imaging research has shown a strong coupling between speakers' and listeners' brains that vanishes when communication is poor. In good communication, the listener can anticipate what is going to be communicated before speech is produced, thus leading to greater understanding of the information conveyed.[15]

Action

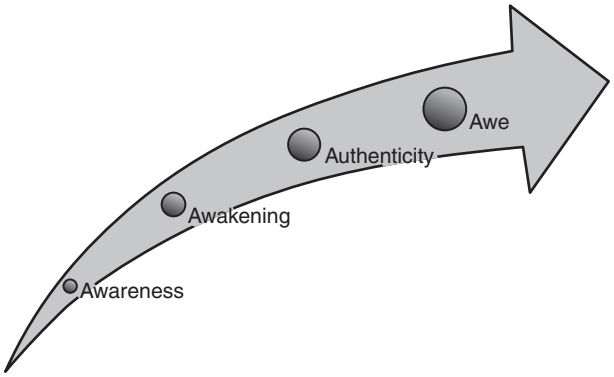
The Buddhists have the following saying: "action without wisdom is dangerous, and wisdom without action is useless." The healing encounter requires a collaborative action that both the clinician and patient believe will bring health. If we do not take a mindful stance to listen before moving to action, we may not serve the needs of the patient and even potentially cause harm. When we recommend a therapy that the patient does not follow through with, the clinician may blame the patient for being noncompliant. In actuality, the clinician should share the blame for not taking the time to understand the patient's concerns and make a recommendation that would better match the need. Noncompliance represents two people working toward different goals. The healing encounter involves a process that must unfold before action can be of service and the patient goals can be met. To simplify, we summarize this process into the three Ps of a healing encounter: pause, presence, and proceed.

The 3 Ps: Pause, Presence, and Proceed

Pause

Before entering the clinical examination room, take a moment to pause, take a deep breath, and allow yourself to direct your attention to the patient in the room. Use the threshold of the examination room doorway to remind you to drop into the sensations of your own breathing, so that you may be more present with the patient. A threshold is a metaphor for a transition to a new understanding or awareness that the clinician and patient find together. Taking advantage of the opportunity to pause, drop in, and be present can help us center and be more attentive to the patient.*

FIGURE 3-3
The four As of the healing encounter.



More information on this topic can be found online at expertconsult.com.

Presence

Intentionally directing the attention to the physical sensations of breathing or feeling the feet making contact with the floor helps ground and center the mind. Taking two to three deep breaths into the lower abdomen just beneath the umbilicus is a good start (see Chapter 89, Breathing Exercises). In martial arts, this area is called the *hara*, and bringing awareness to this area of the body allows the settled mind to respond more appropriately to the changing needs of each moment. According to Eastern practices, life energy flows from the hara (see Chapter 112, Human Energetic Therapies). A suggestion to "practice in your practice" involves using your computer log-in as an opportunity to drop in and check in with your own body as you prepare to work with a patient. When the mind and body show up in the same place at the same time, the clinician is better equipped to engage the patient. The computerized or paper chart does not need to be a barrier between patient and provider.

Being present and alert moment by moment can awaken us to mystery and awe in an authentic way (Fig. 3-3). When we pause and become present with what is really happening, we are more likely to recognize what is beautiful in each moment, such as in seeing a flower or a living cell. The same holds true with suffering. Even though suffering is associated with pain and discomfort, the more we explore and lean into it, the more we come to understand and learn from it. The mindful encounter brings two people together in the fullness of life including suffering, joy, peace, unrest, creativity, and frustration. The mindful clinician is able to remain present with a wide range of emotions and experiences without being overwhelmed by or overidentifying with suffering.

*For more information on this topic, go to http://www.fammed.wisc.edu/mindfulness/pip.

An untended mind that multitasks and ruminates can prevent us from seeing what is actually present. Go here to see image: http://www.fammed.wisc.edu/mindfulness/pip/presence; "Presence and Almonds." Scanning the eyes across the figure creates the illusion of movement. If you allow your gaze to settle on just one object, the movement stops, and we are able to see the figure as it truly is. Pausing and focusing on the patient stops the movement and the delusions of our perceptions and allows us to connect with what is real and authentic.

BOX 3-1. Helpful Questions to Consider Asking in the Healing Encounter

- If those tears could speak, what would they be saying?
- I noticed that your eyes welled up when you talked about your daughter. Why was that?
- What do you feel may be at the root of this illness?
- In a time of need, to whom do you turn for support?
- What gives your life a sense of meaning and purpose?
- In a perfect world, what would your life look like?
- What are you most proud of?
- What words would help me to know what you are feeling?

Modified from Maizes V, Koffler K, Fleishman S. The integrative assessment. In: Rakel DP, ed. *Integrative Medicine*. 2nd ed. Philadelphia: Saunders; 2007:36.

Patients are able to feel whether you are truly present and listening. If they sense that you are compassionate and attentive, they will feel more comfortable and will often share important information and amazing stories. Creating this space results in more meaningful conversation that engenders understanding. In telling their stories, patients are able to reflect on the cause of their symptoms. This insight can be empowering and help motivate the patient to make changes. The clinician's empathy provides comfort and reduces the feeling of isolation that patients with chronic illness often have. Mindful listening may be our most effective therapeutic tool.[16] As the saying goes, "you were given two ears and one mouth to be used in that proportion."

Proceed

In pausing, being present, and listening to the patient, insight arises. This insight allows a plan to be created that both the clinician and patient believe will be of benefit. The plan increases the sense of control that patients feel in taking action that helps them move from disease to wellness. The health plan should recognize both physical and nonphysical factors that the patient can use to manage symptoms and prevent illness in the future. Helpful questions that can bring an understanding to this process are reviewed in Box 3-1.

The health plan may have one recommendation or several, based on the needs of the patient. For example, if a patient has had recurring headaches and diarrhea ever since his or her divorce, the health plan may only involve one recommendation, such as working toward self-care and forgiveness (see Chapter 97, Healing Through Forgiveness). If another patient wants to prevent a recurrence of breast cancer, however, the health plan may include recommendations on stress reduction, nutrition, spiritual connection, improving sleep, and the use of medications and supplements.

Before computerized medical records, the "answer" to the patient's problem was often conveyed as a quick fix on the prescription pad. The practice of integrative medicine recognizes that health is defined by much more than a medication, but the power of the prescription ritual should not be lost (see Chapter 114, Creating Ceremony and Ritual in the Medical Encounter). This ritual transfers knowledge and a sense of control that gives confidence that something may help the patient transcend suffering. The clinician's recommendations, based on the insight that arises from the healing encounter, should be summarized in writing and given to the patient at the conclusion of the visit.

Healing is not something easily reproduced or taught. Often, the best we can do is create an environment where it can unfold, grow, and teach us.

Creating Salutogenesis-Oriented Sessions

A healing encounter can be created in a brief, 5-minute interaction or during an hour-long discussion. To serve the complexity of health and healing most effectively, however, practitioners need to protect time in their schedules to create the ceremony for a healing ritual, the salutogenesis-oriented session (SOS)[17] (see Chapter 114, Creating Ceremony and Ritual in the Medical Encounter).

Recipe for a Salutogenesis-Oriented Session

Any health care clinic can create an SOS that stacks the deck in favor of the healing encounter. The following subsections describe key ingredients that will help create a healing environment for this approach to unfold and be sustainable.

Protect Time in Your Schedule

Carve out time in your work week to schedule an SOS. Some practitioners may schedule these as they would a yearly physical; others may protect a half-day a week focused only on these sessions. Many integrative medicine consultative clinics work in this way. Each session should be scheduled for at least 45 minutes.

Create Space

Consider redecorating an existing examination room to give the feeling that you are in a special and comforting place. Incorporate more soft colors and fabric, and limit sterile and cold medical paraphernalia. If you are unable to do this, simply bring in an element of nature such as a flower, plant, or water fountain.

Create Patient Expectations

Let the patient know that these sessions are intended to allow time for exploring deeper issues that may help you understand how best to facilitate salutogenesis. A typical scenario for creating expectation may be something like the following:

We have ruled out a physical cause for your headaches, and no evidence indicates a tumor. We do not have time scheduled today, but I would like you to come back on a Wednesday morning when I have set aside time for a session that will allow us more time to explore other aspects of life that can have a significant impact on physical health. I want to understand more clearly what may be going on in your life that may be influencing the amount of pain, fatigue, and sleep problems you have been experiencing. Often, in these sessions, we find common underlying causes that may help us get at the root of many of your symptoms.

Offer Support

Relationship-centered care is based on trust and support. An SOS can result in the emergence of past traumas or events that must be supported and further processed. Often, we may need to collaborate with a psychologist colleague to help understand how we can help patients heal from these events. We should not create an environment in which this information comes out and then not offer support and guidance on how to process it. This represents abandonment and turns an SOS into a pathogenesis-oriented session. Collaborative care allows healing to occur within a team that can support it.

Code Appropriately

We need to make sure that our time is appropriately coded so these sessions can be incorporated into clinical care as an important factor. The hope is that the medical system will eventually recognize the cost-saving potential of an SOS. As we explore the root of how the body self-heals, we will need fewer costly interventions. As the cost of disease-focused care escalates, this approach will gain more acceptance.

You need 40 minutes of face-to-face time to bill a "99204" (new patient) or a "99215" (established patient). Be sure to document the amount of time spent and include that "greater than 50% of time was spent counseling and/or coordinating care." This needs to be included if you are billing for time spent with the patient. If you document only total time and not the percentage of time spent counseling and coordinating care, then you must document the required components of the history, examination, and medical decision making.

For integrative medicine consultations, the code is "99244" for a 60-minute appointment and "99245" for an 80-minute appointment. Be sure to document the practitioner who referred the patient for consultation.

Conclusion

Pausing to be present before proceeding toward a plan for health is a simple task that, if practiced, can help two people efficiently find a healing path within a dynamic and complex ecosystem. Ideally, the visit itself is healing even before something is prescribed. Communication between clinician and patient gives the patient perspective and support that encourages both parties to pause, learn from symptoms, and proceed toward a better place, together.

> The meeting of two personalities is like the contact of two chemical substances; if there is any reaction, both are transformed.
>
> *Carl Jung*

KEY WEB RESOURCES

University of Wisconsin Integrative Medicine Program. http://www.fammed.wisc.edu/mindfulness.	This Web site includes instructions, exercises, videos, and audiofiles to help the clinician bring mindfulness into the clinical encounter. It complements this chapter.

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Chapter 4

Depression

Craig Schneider, MD, and Erica A. Lovett, MD

Centers for Disease Control and Prevention surveys indicate that nearly 1 in 10 residents of the United States who is 18 years old or older has a depressive disorder.[1] In fact, depression is one of the chronic conditions for which alternative therapies are most frequently used.[2] This is not surprising considering that pharmaceutical antidepressant medications are not as effective as once believed for many patients with less severe forms of depression.[3] Many people seen in primary care settings do not meet the diagnostic criteria for many of the well-known depressive disorders set forth in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) but rather fall under the DSM-IV category "depressive disorder not otherwise specified (NOS)." The Patient Health Questionnaire (PHQ)-9 (see Key Web Resources, later) is a simple, brief, and well-validated instrument for diagnosing depression and a reliable and responsible measure of treatment outcomes in the primary care setting.[4]

Pathophysiology

The pathophysiology of depression is not fully understood. The stress-diathesis model of illness emphasizes that significant emotional, social, and environmental antecedents such as the loss of a family member or a romantic or professional disappointment, as well as genetic and acquired vulnerabilities, are clearly involved. Significant stressors appear to be more frequently involved with initial episodes. In recurrent depression, vulnerability appears to increase as episodes become less and less related to stress and more autonomous in a process known as kindling.[5,6] With repeated episodes of illness (kindling), central nervous system dysfunction increases, as manifested by hypercortisolemia, decreased slow-wave (restful) sleep, and increased rapid eye movement (arousing) sleep and disruption of neuroplasticity.[7] The biochemical impact of depression may be stored in neurons through changes in the activity of gene transcription factors and neuronal growth factors.[8] The common final pathway is the biochemical imbalance of biogenic amines or neurotransmitters (e.g., serotonin, norepinephrine, gamma-aminobutyric acid [GABA], and dopamine) and their relationships with their respective receptors in the brain. Potential effects on neurotransmitters include impaired synthesis, increased breakdown, and increased pump uptake, with consequent alterations in neurotransmitter levels. Successful pharmaceutical approaches to treating depression involve correction of these altered neurotransmitter levels and of neurotransmitter receptor interactions.

Integrative Therapy

Exercise as Medicine

More than 1000 trials examined the relationship between exercise and depression, and most of these studies demonstrated an inverse relationship between them.[9,10] Physical activity may also prevent the initial onset of depression.[11,12]

Regularly performed exercise is as effective an antidepressant as psychotherapy or pharmaceutical approaches.[9,13–17] Well-designed studies also support that exercise combined with pharmacologic treatment is superior to either alone, but exercise appears to be superior in maintaining therapeutic benefit and preventing recurrence of depression.[18–22] A Cochrane Review, however, demonstrated conflicting results and no statistically significant effect of exercise on depression.[23] The Cochrane Review results may be explained by the inability to blind properly for the active intervention of exercise.[24] The additional benefits that may be attained by patients who exercise, including increased self-esteem, increased level of fitness, and reduced risk of relapse, make exercise an ideal intervention for patients suffering from depression.

Both aerobic and anaerobic activities are effective.[15,19,24,25] Regardless of the type of exercise, the total energy expenditure appears more important than the number of times a week a person exercises, and high-energy exercises are superior to low-energy exercises.

Exactly why exercise relieves or prevents depression is not understood. Although exercise may increase levels of serotonin, norepinephrine, and endorphins, its benefits have been reported even when naloxone is administered to block endorphins. Exercise may also increase nerve cell growth in the area of brain that modulates mood, similar to pharmaceuticals.[26,27]

Exercise is inexpensive, has proven benefits beyond the treatment of depression, has a low occurrence of side effects, and is available to everyone. The appropriate exercise prescription depends on the specific patient's health, motivation, level of fitness, and interests (see Chapter 88, Writing an Exercise Prescription). For more seriously depressed patients and those with significant psychomotor retardation, the exercise regimen should be started as adjunctive therapy.

Write an exercise prescription for all patients; tailor the type of exercise to something the patient enjoys, whether aerobic or anaerobic.

Nutrition

Caffeine and Simple Sugars

Cross-national epidemiologic studies suggest a correlation between sugar intake and rates of major depressive disorders.[28] Examination of the diets of people suffering from depression reveals increased consumption of sucrose compared with the general population.[29] A small cohort trial found that eliminating refined sucrose and caffeine from the diets of people experiencing unexplained depression resulted in improvements by 1 week, and symptoms worsened when patients were challenged with these substances but not with placebo.[30] Regular high-level caffeine consumption (750 mg daily) appears to be associated with depression.[31] A large epidemiologic study in Finland, however, demonstrated an inverse relationship between daily tea drinking and the risk of being depressed.[32]

Dietary Patterns

A large cross-sectional study of women consuming traditional diets (vegetables, fruit, beef, lamb, fish, and whole grains) in Australia found a 35% reduced likelihood of major depression or dysthymia compared with women consuming a Western-style diet (more fried, refined, and processed foods), after adjusting for potential confounders (age, socioeconomic status, education, physical activity, alcohol, smoking, and total energy intake).[33] Populations with high adherence to a Mediterranean dietary pattern ensuring adequate intake of omega-3 fatty acids (from fish), monounsaturated fatty acids (from olive oil), and natural folate and other B vitamins (from legumes, fruit and nuts, and vegetables) demonstrate significant reductions in depression risk as well.[34]

Alcohol

A systematic review confirmed that alcohol-related problems are more common in depressed individuals than in the general population and are associated with worse outcomes.[35] Although consumption of alcohol transiently increases the turnover of serotonin, the long-term result is diminished levels of serotonin and catecholamines.[36] Because of the safety, potential health benefits in other areas, and low cost of this intervention, discontinuation of alcohol consumption is warranted.

Recommend that patients adhere to a traditional or Mediterranean dietary pattern and limit sugar, caffeine, and alcohol consumption.

Omega-3 Fatty Acids

Epidemiologic data suggest that a deficiency of omega-3 fatty acids or an imbalance in the ratio of omega-6 and omega-3 fatty acids correlates positively with increased rates of depression,[37] and this is not explained by known confounders such as inflammation and atherosclerosis.[38] Because dietary polyunsaturated fatty acids and cholesterol are the major determinants of membrane fluidity in synaptic membranes involved in the synthesis, binding, and uptake of neurotransmitters, investigators have hypothesized that alterations may lead to abnormalities contributing to increased rates of depression.[39] Although the current evidence does not support using omega-3 fatty acids as monotherapy to treat depression,[40] small, well-designed studies support the use of omega-3 fatty acids as adjuncts to conventional antidepressant therapy.[41,42] Preliminary evidence also suggests that children with depression and women with depression during pregnancy may benefit from supplementation with omega-3 fatty acids.[43,44]

The effective dose of omega-3 fatty acids for treating depression is not yet known. A dose-ranging study suggested that 1 g daily may be superior to 2 or 4 g daily.[45] Consumption of two or three servings each week of smaller cold-water fish (herring, mackerel, wild salmon, sardine) is comparable. Omega-3 fatty acids also support cardiovascular health and are generally safe. One caveat to consider is the issue of heavy metal and pesticide contamination of available seafood and supplemental fatty acids. Larger fish and farmed fish may bioconcentrate toxins, including mercury and polychlorinated biphenyls. Most studies suggest that eicosapentaenoic acid (EPA) or combinations of docosahexaenoic acid (DHA) and EPA are more helpful than DHA alone. Vegetarian alternatives to consider include flaxseed oil or ground flaxseed meal (2 tablespoons daily) and a small handful of walnuts each day, but these substances have not been studied in depression (see Chapter 86, The Antiinflammatory [Omega-3] Diet).

Docosahexaenoic acid is generally more structural (important for brain and retina development), and eicosapentaenoic acid is generally more functional (improves communication across cell membranes).

Dietary Supplements

Vitamin D

A large Dutch cohort study of people aged 65 years and older demonstrated an inverse relationship among vitamin D levels, depression status, and depression severity even after

adjusting for potential confounders. We do not yet know whether low vitamin D status in patients with depression is a cause or an effect.[46] Supplementing vitamin D is safe and inexpensive, however, and emerging evidence suggests that it may play a role in preventing multiple problems including falls in older persons, cardiovascular disease, and colon cancer.[47–49]

B Vitamins

Folic acid and vitamin B_{12} are intimately linked with the synthesis of *S*-adenosylmethionine (SAMe), and each functions as a methyl donor, carrying and donating methyl molecules to a variety of brain chemicals, including neurotransmitters. Although large-scale clinical studies are lacking, a trial of a B-complex vitamin is advisable, particularly for older patients, in whom B_{12} deficiency is common, and for persons with suboptimal diets. Vitamin B_6 is essential in the manufacture of serotonin, and vitamin B_6 levels have been found to be low in many depressed patients, particularly in premenopausal women taking oral contraceptive pills or replacement estrogen.[21,37,50]

Dosage

Vitamin B complex 100, one tablet daily (contains approximately 100 mg each of the major B vitamins).

Folic Acid

Up to one third of depressed adults have borderline or low folate levels. A subgroup of depressed patients with folate deficiency and impaired methylation and monoamine neurotransmitter metabolism has been identified.[51] In fact, depression is the most common symptom of folate deficiency.[52] Patients with low levels of folate also appear to respond more poorly to therapy with selective serotonin reuptake inhibitors (SSRIs).[52] Limited evidence from a Cochrane Review suggested that the addition of folate to conventional antidepressant therapy is beneficial.[53] Folate is used as an adjunctive treatment.[54]

Folate may also have other health benefits (i.e., prevention of neural tube defects and reduction of elevated homocysteine). It makes sense to supplement with vitamin B_{12} concomitantly to avoid masking a deficiency.

Dosage

400 mcg to 1 mg daily (although doses of 5 to 20 mg daily have been used in studies).

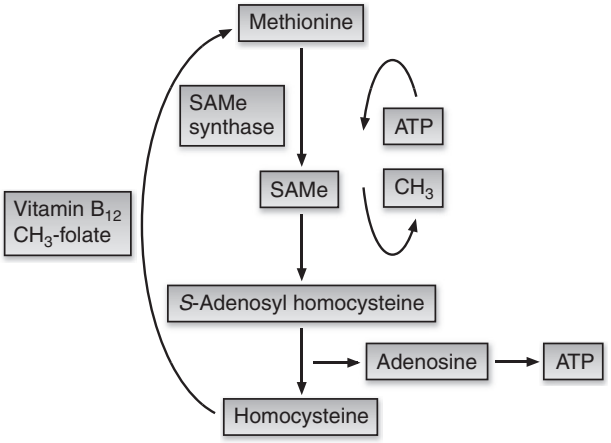
Precautions

High doses of folic acid have been reported to cause altered sleep patterns, vivid dreaming, irritability, exacerbation of seizure frequency, gastrointestinal disturbances, and a bitter taste in the mouth, and concerns have emerged about possible increased risk of some cancers.

S-Adenosylmethionine

SAMe (Fig. 4-1) is the major methyl donor in the body and is involved in the metabolism of norepinephrine, dopamine, and serotonin. Its synthesis is impaired in depression, and supplementation results in increased brain monoamine levels, enhanced binding of neurotransmitters to receptors, and increased brain cell membrane fluidity. Although larger trials are warranted, multiple open and randomized controlled trials (RCTs) suggest that SAMe is an effective natural antidepressant. An RCT comparing SAMe (1600 mg orally, daily) with imipramine (150 mg orally, daily) over 6 weeks demonstrated equivalent efficacy and superior tolerability of SAMe.[55] Another small double-blind placebo-controlled trial of SSRI nonresponders with major depression compared adjunctive SAMe (800 mg orally, twice daily) with placebo and found SAMe significantly more likely to lead to remission.[56] An Agency for Healthcare Research and Quality evidence report and technology assessment in 2002 found SAMe to be superior to placebo and comparable to conventional antidepressants, based on available evidence. SAMe is generally well tolerated and has a more rapid onset of action than that of standard pharmaceutical antidepressants.[57] Because of this characteristic, some clinicians start SAMe concurrently with another dietary supplement or pharmaceutical approach to therapy of depression that has been more thoroughly studied and then taper the dose of SAMe to zero as the other antidepressant begins to take effect. The most stable and bioavailable oral form appears to be 1,4-butane-disulfonate (Actimet), which is stable for up to 2 years at room temperature. SAMe is relatively free of side effects and does not have known cardiac, anticholinergic, or orthostatic effects. Larger clinical trials comparing SAMe with placebo and standard of care will help elucidate its role in treating depression.

FIGURE 4-1
S-Adenosylmethionine (SAMe) metabolism. SAMe may cause hypomania or mania in patients with bipolar disease and should be avoided in this population. ATP, adenosine triphosphate; CH_3, methyl group.



Dosage

Initial treatment of depression may require 1600 mg daily given in equal doses, followed by a maintenance dosage of 200 mg twice daily. We recommend starting with 200 mg once or twice daily, to minimize any gastrointestinal side effects, and then titrating upward to effect over 1 to 2 weeks. In treating SSRI nonresponders, 800 mg orally twice daily may be used.

Precautions

High dosages can cause nausea, vomiting, flatulence, and diarrhea. Avoid giving the second dose close to bedtime because it can cause insomnia.

Hydroxytryptophan

Hydroxytryptophan (5-HTP) is the intermediate in the metabolism of tryptophan to serotonin. Open trials and RCTs have suggested that 5-HTP is as effective as standard antidepressants.[58,59] A Cochrane Review found only 2 of 108 trials of sufficient quality for inclusion, but in these trials, 5-HTP was superior to placebo.[60] Tryptophan itself appeared promising as a treatment for insomnia and depression but was removed from the market (although it is available again) when a contaminated batch was linked to an outbreak of eosinophilia myalgia syndrome in people with abnormal activation of the kynurenin pathway. Although 5-HTP is not metabolized along this pathway, case reports link 5-HTP to an illness resembling eosinophilia myalgia syndrome. The suspected culprit is a family of contaminants known as peak X that is commonly found in commercially available 5-HTP.[61] Because uncertainty surrounding 5-HTP remains, it seems advisable to avoid recommending its use pending further information. Case reports of seizures in Down syndrome and of dermatomyositis in conjunction with the use of carbidopa have appeared in the literature. Use with other serotonin agonists is not recommended, to avoid serotonin syndrome.

Dosage

100 to 200 mg three times daily, enteric-coated 5-HTP, 20 minutes before meals.

Botanicals

St. John's Wort (Hypericum perforatum)

The exact mechanism of action of St. John's wort (SJW) remains unknown, but this botanical affects serotonin, dopamine, norepinephrine, and GABA reuptake inhibition and also in vitro monoamine oxidase inhibition and L-glutamate.[55] SJW also appears to inhibit interleukin-6 and increase cortisol production, which may result in an additional indirect antidepressant effect.[62] Clinical effects are probably the result of a combined contribution of multiple mechanisms, each individually too weak to account for the action.[63] SJW has been a licensed prescription medication in Germany since 1984, and nearly twice the number of prescriptions are written for it as for all other antidepressants in that country. Two large U.S. trials found that SJW was not effective for treating severe major depression.[64] The most recent Cochrane Reviews examined the findings of 29 trials (almost 5500 patients) comparing SJW with placebo or standard antidepressants and concluded that available evidence suggests that SJW is superior to placebo and is as effective as conventional antidepressants and better tolerated.[65] Large-scale postmarketing surveillance studies of SJW extracts (14,245 patients) recorded rates of adverse effects 10-fold lower than for conventional antidepressants.[66]

Indication

SWJ is indicated for mild to moderate depression.

Dosage

SJW, 900 mg daily given in three equal doses, has been used most frequently in clinical trials. Choose a product standardized to a minimum of 2% to 5% hyperforin or 0.3% hypericin such as those used in clinical trials. Examples include Lichtwer LI 160 found in Kira; Lichtwer LI 160 WS, the hyperforin stabilized version of LI 160 found in Quanterra Emotional Balance; ZE 117, containing 0.2% hypericin in Remotiv. Once clinical improvement has been obtained, consider twice-daily dosing. Up to 2 months may be required before full effects are noted.

Precautions

Although side effects are fewer than with current pharmacologic antidepressants, they can include gastrointestinal upset, allergic reaction, fatigue, dry mouth, restlessness, constipation, sexual side effects, and possibly increased risk of cataracts.

St. John's wort can activate the cytochrome P-450 3A4 detoxification system in the liver and thereby reduce the serum levels of drugs metabolized by this pathway. Caution should be used in patients receiving antiretroviral, warfarin, cyclosporine, and oral contraceptive therapy.

Ginkgo biloba

Ginkgo, the most prescribed botanical in Europe, is considered "safe and effective" by the German Commission E for treatment of cerebral insufficiency. It also has been found to be useful in treating older patients with depression related to organic brain dysfunction. Small double-blinded placebo-controlled trials support the effectiveness of giving ginkgo to older adults (51 to 78 years of age) with depression unresponsive to standard drug treatment.[67,68] Larger, well-designed prospective trials are warranted, but ginkgo is generally well tolerated.

Indication

Ginkgo is given as an adjunctive agent for treatment-resistant depression in patients older than 50 years of age.

Dosage

The recommended regimen is 40 to 80 mg three times daily of an extract standardized to 24% ginkgo flavonglycosides and 6% terpenoids. Many patients respond within 2 to 3 weeks, but it may take up to 3 months for full effects to be noted.

Precautions

Rare cases of mild gastrointestinal upset, headache, and allergic skin reactions have been reported. Ginkgo has an antiplatelet effect, so caution should be taken when prescribing this to patients taking anticoagulants.

Mind-Body Therapy

Antidepressants and psychotherapy are first-line treatments for depression according to the American Psychiatric Association (APA); even so, only 60% of those treated will have a clinically significant response, and many others may have residual symptoms.[69] Many patients turn to a

mind-body approach as another tool to improve their health. Additionally, the use of multiple treatment methods may end up being the best approach for preventing relapse and treating current depressive episodes.

The mind-body approach is common for those suffering from depression. One fourth of patients have tried some type of mind-body therapy,[27,70] and two thirds of those who tried a mind-body approach found it beneficial.[27]

With an understanding that no single mind-body exercise will treat all individuals or one individual completely, a pilot study by Little and Kligler demonstrated a positive response using a variety of mind-body techniques including psychoeducation, lifestyle modification, meditation, and mind-body skills training.[71] A larger study is pending. Another small study demonstrated that depressed pregnant patients treated with interpersonal psychotherapy and massage therapy (MT) improved more compared with those who had only psychotherapy.[72] One benefit of MT was that the patients also participated in more of their psychotherapy sessions.

Psychotherapy and Meditation

Depression-specific psychotherapies are designed to provide acute, time-limited interventions. They are present oriented and pragmatic, focusing on depression and issues considered relevant to both its onset and its perpetuation.[73] According to the APA, psychotherapy is a reasonable first-line or combination approach to all levels of depression, whether mild, moderate, or severe.[74] Primary care physicians can provide limited, supportive psychotherapy at frequent visits necessary to monitor the effectiveness of medications.[75] In fact, generic counseling appears to be preferred by patients over antidepressant drugs and is as effective, although slower in onset for treating mild to moderate depressive illness.[76]

Cognitive Therapy

Cognitive therapy is the most-studied psychotherapeutic approach to major depression. The physician or the therapist assists the patient in replacing negative patterns of thinking with a more positive, realistic approach. Multiple studies have demonstrated the equivalency of this modality to rigorous antidepressant medication regimens.[73] One controlled trial demonstrated that monthly cognitive therapy was as effective as antidepressant medications were for prophylaxis against recurrence over 6 months, but not all studies support this.

Mindfulness-Based Cognitive Therapy

A specific type of cognitive therapy that includes meditation is called mindfulness-based cognitive therapy (MBCT). This specific method has been successful for treating depression in a variety of patient populations from those with chronic pain or different types of cancer to patients with congestive heart failure or myocardial infarctions.[77] Several initial studies also demonstrated that MBCT can decrease recurrence of depression.[78–80] One study followed depressed patients through their acute treatment with pharmaceutical antidepressant medication and into remission and maintenance care. Once in remission, subjects were randomized into continued preventive strategies of medication, MBCT, or placebo. Patients with an unstable remission ("periodic symptom flurries") during the acute phase of improvement had a significantly and equally reduced risk for subsequent relapse when they were in the continued medication or MBCT groups. Patients who were stable during the acute phase of remission did not benefit more from the active preventive interventions.[81] Mindfulness may be a critical component in patients with depression. Interpersonal therapy and problem-solving therapy have also been successful.[73,82]

Other Mind-Body Therapies

Yoga

Yoga is a specific form of exercise that combines poses, breath work, and meditation. Several studies, including one RCT, examined the effect of 4 to 6 weeks of yoga classes lasting 45 to 60 minutes per session; the results showed a positive trend toward supporting yoga as a therapeutic treatment for patients suffering mild to moderate depression.[27,83,84] At this point, distinguishing among the different types of yoga is not possible, although initial studies using Hatha and Vinyasa yoga both appeared promising.[83,85]

Other Traditional Healing Techniques

Although well-designed clinical studies investigating the role of meditation, hypnosis, and imagery in the treatment of depression have been limited, centuries of experience in traditional healing systems (e.g., Ayurvedic, Tibetan) support this kind of therapeutic approach. In our experience, these mind-body techniques are often extremely useful therapeutic adjuncts that appear to enhance the efficacy of other treatments. Emerging data suggest that relaxation therapy appears promising.[86] Evidence has also shown the effectiveness of prayer as an adjunct to other therapy for depression.[87] We recommend that interested patients explore one of these approaches (see Chapter 92, Prescribing Relaxation Techniques).

Acupuncture

Acupuncture has been used for centuries in Asia for the treatment of virtually all known disease states. The exact mechanism of action is unknown, but human and animal studies have demonstrated that the stimulation of certain acupuncture points can alter neurotransmitter levels.[88] The United Nations World Health Organization recognized acupuncture as effective in treating mild to moderate depression. Case series indicate that acupuncture is promising for treating depression; this finding is supported by several uncontrolled and controlled studies. Some trials detected an additive benefit of combining acupuncture with medications for treating depression. Reviews of available RCTs of acupuncture for depression (including translations of relevant Chinese language studies) found general trends suggesting that acupuncture is as effective as antidepressants in the limited studies available for comparison. Placebo acupuncture tends to perform as well as true acupuncture, however, so it remains unclear whether condition-specific needling has a precise effect on depression. Because of the limitations of these studies (small sample sizes, imprecise enrollment criteria, problems with randomization and blinding, brief duration of study, and

lack of follow-up), evidence supporting acupuncture for depression remains inconclusive pending further study, and the Cochrane Reviews investigators concluded that evidence was insufficient to recommend acupuncture for depression.[89,90]

Serious adverse effects of acupuncture have been reported but are rare. One prospective survey of more than 34,000 treatments (for all conditions) by traditional acupuncturists in Britain revealed no serious adverse events over a 1-month period.[91] Another review of 12 prospective studies surveying more than a million treatments concluded that the risk of a serious adverse event with acupuncture is estimated to be 0.05 per 10,000 treatments.[92]

Phototherapy

Phototherapy is commonly used for patients with seasonal affective disorder, but it may also be useful as an adjunctive modality with pharmacotherapy in both unipolar and bipolar depression.[93] Two meta-analyses supported at least modest benefit of bright light phototherapy when compared with placebo for nonseasonal depression.[94,95] The APA guidelines for the treatment of major depressive disorder consider bright light therapy a low-risk and low-cost option.[96] Consider recommending 30 to 60 minutes of bright, white (full-spectrum, 10,000 Lux) light daily from special bulbs, lamps, or light boxes.

Pharmaceuticals

Antidepressants are believed to work by inhibiting the degradation and reuptake of neurotransmitters important in regulating psychological and neurovegetative function (i.e., serotonin, norepinephrine, dopamine) and thus increasing neurotransmitter availability at the synaptic level. Newer theories suggest that pharmaceuticals may also mediate intracellular signaling systems that affect neurotrophic factors vital to the functioning of neuronal systems involved in mood regulation. Attempts to determine the most cost-effective approach to treating depression are limited by the quality of these evaluations, but SSRIs and newer antidepressants such as venlafaxine, mirtazapine, and nefazodone consistently are superior to tricyclic antidepressants (TCAs).[97] Studies of antidepressant medications increasingly are questioned because of the potential bias owing to unblinding, given that side effects of the drugs (as opposed to inert placebos) may reveal the identity of the true medication to participants or investigators. Trials using an "active" placebo that mimics some of the side effects of antidepressants to counteract this potential bias suggest that differences between antidepressants and active placebos are small.[98]

Selective Serotonin Reuptake Inhibitors and Mixed Reuptake Blockers

The APA continues to recommend the use of an SSRI as first-line treatment for all levels of depression: mild, moderate, and severe.[74] Recommendations for secondary steps include switching or augmenting current therapy (pharmacotherapy or psychotherapy) and depend on the initial treatment choice. *Maintenance therapy* is defined as continuation of the initial treatment to prevent recurrence of depression.

Safety in overdose and side effect profiles for SSRIs and mixed reuptake blockers are greatly improved over those for cyclic antidepressants and monoamine oxidase inhibitors. Even so, 50% of patients discontinue their medication in the first 4 months after treatment initiation, and two thirds of these patients report a side effect as the reason for stopping treatment.[99] Be aware that concern is emerging over the long-term effects of SSRIs, including uncommon but serious neurologic sequelae of seizures and extrapyramidal symptoms,[100] as well as worsening of long-term outcomes despite effective short-term control.[101] The Food and Drug Administration (FDA) has mandated a black box warning on SSRIs regarding the risk of increasing suicidality in children and adolescents. This risk appears to occur within the first 2 weeks of initiating therapy, and whether this risk exists for adults is unclear.[99]

Dosage

See Table 4-1.

Precautions

Nausea, cramping, agitation, insomnia, headache, decreased libido, delayed ejaculation, erectile dysfunction, and anorgasmia have been reported in patients taking SSRIs.[99] Gastrointestinal side effects are more pronounced with sertraline but may be minimized by taking the drug with food and water. Fluoxetine is generally the most activating. Paroxetine has mild anticholinergic properties, including nausea and possibly weight gain. Venlafaxine has side effects similar to those of the other SSRIs but may cause serious hypertension over time. Although venlafaxine and paroxetine may have an increased risk of nausea, this can be reduced by using the extended-release forms.[99] Citalopram and escitalopram have the fewest side effects and the least impact on the cytochrome P-450 enzyme system. Duloxetine appears to play a role in mediating chronic pain and appears effective in older patients.[102] Rare side effects of SSRIs may include increased risk of gastrointestinal bleeding when these drugs are used with nonsteroidal antiinflammatory drugs, but more research is needed.[99] Other rare side effects include cardiac conduction abnormalities with venlafaxine and liver enzyme abnormalities with duloxetine.[99]

Tricyclic Antidepressants

TCAs have significant side effects (anticholinergic effects, weight gain, and cardiac dysrhythmias) and can be lethal in overdoses as small as an average 10-day supply.

Heterocyclic Antidepressants

Heterocyclic antidepressants are much safer than TCAs in overdose, and they have side effect profiles that make them useful in specific clinical circumstances. Several studies demonstrated that heterocyclic antidepressants are equally effective compared with SSRIs.[103] Amoxapine is useful in treating psychotic depression. Trazodone is highly sedating and is useful in low doses (25 to 50 mg nightly) when it is taken in combination with SSRIs to induce sleep. Bupropion is highly stimulating and may be a good option for patients wishing to discontinue smoking tobacco; it also has decreased fatigue and somnolence, but it is associated with seizures in underweight people. Nefazodone has anxiolytic properties and

TABLE 4-1. Drug and Supplement Dosages Used in Depression Treatment

DRUG/SUPPLEMENT	INITIAL DOSE (mg[†])	RANGE (mg/day[†])	FREQUENCY
Vitamin B complex 100	1 tablet	—	Daily
Folic acid	400 mcg	400–800 mcg	Daily
Fish oil	1,000	1000–6000	Daily
SAMe (1,4-butane-disulfonate)	200	200–800	bid
Hydroxytryptophan (enteric coated)	100	100–200	tid
St. John's wort (standardized to 5% hyperforin)*	300	900–1200	tid
Ginkgo biloba extract (standardized to 24% ginkgo flavonglycosides and 6% terpenoids)	40	60–240	tid
Selective Serotonin Reuptake Inhibitors and Mixed Reuptake Blockers			
Fluoxetine	20	20–80	Daily (AM)[‡]
Sertraline	50	50–200	Daily
Paroxetine	20	20–50	Daily (AM)
Paroxetine, extended release	12.5	25–62.5	Daily
Fluvoxamine	50	50–300	Daily (at bedtime)[§]
Citalopram	20	20–60	Daily
Escitalopram	10	10–20	Daily
Serotonin Norepinephrine Reuptake Inhibitors			
Venlafaxine, immediate release	37.5	75–375	bid
Venlafaxine, extended release	37.5	75–225	Daily (at bedtime)
Desvenlafaxine	50	50	
Duloxetine	40–60	60–120	Divided daily-bid
Dopamine Norepinephrine Reuptake Inhibitor			
Bupropion, immediate release	150	300–450	tid[‖]
Bupropion, sustained release	150	300–400	bid
Bupropion, extended release	150	300–450	Daily
Heterocyclic Antidepressants/Serotonin Modulators			
Nefazodone	200	200–600	bid
Norepinephrine Serotonin Modulator, Alpha 2 Antagonist			
Mirtazapine	15	15–45	Daily (at bedtime)

bid, twice daily; SAMe, *S*-adenosylmethionine; tid, three times daily.
*Cytochrome P-450 3A4 and drug pump P-glycoprotein induction by St. John's wort requires that care be taken when prescribing this botanical in the setting of other drugs metabolized along these pathways. Perhaps the most clinically relevant interactions occur with cyclosporine (lowering serum cyclosporine concentration) and with other antidepressants, particularly the selective serotonin reuptake inhibitors (SSRIs; serotonin syndrome), antiretroviral therapy (reducing the concentration of protease inhibitors in patients infected with human immunodeficiency virus), and warfarin-type anticoagulants (increasing anticoagulation). Concern exists that St. John's wort may interfere with the efficacy of oral contraceptives. Avoid the use of St. John's wort concurrently with SSRIs; also avoid its use in pregnancy and lactation. High doses may predispose patients to photodermatitis.
[†]Unless otherwise indicated.
[‡]Maximum range is 20 to 80 mg.
[§]Doses greater than 100 mg should be divided dose, with the greater dose given at bedtime.
[‖]Initial dose: 100 mg bid for 3 days; then 100 mg tid.

may be useful in patients who develop anxiety and insomnia while taking SSRIs. Nefazodone and bupropion also tend to have fewer sexual side effects compared with the SSRIs and serotonin norepinephrine reuptake inhibitors. Nefazodone and bupropion have the least likelihood of causing weight gain compared with SSRIs, whereas mirtazapine increases appetite and tends to cause weight gain. Mirtazapine also increases fatigue and somnolence, which may be desirable in some cases.[99]

Rare side effects that need further investigation in heterocyclic antidepressants include the following: seizures and atopic reactions with bupropion; thrombocytopenia, neutropenia, and bone marrow suppression with mirtazapine; and hepatotoxicity, cardiac conduction problems, and priapism with trazodone.

Electroconvulsive Therapy

Electroconvulsive therapy (ECT) reportedly is effective in achieving remission in 70% to 90% of patients with depression within 7 to 14 days in clinical trials (although it is less effective in community settings).[104] Generally, ECT is reserved for suicidal, psychotic, or catatonic patients; it is also helpful in patients refractory to other treatment modalities. ECT should be used with caution in patients with recent myocardial infarction, cardiac arrhythmia, or intracranial space-occupying lesions. Transient postictal confusion and anterograde and retrograde memory impairment are expected.[96]

Dosage

ECT, which requires referral to an experienced treatment center, generally involves sessions three times a week for up to 4 weeks, until symptoms abate.

Therapies to Consider for Depression

Estrogen Replacement Therapy

No abnormality of ovarian hormones has been identified that distinguishes women with depression from those without depression during the menopause transition.[105] However, estrogen replacement was demonstrated to reduce symptoms in perimenopausal and postmenopausal women with depression in some small studies, and discontinuation of hormone replacement therapy (HRT) appears to be associated with the rapid recurrence of depression in some women with a history of depression.[106] An RCT comparing HRT (estradiol valerate 2 mg, dienogest 2 mg) with placebo suggested that in women with mild to moderate depression in the setting of postmenopausal syndrome, HRT clearly and clinically relevantly reduced symptom severity by the Hamilton Rating Scale for Depression HAM-D at 24 weeks.[107] Studies assessing the relationship between hormone status and depression are inconsistent, and this remains an active area of research. Practitioners should consider recommending HRT after weighing the risks and benefits.

Transcranial Magnetic Stimulation

Transcranial magnetic stimulation uses a magnetic coil close to the scalp to generate rapidly alternating magnetic fields to produce electrical stimulation of superficial cortical neurons. It requires no general anesthesia and has minimal side effects. This technique was cleared by the FDA in 2008 for use in patients with major depressive disorder who have not responded adequately to at least one antidepressant trial. It is currently being studied as an alternative to ECT, but it has not consistently demonstrated superiority to ECT or sham.[108]

Aromatherapy

Aromatherapy, which is the use of essential oils most often topically combined with MT or as inhaled vapors, has roots in ancient healing traditions. Several small studies demonstrated the impact of aroma on mood. One small open pilot trial found that adjunctive aromatherapy allowed for reductions in dose of antidepressants compared with usual therapy. This nonrandomized trial included patients using various types and doses of antidepressants.[109] Short-term but not persistent benefits were found for aromatherapy MT with citrus oil in patients with cancer who were dealing with depression.[110] Aromatherapy may be promising as a gentle adjunctive therapy, but larger, well-designed trials are necessary before conclusions can be drawn.

Music Therapy

In music therapy, patients actively perform or listen to music to promote health and healing. This is an active area of research, but most trials are small and lack appropriate control for attention of professionals. In addition, concurrent interventions that are not music specific (e.g., guided imagery and relaxation) make conclusions difficult to draw. Numerous trials of music therapy, largely in an older population, suggested potential antidepressant benefits when this modality was added to usual care, and a dose effect appeared to occur with increased response as treatment continued.[111] However, a Cochrane Review identified only five trials meeting inclusion criteria and concluded that although music therapy is well tolerated by people with depression and appears to be associated with improvements in mood, the small number and low quality of studies preclude clear determination of effectiveness until better studies are conducted.[112] The risks of music therapy are low, and although proof of benefits will require more thorough study, interested patients so inclined should not be discouraged.

Massage

Several studies reported the benefits of MT for improving mood in healthy and ill individuals, but MT has not been studied extensively for the treatment of depression. Small randomized trials have suggested that the addition of MT to psychotherapy in pregnant women with depression may be more helpful than psychotherapy alone[113] and that MT by the woman's partner is superior to standard treatment.[114] However, the most recent systematic review continues to point to a lack of evidence for MT in the treatment of depression.[115] When performed by a qualified therapist, MT can be a safe and pleasant experience and may be considered appropriate adjunctive therapy for depressed individuals who are so inclined.

Prevention Prescription

The following steps are recommended for prevention of depressive symptoms:

- Remove exacerbating factors.
- Review current medications and supplements that could be contributing to depression, and consider decreasing dosages or discontinuing drugs that are suspect if they are not vital to the patient's well-being.
- Recommend a whole foods/low–processed foods diet such as the Mediterranean or antiinflammatory style eating plan, low in refined sugar (sucrose), caffeine, and alcohol. Encourage a diet rich in omega-3 fatty acids. Recommend two or three servings of cold-water fish (salmon, herring, mackerel, sardines) each week and 2 tablespoons of ground flaxseed or flaxseed oil daily.
- Consider recommending vitamin D_3 1000 units daily.
- Consider recommending a B-complex vitamin daily.
- Prescribe physical activity. Encourage daily aerobic (e.g., walking, jogging, cycling) or anaerobic (weight-lifting) exercise. Explore options, and help patients select activities they feel are enjoyable. Emphasize starting slowly and setting realistic short-term goals. Gradually increase to an ideal exercise prescription (see Chapter 88, Writing an Exercise Prescription).
- Foster an increase in a sense of community and investment in meaningful relationships to reduce social isolation.

Therapeutic Review

Lifestyle

- Suggest regular practice of aerobic or anaerobic exercises most days of the week. B1
- Encourage activities that will increase social connection and enhance meaningful relationships. B1

Nutrition

- Eliminate caffeine and simple sugars from the diet. B1
- Consume a Mediterranean-style or whole foods (low–processed foods) diet. B1

Dietary Supplements and Botanicals

- Vitamins: Augment conventional antidepressant medication with vitamin B complex and 400 mcg to 1 mg of additional folic acid daily. B2
- St. John's wort: Take 900 mg daily in three equal doses. Choose a product standardized to a minimum of 2% to 5% hyperforin or 0.3% hypericin. Examples include Kira, Quanterra Emotional Balance, Remotiv, or Movana. If no improvement is seen after 4 to 6 weeks, consider switching to SAMe or a pharmaceutical antidepressant. Concurrent psychotherapy is recommended, if this approach is acceptable to the patient. A2
- *S*-Adenosylmethionine (SAMe): Start at 200 mg once or twice daily to minimize gastrointestinal side effects; then titrate upward to effect over 1 to 2 weeks. Initial treatment of depression may require 1600 mg daily given in two equal doses, followed by a maintenance dose of 200 mg twice daily. B2
  - If recommending a pharmaceutical antidepressant, consider using SAMe initially (because of its rapid onset of action) along with it to minimize the latency period. SAMe may be withdrawn after 4 to 6 weeks.
  - If SAMe is given without a pharmaceutical antidepressant, consider switching to another agent if no resolution of symptoms is noted after 2 weeks. Choose a product containing 1,4-butane-disulfonate (Actimet), which is stable for up to 2 years at room temperature. Concurrent psychotherapy is recommended, if this approach is acceptable to the patient.
- Fish oil: Take 1 g daily. If this dose is not effective, consider titrating up to 6 g of omega-3 fatty acids. In the case of an intake higher than 3 g per day, caution must be used because antiplatelet effects are more likely. Choose a product that has been tested for pesticides and heavy metal residues and keep refrigerated. B2

Psychotherapy

The combination of supportive psychotherapy with antidepressant supplements or pharmacotherapy is generally recommended. Primary care physicians can provide limited psychotherapy at frequent visits to monitor lifestyle modifications, dietary supplements, or drug therapy. Alternatively, referral for cognitive or interpersonal therapy is recommended. A1

Pharmaceuticals

If no improvement is obtained with the use of lifestyle modification measures and dietary supplements (or if the patient has severe depression), discontinue the supplements, and start a pharmaceutical antidepressant. All currently approved antidepressant drugs are equally effective and have similar latency periods.[47] Choice of a selective serotonin reuptake inhibitor, mixed reuptake blocker, or heterocyclic antidepressant should be guided by matching the most appropriate side effect profile to each patient's symptoms. Continue treatment for

at least 6 months after improvement, and consider full-dosage maintenance if the patient has a history of recurrent depression ([moderate to severe depression] or [mild depression]). If only a partial response has occurred at 6 weeks, either change the class of antidepressant medication or continue the antidepressant and consider adding lithium carbonate, 300 mg three times a day (necessitates experience in monitoring serum levels), or liothyronine sodium (Cytomel), 25 to 50 mcg.

Phototherapy

Suggest phototherapy with 30 to 60 minutes of bright, white (full-spectrum, 10,000 Lux) light daily from special bulbs, lamps, or light boxes.*

Referral

Consider referral to a psychiatrist if the patient remains refractory to treatment, is suicidal or psychotic, or requires psychiatric hospitalization or electroconvulsive therapy or transcranial magnetic stimulation.

*Information and therapeutic lights are widely available, including from the following manufacturers: BioBrite, Inc., 1-800-621-LITE (1-800-621-5483), www.biobrite.com; and SunBox Company, 1-800-548-3968, www.sunboxco.com

KEY WEB RESOURCES

American Psychiatric Association. http://www.psychiatryonline.com/pracGuide/pracGuideTopic_7.aspx	American Psychiatric Association Guidelines for Treatment of Major Depression
http://www.depression-primarycare.org/clinicians/toolkits/materials/forms/phq9/	The PHQ-9 questionnaire, a useful tool to diagnose and monitor depression treatment.
http://www.consumerlab.com	Independent testing of dietary supplements
http://naturaldatabase.therapeuticresearch.com	Evidence-based resources on dietary supplements

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Chapter 5

Anxiety

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Anxiety disorders are one of the most commonly encountered medical conditions in primary care. According to the National Institute of Mental Health, the 1-year prevalence rate is 18.1% of the population, or 40 million people. Underdiagnosis is common; the average patient with an anxiety disorder consults 10 health care professionals before a definitive diagnosis is made.[1] Furthermore, patients who carry the diagnosis use primary care services three times as often as other patients.[2] In the past, when underdiagnosis was more common, patients received elaborate medical workups, but the definitive diagnosis remained elusive. These patients became categorized as the "worried well." Nevertheless, because anxiety can be masked in numerous psychosomatic ways, practitioners must maintain a high index of suspicion for this disorder.

Anxiety disorders encompass a wide variety of subtypes, the most common being generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), panic disorder, phobias, and posttraumatic stress disorder (PTSD). All are marked by irrational, involuntary thoughts. One of the most defining diagnostic elements of anxiety disorders is the disruption of daily life by overt distress. Frequently, patients have a significant reduction in the ability to carry out routine tasks, whether social, personal, or professional.[3] In this chapter, the focus is on an integrative approach to the management of GAD, as defined in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV). In primary care practice, the prevalence of GAD can be as high as 10% to 15%.[2]

Definition and Diagnostic Criteria

GAD involves unremitting, excessive worry involving a variety of issues. These concerns may be related to family, health, money, or work. Once the initial concern subsides, another quickly takes its place. The practitioner observes over time that the concerns seem pervasive and repetitive. Additionally, the distress seems out of proportion to the actual life circumstance.

To meet the DSM-IV criteria for GAD, intense worrying must occur on a majority of days during a period of at least 6 continuous months.[3] In addition, three of the following signs and symptoms must be present: easy fatigability, difficulty concentrating, irritability, muscle tension, restlessness, and sleep disturbance. Patients usually present with physical complaints and fail to recognize the stress-related origin. The most frequent signs and symptoms are diaphoresis, headache, and trembling.[4] GAD can have psychological manifestations as well. Patients often report impaired memory or a diminished ability to concentrate or take directions, and they frequently make statements such as "I can't seem to stop thinking of. . . ."

Comorbid Conditions

Approximately 40% of people with GAD have no comorbid conditions, but many develop another disorder as time evolves.[5] In fact, concurrent or coexistent organic or psychiatric disease is the rule rather than the exception in patients with GAD.[5] For example, panic disorder is common among persons who have irritable bowel syndrome; a shared brain-gut mechanism incorporating a serotonin link has been theorized.[6] Psychiatric overlap is common. Anxiety disorders and depression frequently coincide—either can trigger the other. In the case of coexisting depression, especially of significant severity, treatment of the depression is the primary objective. Subsequent visits will reveal whether the anxiety is relieved simply by addressing depression. Many persons coping with anxiety use alcohol or drugs to mask their distress. Approximately 30% of people with panic disorder abuse alcohol, and use of drugs occurs in 17%.[1]

Pathophysiology

The pathophysiology of GAD is multifactorial and remains incompletely understood. Studies in animals and humans have attempted to pinpoint body structure and systems involved

in the pathogenesis of anxiety. One that has been identified is the amygdala, a small structure deep inside the brain that communicates with the autonomic nervous system to relay perceived danger to other centers of the brain, which, in turn, ready the body for the perceived danger. Furthermore, the memory of these dangers stored in the amygdala appears to be indelible, thus creating a pathophysiologic phenomenon that may progress to GAD.

Although the pathophysiology of generalized anxiety disorder is multifactorial, the amygdala in the brain appears to be a focus for stressful memories that stimulate the autonomic nervous system when the body and mind perceive danger.

Other contributing factors may lie in the realm of cognitive phenomena. Research is currently under way to evaluate exposure to stress early in life and subsequent development of GAD.[7]

In PTSD, a subtype of anxiety, studies have identified low cortisol levels (and high levels of corticotropin-releasing factor) and an overabundance of norepinephrine and epinephrine as contributing factors.[8]

Finally, genetic factors are thought to be another influence. Studies indicate genetic concordance with certain genetic loci that produce functional serotonin polymorphisms.[9]

Ruling Out Organic Disease

The symptoms of anxiety disorders can resemble those of a variety of medical conditions, and a full medical workup is in order if the possibility of disease exists (Table 5-1).

TABLE 5-1. Medical Conditions Often Associated With Symptoms of Anxiety

SYSTEM	SPECIFIC DISORDER
Cardiovascular	Acute myocardial infarction Angina pectoris Arrhythmias Congestive heart failure Hypertension Ischemic heart disease Mitral valve prolapse
Endocrine	Carcinoid syndrome Cushing's disease Hyperthyroidism Hypothyroidism Hypoglycemia Parathyroid disease Pheochromocytoma Porphyria Electrolyte imbalance
Gastrointestinal	Irritable bowel syndrome
Gynecologic	Menopause Premenstrual syndrome
Hematologic	Anemia Chronic immune diseases
Neurologic	Brain tumor Delirium Encephalopathy Epilepsy Parkinson disease Seizure disorder Vertigo Transient ischemic attack
Respiratory	Asthma Chronic obstructive pulmonary disease Pulmonary embolism Dyspnea Pulmonary edema

Integrative Therapy

Exercise

Numerous studies assessing the effects of both short-term and long-term exercise on anxiety exist. The bulk of these studies measured the effects of exercise by the presence of signs and symptoms of elevated anxiety, rather than by using a diagnostic system such as that of the DSM.[10] Nonetheless, the results of most studies generally showed a reduction in symptoms with increased physical activity.

Aerobic exercise programs seem to have produced a larger effect than obtained with weight training and flexibility regimens, although all appear effective for improvement in mood.[10,11] The length of physical activity also seems important. In one study, programs exceeding 12 minutes for a minimum of 10 weeks were needed to achieve significant anxiety reduction.[12] The beneficial effect appeared to be maximal at 40 minutes per session.[10] Furthermore, the benefits seem to be lasting. In one study assessing the long-term effects of aerobic exercise, participants evaluated at 1-year follow-up examination were found to maintain the psychological benefits initially recorded. Their exercise routines over the 12-month follow-up were either the same as those in the original study design or less intensive.[13]

The exact reason for the improvement of mood with exercise is not completely known. However, increased physical activity has been correlated with changes in brain levels of monoamines—norepinephrine, dopamine, and serotonin—that may account for improved mood.[14] The endorphin hypothesis is another explanation for the beneficial effects of exercise on mood. Many studies have demonstrated significant endorphin secretion with increased exercise, with beneficial effects on state of mind. However, blockade of endorphin elevation with antagonists such as naloxone during exercise does not correlate with decreased mental health benefits.[14] Some investigators have argued that the latter finding reflects flaws in methodologic design.

Both the length of the exercise session and the duration of the physical activity program seem important in maximizing the beneficial effect of exercise on anxiety reduction.

No matter what the hypothesis, the involvement of each patient in active recovery may confer a sense of independence leading to increased self-confidence. In turn, the patient's ability to cope with challenging life events is increased. This process is consistent with the integrative philosophy of healing. Furthermore, paucity of side effects, low cost, and general availability all make exercise a crucial component of integrative management.

The level of exertion and the specific exercise prescription should be determined by the patient's level of fitness, interests in specific physical activities, and health concerns (see Chapter 88, Writing an Exercise Prescription).

Nutrition

Caffeine

On average, U.S. residents consume 1 or 2 cups of coffee a day, which represents approximately 150 to 300 mg of caffeine. Although most people can handle this amount with no effect on mood, some experience increased anxiety. People who are prone to feeling stress have reported that they experience increased anxiety from even these small amounts. With long-term use, caffeine has been linked with anxiety as well as depression. Discontinuation is warranted.[15]

Alcohol

With long-term use, alcohol has been found to diminish levels of serotonin and catecholamine. Discontinuation of alcohol consumption is therefore warranted.[16]

Omega-3 Fatty Acids

Epidemiologic data suggest that an omega-3 fatty acid deficiency or imbalance between the ratio of omega-6 and omega-3 fatty acids in the diet correlates with increased anxiety and depression. Investigators clearly documented in animal studies that levels of polyunsaturated fats and cholesterol metabolism influence neuronal tissue synthesis, membrane fluidity, and serotonin metabolism.[17] Primarily indirect evidence, particularly in depression, suggests that correction of the ratio of omega-6 to omega-3 consumption may improve mood. Given the evidence concerning neuronal tissue synthesis and serotonin metabolism, increased supplementation with omega-3 fatty acids seems beneficial.[18] Recommending consumption of cold water fish (sardines, mackerel, tuna, salmon, herring) at least two or three times a week or flaxseed oil (1000 to 2000 mg) or freshly ground flaxseed (2 tablespoons daily) or as a supplement seems reasonable (see Chapter 86, The Antiinflammatory Diet).

Supplements

B Vitamins

A deficiency of a variety of nutrients can alter brain function and therefore lead to anxiety. Deficiency of certain vitamins, including the B vitamins, has been linked with mood disorders. The B vitamins, including B_6 (pyridoxine) and B_{12}, are linked with the synthesis of *S*-adenosylmethionine (SAMe), which carries and donates methyl molecules to many chemicals in the brain including neurotransmitters. Vitamin B_6 is essential for the production of serotonin and has been linked with improvement in various mood disorders including anxiety when it is used as a supplement.[19] Although large-scale clinical studies are lacking, a trial of a B-complex supplement seems advisable, especially in older persons and in persons taking medications that may deplete this vitamin (e.g., oral contraceptives or replacement estrogen [Premarin].[20])

Dosage

The dose is a B-complex vitamin.

Folic Acid

Studies have shown that folic acid supplementation is helpful in persons who are depressed (see the section on folic acid use in Chapter 4, Depression). Patients with low levels of folic acid also have been reported to respond less well to selective serotonin reuptake inhibitors (SSRIs).[21] Serum vitamin B_{12} levels should be checked if folic acid supplementation is used, especially if megaloblastic anemia is noted in laboratory tests, because vitamin B_{12} deficiency can be masked by folic acid supplementation.

Dosage

The recommended dose of folic acid for supplementation is 400 to 800 mcg per day.

Precautions

High doses of folic acid have been reported to cause altered sleep patterns, exacerbation of seizure frequency, gastrointestinal disturbances, and a bitter taste in the mouth.

5-Hydroxytryptophan

5-Hydroxytryptophan (5-HTP) is an amino acid precursor used in the formation of serotonin. 5-HTP has been used as an oral supplement alternative to boost serotonin.[22] It has been shown in studies to improve depression, but only preliminary evidence is available suggesting that 5-HTP also may improve anxiety. L-Tryptophan, another amino acid found to improve mood, is converted to 5-HTP and then to serotonin. 5-HTP readily crosses the blood-brain barrier. The metabolism of 5-HTP by monoamine oxidase and aldehyde dehydrogenase forms 5-indoleacetic acid, which is excreted in the urine.

Dosage

For anxiety or depression, the dose is 150 to 300 mg daily.

Precautions

Anyone using conventional medications for depression or anxiety, particularly those agents that boost serotonin, should discuss the use of 5-HTP with his or her health care practitioner before initiating supplementation, to avoid excessively elevated levels of serotonin. 5-HTP can cause gastrointestinal side effects such as nausea, belching, and heartburn.

Caution

Some concern exists that 5-HTP, like L-tryptophan, can cause a condition known as eosinophilia myalgia syndrome. The suspected culprit is a group of contaminants identified from the peak X family. However, current evidence is insufficient to suggest that this element is consistently responsible. Case reports have been sporadic.[23]

Pharmaceuticals

Conventional options for initial therapy in GAD are based on various factors and drug side effect profiles. Depression frequently coexists with GAD, so antidepressants are often considered.

None of the SSRIs has a formal indication for the treatment of GAD, although some agents have been approved for panic disorder, social phobia, and PTSD. Because less cardiotoxicity is associated with SSRIs than with tricyclic antidepressants, an SSRI may be a better choice for patients with heart disease. Other conventional options for treatment of GAD involve the use of multiple receptor agents. Venlafaxine (Effexor) is the only serotonin norepinephrine reuptake inhibitor approved for GAD. The use of tricyclic antidepressants has always been a consideration, but the difficulty in using these medications is that they can have anticholinergic and cardiovascular side effects, as well as a more pronounced sedative effect. Most experts recommend a trial of at least 4 to 6 weeks to determine efficacy.

For short-term treatment of GAD, the use of anxiolytics, especially benzodiazepines, has always been a consideration. However, the risk of abuse and habituation has made most primary care practitioners cautious about prescribing these medications. The nonbenzodiazepine anxiolytic buspirone (BuSpar) may be a conventional alternative lacking the problematic issue of drug dependence and excessive sedation.

Dosage

See Table 5-2.

Botanicals

Kava (Piper methysticum)

In the realm of botanical pharmaceuticals, kava has become known as a botanical option for the treatment of GAD in the United States and Europe. It is derived from the pulverized lateral roots of a subspecies of a pepper plant, *Piper methysticum*, and is indigenous to many Pacific Island cultures. In Europe, kava is recognized by health authorities as a relatively safe remedy for anxiety.[24] Seven small clinical trials evaluated the efficacy of kava in GAD.[25] In all trials, kava was found to be superior to placebo in the symptomatic treatment of GAD.

The constituents considered to be most pharmacologically active are the kava lactones, which have a chemical structure similar to that of myristicin, found in nutmeg.[26] These lactone structures are present in the highest concentration in the lateral roots and are lipophilic. Of the 15 isolated kava lactone structures, 6 are concentrated maximally in the root and vary depending on the variety of *Piper methysticum*.[27] The mechanism of action of kava in GAD has not been completely elucidated, although the action seems similar to that of benzodiazepines. Results of studies in rats and cats are conflicting, however.

Benzodiazepines exert their actions by binding to the gamma-aminobutyric acid (GABA) site and benzodiazepine receptors in the brain; animal studies analyzing kava's anxiolytic action, however, show mixed and minor effects at both sites. Other studies indicate that kava constituents produce anxiolytic effects by altering the limbic system, especially at the amygdala and hippocampus.[28] Other documented uses of kava have been as a muscle relaxant, an anticonvulsant, an anesthetic, and an antiinflammatory agent.

Indication

Mild to moderate GAD.

TABLE 5-2. Supplement and Drug Recommendations for Treatment of Anxiety

DRUG/SUPPLEMENT	INITIAL DOSE (RANGE)	FREQUENCY
Vitamin B complex 100	1 tablet	Daily
Folic acid	400–800 mcg	Daily
Kava	50–70 mg (of kava lactones)	tid
Valerian root	150–300 mg every AM and 300–600 mg at bedtime	
5-Hydroxytryptophan	150–300 mg	Daily
Selective Serotonin Reuptake Inhibitors and Mixed Reuptake Blockers		
Fluoxetine (Prozac)	10–20 mg (10–80)	Daily
Fluvoxamine (Luvox)	50 mg (50–300)	Daily
Paroxetine (Paxil)	10 mg (10–60)	Daily
Sertraline (Zoloft)	50 mg (50–200)	Daily
Escitalopram (Lexapro)	10 mg (10–20 mg)	Daily
Citalopram (Celexa)	20 mg (20–40 mg)	Daily
Others		
Venlafaxine (Effexor)	75 mg (37.5–75 mg)	bid
Nefazodone (Serzone)	200 mg (100–300 mg)	bid
Bupropion (Wellbutrin)	100 mg (50–125 mg)	bid
Azapirones		
Buspirone (BuSpar)	5 mg (15–30 mg)	bid

bid, twice daily; tid, three times daily.

Dosage
Kava is taken for anxiety at a dose of 50 to 70 mg (of the purified extract, kava lactones) three times daily or kava dried root 2 to 4 g boiled as a decoction three times daily.

Precautions
Anecdotal reports have noted excessive sedation when kava is combined with other sedative medications.[29] Extrapyramidal side effects were reported in four patients using two different preparations of kava. Kava thus should be avoided in patients with Parkinson syndrome.[30] The effects diminished once the extract was discontinued. In patients taking high doses from heavy kava consumption, a yellow, ichthyosiform condition of the skin known as kava dermopathy has been observed. This condition is reversible with discontinuation of the kava.[31] The overdose potential appears to be low. In many cases, the rash, ataxia, redness of the eyes, visual accommodation difficulties, and yellowing of the skin reported in the literature from Australia and the Pacific region emerged after ingestion of up to 13 liters per day, equivalent to 300 to 400 g of dried root per week. This amount represents a dose 100 times that of the recommended therapeutic dose.[32]

Caution
Data are insufficient to determine teratogenicity; for this reason, it is wise to avoid use of kava during pregnancy. Kava is present in the milk of lactating mothers; therefore, use is discouraged during breast-feeding.[33] The use of kava should be avoided with other sedative medications.

Kava has been reported to cause idiopathic hepatotoxic hepatitis. To date, all case reports (a total of 31) have been in patients from Europe who used concentrated extracts manufactured in Germany or Switzerland. The exact cause of the effects is under investigation. Kava should not be used in individuals who have liver problems, nor should it be used concomitantly in patients who are taking multiple medications that are metabolized in the liver or in individuals who drink alcohol on a daily basis.[34] Liver tests should be routinely performed in individuals who use kava on a daily basis, and patients should be counseled on the signs and symptoms of hepatotoxicity (jaundice, malaise, and nausea). Furthermore, kava should be discontinued from daily use after approximately 4 months.

Valerian (Valeriana officinalis)
Valerian is another botanical alternative for the treatment of GAD. The clinical efficacy of valerian has been evaluated mostly for treating sleep disturbances; fewer clinical studies assessing its use in anxiety are available. Nevertheless, valerian has been used in Europe for more than a thousand years as a tranquilizer and calmative.[35] The use of valerian in combination with either passionflower *(Passiflora incarnata)* or St. John's wort *(Hypericum perforatum)* for anxiety has been studied in small clinical trials. One study evaluated valerian root in combination with passionflower (100 mg of valerian root with 6.5 mg of passionflower extract) compared with chlorpromazine hydrochloride (Thorazine) (40 mg daily) over a period of 16 weeks. In this study, 20 patients were randomly assigned to the two treatment groups after being identified as suffering from irritation, unrest, depression, and insomnia. Electroencephalographic changes in both groups consistent with relaxation were comparable; two psychological scales measuring these qualities demonstrated scores consistent with reduction in anxiety.[36] Another study evaluated anxiety in 100 anxious persons receiving either a combination of 50 mg of valerian root plus 90 to 100 mg of standardized St. John's wort for 14 days or 2 mg of diazepam (Valium) twice daily in the first week and up to 2 capsules twice daily in the second week. The results showed reduction of anxiety in the phytomedicine treatment group to levels in healthy persons. Patients in the diazepam treatment group still had significant anxiety scores.[37]

Indication
Mild to moderate anxiety.

Dosage
For adults with anxiety, a dose of 150 to 300 mg in the morning and another dose of 300 to 600 mg in the evening, using a standardized product containing 0.1% valerenic acid, can be taken. Combinations with lemon balm and hops *(Humulus lupulus)* may be considered. These additions are based on herbal tradition and empirical medicine; no clinical trials demonstrating efficacy are available.[38,39]

> Contrary to common belief, valerian is not suitable for acute treatment of anxiety or insomnia. A beneficial effect may take several weeks.

Precautions
Valerian root is not suitable for the treatment of acute insomnia or nervousness because it takes several weeks before a beneficial effect is obtained. An alternative that gives a more rapid response should be taken when valerian root is initiated.[13] Products with Indian and Mexican valerian should be avoided owing to the mutagenic risk associated with their high concentrations of valpotriates and baldrinals (up to 8%).[38] Adverse effects are rare with products that do not contain valpotriates. Occasional reports have noted headache and gastrointestinal complaints.

Mind-Body Therapy

Psychotherapy
Psychotherapy has been shown to be effective as a therapeutic option in the treatment of GAD with or without medical intervention. Two clinically proven forms are used frequently: behavioral therapy and cognitive-behavioral therapy. Behavioral therapy focuses on changing the specific unwanted actions by using several techniques to stop the undesired behavior. In addition, both behavioral therapy and cognitive-behavioral therapy help patients to understand and change their thinking patterns so that they can react differently to their anxiety.

Relaxation Techniques
Relaxation training, stress reduction techniques, and breath work are of proven benefit. In fact, imaginal exposure is used as a tactic for repeated exposure to induce anxiety (in a gradual way). Patients learn through repeated exposure to cope with and manage their anxiety, rather than to eliminate it. Relaxation training paired with this interceptive therapy is useful. I often encounter patients who admit to their anxiety and are willing to confront and learn to cope with it but lack

the ability to relax completely. Depending on their preferences, I help them choose a relaxation technique that reinforces a sense of calm. Therapies that can be used for this purpose are massage, sound therapy, aromatherapy, guided interactive imagery, and hypnosis. Because many patients have somatic sensations that accompany their anxiety, a complementary therapy that imparts a "remembrance" of a deeply relaxed state (see Chapter 93, Relaxation Techniques) should also be reinforced on a more somatic-kinesthetic level.

Therapies to Consider

Traditional medical systems such as acupuncture and Ayurvedic medicine can provide other options for the treatment of anxiety.[41,42] Several small trials assessing relaxation in an anxiety state showed reduction of anxiety in a psychologically normal patient population through the use of auricular acupuncture.[41–43] Although the mechanisms are not well elucidated, these systems may somehow interface favorably to balance the autonomic nervous system.

Prevention Prescription

- Maximize nutrition to include foods rich in omega 3-fatty acids, B vitamins, and folic acid.
- Follow a regular exercise routine (even walking and tracking use with a pedometer).
- Institute a daily mind-body exercise program to enhance the relaxation response.
- Keep a journal; take a "feeling inventory," and enhance self-awareness.
- Limit your use of personal digital assistants, cellphones, and BlackBerry devices. Do not access these devices during meals and special times with family and friends. Turn to "off" at 10 AM and "on" at 6 to 7 AM, and do not recharge these devices right next to your bed!
- Get enough sleep to feel refreshed.

Therapeutic Review

The following four steps are recommended for initial management of patients with generalized anxiety disorder (GAD).

1. Remove exacerbating factors. Review current medications and supplements that could contribute to anxiety (especially botanical supplements such as ephedra and over-the-counter preparations that are stimulants). Supplements that are unnecessary should be discontinued.
2. Screen for diseases that mimic anxiety. Screening should be performed for underlying medical conditions that produce anxiety, for instance, hyperthyroidism or a withdrawal syndrome.
3. Improve nutrition. Nutritional support such as with omega-3 fatty acid supplementation (two to three servings of cold water fish per week, or flaxseed oil 2 tablespoons a day or 1000 mg of flaxseed oil in a capsule) is recommended. In addition, caffeine and alcohol consumption should be avoided. A1
4. Institute physical activity. Physical activity (aerobic or anaerobic) at least 5 days out of 7 should be encouraged. To ensure long-term compliance, an activity that is enjoyable to the patient is important. Furthermore, adherence to a regular exercise regimen and setting realistic short-term goals may need emphasis. Increases in exercise level and intensity should be gradual (see Chapter 88, Writing an Exercise Prescription). A1

Supplements

- Vitamin B_6 included in a vitamin B 100 complex preparation with the addition of folic acid (400 mcg daily) should be considered. B1
- Vitamin B_6 A2
- Folic acid B2
- 5-Hydroxytryptophan (150 to 300 mg daily) could be considered as a serotonin boosting alternative, but close monitoring should be undertaken to screen for eosinophilia myalgia syndrome. C3

Botanicals

- Kava, 50 to 70 mg three times a day (of the purified kava lactones), can be given. Choose a standardized product with either a 30% or a 50% to 55% kava lactone concentration.
- If no improvement is observed over 4 to 6 weeks, consider valerian or a valerian combination or a pharmaceutical anxiolytic (use for at least 6 weeks before evaluating efficacy). B2
- Concurrent psychotherapy is highly recommended if this approach is acceptable to the patient.

Mind-Body Therapy

- Psychotherapy: The combination of psychotherapy in conjunction with supplements, botanicals, or a pharmaceutical anxiolytic or antidepressant is highly recommended, especially in GAD. An integrative therapeutic approach is associated with higher success rates in cases of severe anxiety. Often, psychotherapy can provide the patient with skills for coping with anxiety, as opposed to extinguishing the symptoms. Primary care physicians can monitor lifestyle modification, dietary and supplement interventions, and drug therapy. However, referral to a psychotherapist is advised. A1
- Relaxation training: Educate the patient in relaxation techniques that will empower him or her to bring anxiety symptoms under control when needed.

Continued

Traditional Medical Systems

- Use of traditional medicine systems (TMSs) is problematic in that TMSs have historically been used to provide primary care for a variety of medical ailments (including anxiety). As an allopathic physician, I generally designate the use of TMSs as an adjunctive modality. However, for those patients who have strong feelings about the use of singular botanical preparations (mostly as being insufficient for treatment) or whose medical conditions appear mild, I am more than willing to be a medical partner and consider the use of a TMS (e.g., Chinese medicine or Ayurvedic medicine) as a primary therapeutic option, as long as the well-being of the patient is not in jeopardy.

Pharmaceuticals

- If no improvement is obtained with lifestyle measures, dietary measures, and supplement interventions in conjunction with botanical supplements, use of a pharmaceutical anxiolytic or antidepressant should be considered. Depending on the severity of the anxiety and the degree of lifestyle impairment, I often use a conventional prescriptive option with dietary and lifestyle interventions in combination with complementary therapy (e.g., acupuncture, mind-body therapy) to induce a sense of relaxation before the patient is weaned off the prescriptive treatment (often a couple of months later). Depending on the severity of the disorder, I may introduce a botanical supplement (e.g., kava).
- Obviously, different clinical responses will be obtained with the various anxiolytics (and selective serotonin reuptake inhibitors). Optimal management may require a change of medication, depending on the patient's symptoms. For long-term therapy, I refrain from the use of benzodiazepines because tolerance can be problematic.
- Consider referral to a psychiatrist if the patient remains refractory to treatment, is suicidal or psychotic, or requires psychiatric stabilization in a hospital unit.

KEY WEB RESOURCES

Benson-Henry Institute for Mind Body Medicine. http://www.massgeneral.org/bhi/.	The Institute was founded in 1988 as a nonprofit scientific and educational organization building on the work of Herbert Benson at Harvard Medical School on the relaxation response. The Web site covers research, education, training programs, clinical programs, books, videotapes, audiotapes, and more.
Mind and Life Institute. www.MindandLife.com.	The Institute is dedicated to creating dialogue and collaboration in research at the highest possible level between modern science and the great living contemplative traditions, especially Buddhism. The Web site describes conferences and events, research initiatives, publications, and the work of the Dalai Lama.
Mindfulness-Based Stress Reduction (MBSR). www.umassmed.edu/cfm.	The Center for Mindfulness at the University of Massachusetts sponsors the MBSR program. The Web site covers clinical care, education, research, training, a bibliography, and more.
Continuum Center for Health and Healing: Preparing for Surgery/Learning Mind/Body Techniques. http://www.preparingforyoursurgery.org/.	This free online course teaches stress management techniques that are easy to learn and simple to practice. These techniques can help manage fear, worry, and anxiety and can help promote faster healing with less pain or discomfort. These same relaxation practices can be used whenever one feels stress building up in daily life.
Shambhala. www.shambhala.org/.	This worldwide network of meditation centers was founded by Chogyam Trungpa Rinpoche, a Tibetan Buddhist master of the Shambhala and Buddhist teachings. The Web site is a guide to Shambhala centers internationally and their activities, books and recordings, and essays on mindfulness meditation.
Transcendental Meditation (TM) Program. www.tm.org/.	The official U.S. Web site of the TM program, the Web site covers a description of the program, the scientific research on TM, news articles and books, places to study, and an explanation of the uses of TM to enhance function and treat a variety of conditions.
Wildmind Buddhist Meditation. www.wildmind.org/.	This Web site provides a wealth of information on Buddhist practices, including guided meditations in RealAudio format and online meditation courses led by an experienced instructor.

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Chapter 6

Attention Deficit Hyperactivity Disorder

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Pathophysiology, Definitions, and Epidemiology

In the 1930s, hyperactivity, impulsivity, learning disability, and distractibility in childhood were described as "minimal brain damage" or "minimal brain dysfunction." This label was modified in the 1950s to "hyperactive child syndrome" and in 1968 to "hyperkinetic reaction of childhood." More recently, investigators have recognized that for nearly 66% of patients, the core symptoms of impulsivity and distractibility characteristic of attention deficit hyperactivity disorder (ADHD) persist into adulthood.

One of the most commonly diagnosed and costly mental health problems in the United States, ADHD is diagnosed in 3% to 10% (depending on age and gender) of school-age children. It is diagnosed more commonly in boys than girls (3:1 ratio); the peak age of diagnosis is between 8 and 10 years old. The drugs used to treat ADHD, such as methylphenidate (Concerta), atomoxetine (Strattera), and a combination of amphetamine and dextroamphetamine (Adderall), are three of the top five (ranked by spending) for children younger than 18 years in the United States. The prevalence of ADHD in adults is estimated at 2.5%. Unlike an acute bacterial infection, ADHD is a chronic condition requiring ongoing management.

The classic image is that of an energetic boy who talks a lot, interrupts others, acts as if driven by a motor, fidgets and squirms, has a messy room, acts impulsively, has trouble following rules, and often breaks or loses things; he is often admonished to sit still, pay attention, and clean up his room. The quiet girl who daydreams and is inattentive in class has a second classic type of ADHD (ADHD without hyperactivity). The diagnosis is based on consistent perceptions of a particular pattern of behavior:

- Early onset (by age 7 years)
- Persistence (at least 6 months)
- Pervasive (present in at least two settings) pattern of distractibility and impulsivity (at least 6 symptoms of each), with or without hyperactivity, that
  - Disrupts age-appropriate academic, social, or occupational functioning

Knowledge of normal child development is essential to making the diagnosis because normal behavior for a 2 year old includes impulsivity and a short attention span that would be abnormal in an 8 year old.

Most clinicians use behavioral checklists such as the Vanderbilt Parent and Teacher Rating Scales to make the diagnosis and monitor progress. No laboratory or imaging study exists to confirm the diagnosis, although clinicians often use laboratory or neuropsychological tests to rule out contributory problems such as hearing or vision problems, anemia, hypothyroidism, absence seizures, reading or math learning disabilities, and short-term memory impairment.

Common comorbidities include oppositional defiant disorder and conduct disorders (30% to 50%), mood or anxiety disorders (15% to 30%), learning disabilities (20% to 25%), sleep problems, and tic disorders such as Tourette syndrome.[1,2] Strengths often include creativity, imagination, sociability, and flexible attention, interest in the environment, energy, vitality, enthusiasm, adaptability, confidence, exuberance, spontaneity, and desire to please others.[3] A strengths-based, specific behavioral goal-oriented approach to management is popular.

Consequences of persistent, poorly treated ADHD include the following: an increased risk of injuries; increased cost of medical care; an increased risk of addiction to tobacco, alcohol, and illicit drugs; an increased risk of incarceration; and a diminished ability to maintain employment or relationships.[4,5]

Although a single pathophysiologic pathway has not been determined, genetic associations, multiple environmental

agents, and psychosocial characteristics (e.g., poverty, stressed parents and households, families with mental health or substance abuse challenges, difficulty setting limits, disorganized routines) affect the risk of developing or being labeled with ADHD. Genes showing significant associations with ADHD include *DRD4, DRD5, DAT, DBH, 5-HTT, HTR1B,* and *SNAP-25.* Other risk factors for ADHD include male gender, maternal tobacco use during pregnancy or early childhood, intrauterine growth retardation, excessive exposure to television, and exposure to certain pesticides.[6–8] Of the 358 industrial chemicals, pesticides, and pollutants found in studies of the umbilical cord blood of infants in the United States, more than 200 are known to be toxic to the brain. Multiple brain regions, including the prefrontal cortex, frontostriatal networks, and cerebellum, and neurotransmitters, particularly dopamine and norepinephrine, appear to be involved in ADHD deficits.[9–12]

In summary, ADHD is a common clinical diagnosis in both children and increasingly in adults, and it has multiple genetic, environmental, and psychosocial contributions to dysfunction from several neurotransmitter systems and regions of the brain.

Integrative Therapy

Integrative therapy focuses on the goals of the patient and family in the context of values, culture, and community. Goals for treating ADHD may include improvements in the ability to focus or pay attention and in following directions, greater persistence in the presence of difficulty, improved ability to delay gratification, more consistent anticipation of consequences, improving grades, better organizational skills, better short-term memory, greater neatness, less procrastination, improved social relationships, greater obedience, better sleep, and fewer injuries, among other goals. Each of these goals requires a complex interaction of specific skills and resources.

Requirements for learning to manage attention are as follows:

1. Motivation (it is easier to pay attention to things that interest us)
2. The ability to *perceive* sensory data such as sounds (as words) and symbols (written words or gestures) accurately and to *process* these data into meaningful information
3. *Tuning out of irrelevant* sensory information (e.g., ignoring music or conversation in the background while reading a book) while being *flexibly responsive* to changing priorities (a fire by a smoke detector, a cry for help, or ringing telephone)
4. *Monitoring* of one's own attention ("Oh, was I listening to the music instead of focusing on the words? How many times have I read this sentence?")
5. *Redirection* of attention (let us get back to the book.)

In addition to managing attention, learning to *follow directions* also requires certain abilities:

1. Understanding the meaning of the request
2. Recognizing the tools and skills needed to complete it
3. Assessing the availability of these tools and skills
4. Using available resources and asking for help when needed
5. Monitoring performance

The choice of specific therapies depends to some extent on an individual's specific goals, but general mental and physical health can always be supported by appropriate attention to the fundamentals: *healthy habits in a healthy habitat*. Four fundamental healthy habits have been identified: exercise, balanced with optimal sleep; nutrition and avoidance of toxins in the diet; management of stress and emotions; and establishment of healthy communication and supportive, rewarding social relationships. A healthy habitat includes the physical and psychosocial environment (Fig. 6-1).

Exercise

A minimum of 30 to 60 minutes of aerobic activity daily is necessary for general physical and mental health.[13] A 2009 study in children with developmental coordination disorder found that regularly playing table tennis was helpful both for their coordination and for their ability to sustain focus.[14] Exercise outdoors in nature is even better than exercise in a gym or urban setting.[15] Exercise increases brain-derived neurotrophic factor levels and enhances neurogenesis, thus promoting overall cognitive function, including attention and memory, which are both required for academic achievement.[16,17] Cerebellar dysfunction has been implicated in ADHD.[18] This has led to growing interest in activities that build balance and coordination such as yoga, juggling, cross-midline exercises, the Interactive Metronome method, and Brain Gym. Quiet, mindful exercises such as tai chi and yoga encourage focus on the body as it moves and can thereby improve the ability to focus and to be more deliberate and less impulsive.[19] Martial arts training promotes discipline. Dr. David Katz of Yale University in Connecticut recommends the ABCs—Activity Bursts in the Classroom (or Corporation).[20]

A minimum of 30 to 60 minutes of aerobic activity daily is needed for mental and physical health.

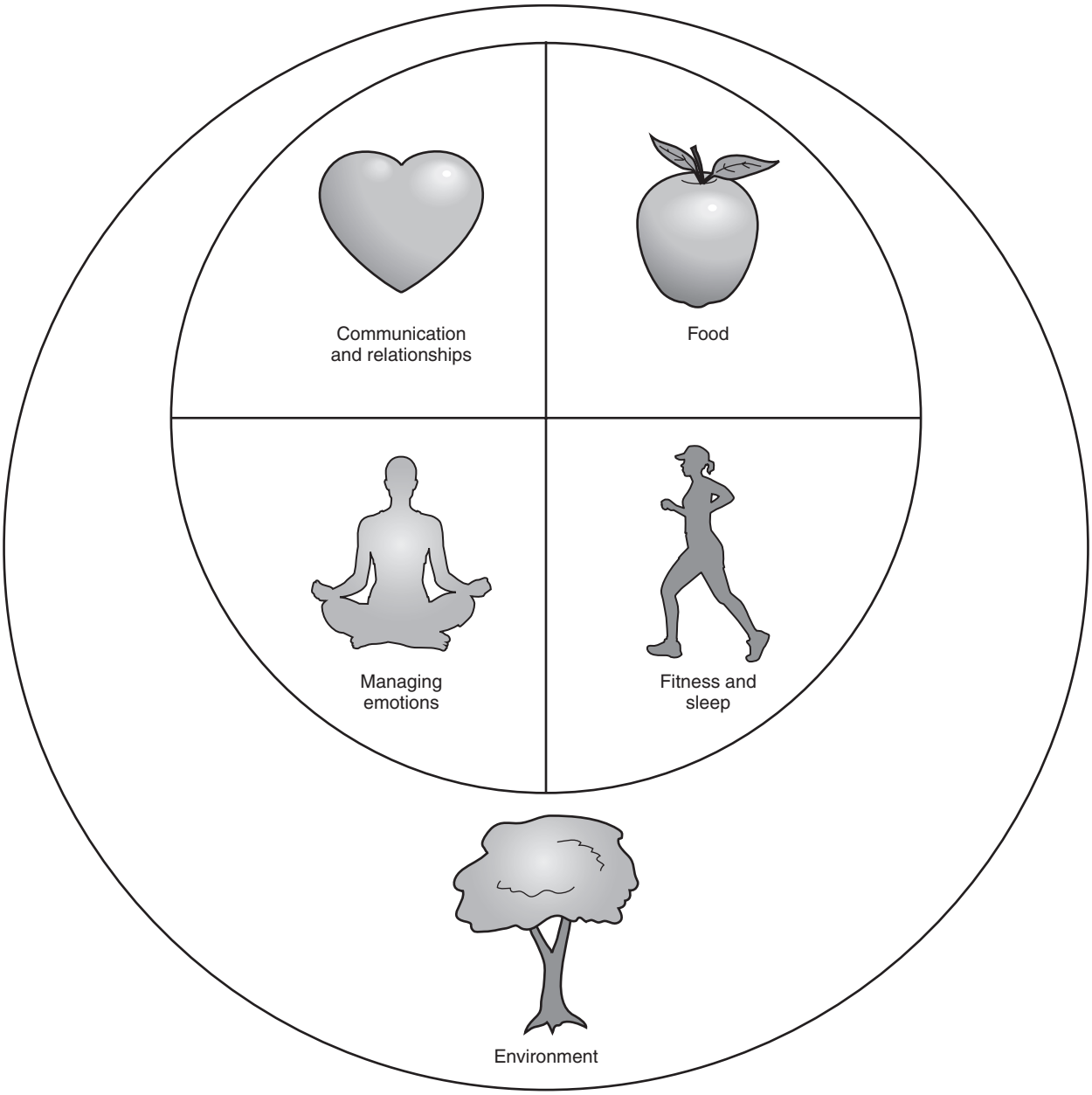
Safety

Impulsive, distracted people are prone to injuries. Encourage appropriate use of bike and ski helmets, as well as protective padding for skateboarding. Encourage enrollment in organized sports or lessons with small classes with close supervision and low student-teacher ratios (karate, tae kwon do, tai chi, or yoga) to help develop better body awareness and self-discipline. Counsel the patient to avoid overuse injuries.

Sleep

Sleep deprivation impairs focus, organizational skills, diligence, and self-discipline during boring tasks. Inadequate sleep and poor sleep quality impair attention and judgment, increase fidgeting, lower performance, and lead to more mistakes, automobile collisions, and injuries. Although many patients with ADHD report sleep problems even before starting treatment, stimulant medications can contribute to insomnia. Improved sleep may lead to improvements in daytime focus on behavior. Clinicians should inquire routinely about sleep and recommend sleep hygiene measures

FIGURE 6-1
Healthy habits in a healthy habitat.



(e.g., cool, quiet, dark room; comfortable bedding; avoidance of television in the bedroom or exercise late in the day; routine bedtime) to promote optimal sleep.

Nutrition

Although its weight is less than 5% of the body's total, the brain uses approximately 20% of the body's energy supply. To function well, it needs a steady supply of high-quality fuel (Table 6-1). This means regular meals supplying optimal amounts of essential fatty acids for cell membranes, of the amino acids used to make neurotransmitters, and of the vitamin and mineral cofactors necessary for their production and metabolism, as well as a steady supply of glucose for energy needs. Optimally, these nutrients are ingested in the diet, but for those who do not eat well, supplements may be useful.

Omega-3 Fatty Acids

Low levels of omega-3 fatty acids are linked to ADHD and behavioral problems in both adults and children.[21,22] Supplementing with fish oils (which are rich sources of omega-3 fatty acids) can alleviate ADHD symptoms and decrease depression, anger, anxiety, impulsivity, and aggression; it can also improve academic achievement.[23–29] Although flaxseed, walnuts, and green leafy vegetables contain the omega-3 fatty acid

TABLE 6-1. Dietary Essentials for Optimal Attention

DIETARY ESSENTIALS	FOODS SOURCES
Amino acids	Soy, tofu, beans, lentils Seeds and nuts Milk, cheese, eggs Fish, fowl, meat
Essential fatty acids (omega-3 fatty acids: EPA, DHA and linolenic acid)	Fish (tuna, salmon, sardines, and mackerel) Flax seeds, walnuts Dark green leafy vegetables Animals that have eaten omega-3–rich diets (e.g., eggs from chickens fed flaxseed; pasture-raised and grass finished beef; lamb; bison; wild game)
B vitamins, including folate and B_{12}	Beans, lentils, nuts and seeds Leafy green vegetables, asparagus Oranges and other citrus fruits and juices Whole grains Yeast (e.g., brewer's), dairy, eggs, meat, poultry, fish and shellfish
Minerals: iron, magnesium, zinc	Peas, beans, lentils, peanuts, peanut butter Leafy green vegetables: spinach, avocado Raisins Whole grains, brown rice, wheat bran and germ Nuts: almonds, cashews Dairy, eggs Meat, fish, poultry, oysters

DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid.

linolenic acid, humans convert only 5% to 10% of linolenic acid to the useful *eicosapentaenoic acid* (EPA) and *docosahexaenoic acid* (DHA). Encourage patients either to eat sardines, salmon, or mackerel twice weekly or consume 1 to 2 tablespoons of flaxseeds daily or to consider a supplement containing between 500 and 2000 mg of combined EPA and DHA.

Amino Acids

Two small studies suggested that *carnitine* supplements can help improve attention and behavior in children and adults with ADHD, particularly the inattentive type.[30,31] Additional studies are desirable to determine optimal dosing, frequency, and duration, particularly for patients with varying intake of foods rich in amino acids.

Minerals

Iron deficiency interferes with memory, concentration, behavior, and both physical and mental performance, and correcting deficiencies (indicated by low ferritin levels) can improve attention and restlessness.[32–36] *Magnesium* supplements have helped children with ADHD who are excitable, easily stressed, or worriers, as well as those who also suffer from constipation.[37] *Zinc* supplements can improve behavior for those who are deficient in zinc.[38,39] The best dietary sources of essential minerals are plants and animals raised on mineral-rich soils.

Vitamins

The B vitamins serve as essential cofactors in the production of neurotransmitters. Many children who avoid leafy green vegetables consume insufficient amounts of folate. Those who are strict vegans may benefit from vitamin B_{12} supplements. For picky eaters or those who eat poor-quality diets, multivitamin and mineral supplementation may be helpful, but megadoses are not useful and may have side effects.[40]

Water

Dehydration can impair attention and mood.[41] In a small study of first graders, ingestion of some water before taking a test led to better attention and greater happiness.[42]

Sugar

At least a dozen double-blind studies have shown that sugar does not cause hyperactivity. However, eating simple sugars can cause blood sugar swings that impair mental and emotional stability. It is preferable to consume calories from complex carbohydrates such as whole grains rather than simple sugars.[43] Furthermore, many sweet processed food products also contain artificial colors and preservatives that can contribute to behavior problems.

Feingold Diet, Artificial Colors, Flavors, and Preservatives

The Feingold diet does not ban sugar, but it does eliminate salicylates (at least initially; it slowly reintroduces fruits containing them), several synthetic food additives, and certain synthetic sweeteners:

- Artificial colors (petroleum-based certified FD&C and D&C colors)
- Artificial flavors
- BHA, BHT, TBHQ (preservatives)
- The artificial sweeteners Aspartame (now called Truvia), Neotame, and Alitame

Artificial food colors significantly worsen hyperactivity for many people.[44] The Center for Science in the Public Interest (CSPI) has called on the U.S. Food and Drug Administration (FDA) to ban dyes linked to hyperactivity and behavior problems. The colorings the CSPI would like to see banned are as follows:

- Blues 1 and 2
- Green 3
- Orange 8
- Reds 3 and 40
- Yellows 5 and 6

In studies of children with ADHD who received the Feingold diet, 73% had improved behavior.[45,46] Studies involving more than 1800 children showed significant improvements in the children's hyperactive behavior on a diet free of benzoate preservatives and artificial colors and flavors.[47,48] Some families find whole foods diets free of artificial colors, flavors, and preservatives difficult to follow. When families focus on healthy foods, use supplements wisely, and avoid exposure to artificial ingredients and environmental toxins,

however, they often see remarkable improvements in mood, attention, and behavior. Some patients have been able to reduce their reliance on stimulant medications.

Coffee and Other Caffeine-Containing Foods

Caffeine improves attention better than placebos, but it is not as potent as prescription medications.[49–52] Some families find caffeine a useful substitute for stimulant medications. In addition to caffeine, green tea also contains the amino acid theanine, which leads to a feeling of calm that can counteract the jitteriness some people experience with coffee.[53] Coffee and tea contain variable amounts of caffeine, depending on growing conditions and preparation techniques. Side effects include insomnia, jitteriness, anxiety, palpitations, panic attacks, and dehydration. Coffee can be addictive; withdrawal symptoms include headaches and feeling irritable, sleepy, depressed, anxious, or fatigued. Withdrawal symptoms can occur with as little as 1 to 2 cups daily. Caffeinated sodas or energy drinks often contain artificial flavors, colors, and preservatives and are not as good a choice as coffee or tea. Caffeine should not be used as a substitute for regularly getting a good night's sleep.

Food Sensitivities

Approximately 6% to 10% of children have allergies or sensitivities to foods. In addition to classic allergies, many people are lactose intolerant, and approximately 1% of people are sensitive to gluten. The most common food sensitivities are to wheat, corn, soy, milk products, eggs, tree nuts, shellfish, citrus, and peanuts. If sensitivities are suspected, encourage families to keep a careful *food diary*. In some cases, blood testing, skin testing, biopsies (for gluten sensitivity), and elimination diets may be useful. However, because many reactions are not true allergies, allergy test results may be negative even if a food is problematic. Some studies support the use of few foods or oligoantigenic diets to improve symptoms in more than half the children with ADHD.[54] An elimination diet typically removes all the foods and artificial ingredients that commonly cause problems for at least 2 weeks and then slowly reintroduces one at a time every 3 to 4 days. Recommend nutritional counseling to avoid deficiencies if families pursue this option.

Organic or Not?

Produce with the highest levels of pesticide contamination includes apples, bell peppers, celery, cherries, imported grapes, nectarines and peaches, pears, potatoes, raspberries, spinach, and strawberries. Organic crops contain lower levels of pesticides and other agrochemical residues than do nonorganic crops.[55] Children who eat organic produce have lower levels of these toxic pesticide chemicals than do children who eat nonorganic produce.[56] As historical farming practices waned, mineral levels in fruits, vegetables, meat, and milk fell up to 76% between 1940 and 1991.[57] Organic crops contain significantly more minerals and antioxidants than do crops raised with petroleum-derived (so-called conventional) fertilizers.[58,59] Milk from cows that graze on grass (botanically diverse pasture) has higher levels of the essential omega-3 fatty acids than does milk from cows that eat grain such as corn.[60,61]

TABLE 6-2. Stress Management Strategies

Common Sense
Gratitude. Develop the habit of listing three things you are grateful for before meals or bed.
Count on it. Count to 10 before reacting.
Identify your early warning signs: tight muscles, faster breathing, red face, clenched hands, and tight jaw.
Know yourself. Plan activities based on whether you are a morning person or a night owl and a visual or auditory learner.
Plan ahead. Being organized and consistent reduces stress.
Reflect. Develop the daily practice of reflecting on what went well and what could be improved.
Rehearse. Anticipate difficult situations and rehearse or role play before the situation.
Formal Practices, Often Learned With a Teacher or Trainer
Sitting meditation (concentration or mindfulness types)
Moving meditation (e.g., yoga, tai chi, qi gong)
Other Practices, Often Best Learned with Professional Coaching
Biofeedback
Autogenic training, guided imagery

Managing Stress and Emotional Self-Regulation

Learning to manage stress is an important lifelong skill. Major pediatric stressors include divorce, moving, parental loss of a job or loss of a house, serious health challenges, war, neighborhood violence, parental addiction or depression, and loss of a loved one. Stress interferes with concentration and self-discipline. Numerous successful strategies for managing stress are available. Some are common sense, and some require training and practice or professional counseling.

Common Sense Stress Management

Common sense strategies include preventive strategies such as practicing gratitude (counting blessings) and in-the-moment strategies such as taking a deep breath and counting to 10. Learning to understand one's own triggers, strengths, and weaknesses is also helpful to plan proactively how to manage stressful situations such as tests, running late, and losing something. Night owls may want to save perplexing problems until later in the day, whereas morning people (larks) may want to get up earlier to tackle challenging tasks. Reflecting on the day's events after the heat of the moment can also identify unskillful patterns and create opportunities for meeting challenges. Similarly, rehearsing an anticipated event can help decrease the stress of the actual experience (Table 6-2).

Meditation

Meditation improves attention, creativity, and mental clarity and reduces errors, aggressiveness, anxiety, and depression, particularly in the presence of stress or distractions. Meditation leads to calm coherence with more focused

electroencephalographic (EEG) patterns.[62,63] Regular meditation practice changes cortical blood flow and increases the size of areas dealing with attention, focus, planning, emotional self-regulation, and mood.[64–69]

Just as many kinds of sports improve physical fitness, many kinds of meditation improve attention and reduce stress reactivity. Just as some kinds of sports involve rackets, bats, or balls, meditation can be done with eyes open or closed, while sitting still or moving, in silence or not, while visualizing or not, and alone or in groups. *Concentration-based* meditation practices involve focusing on a word, sound, object, idea, emotion (e.g., gratitude) or movement; when other thoughts, sensations, or emotions arise, they are gently placed aside, and the mind returns to its object of concentration. Students who practiced concentration-types of meditation had fewer problems with absenteeism and suspension for behavioral problems,[70] less distractibility and better creativity,[71] and better cognitive function and grades.[72,73] *Mindfulness* meditation is the moment-to-moment practice of nonjudgmental awareness of sensations, thoughts, emotions, and experiences; when the mind wanders to past or future concerns, it is also gently returned to the present. Studies in school settings show that mindfulness-based meditation training can improve attention, emotions, and behavior; students have fewer fights and better grades.[74–80] For hyperactive patients, moving meditation such as yoga, tai chi, or qi gong may be a better fit than sitting meditation.[19,81] Regular practice reduces test anxiety and improves academic achievement. Those who practice the most reap the greatest rewards.[82]

The need for formal training and the intensity, duration, and frequency of practice vary. Some clinicians undertake specific training and certification to provide specific kinds of meditation training (e.g., mindfulness-based stress reduction, mindfulness-based cognitive-behavioral therapy, or dialectical behavior therapy). Nevertheless, because of the absence of consistent state or national certification for mind-body training, it is prudent to ask about a provider's training and experience. As with other clinicians, look for those who are welcoming, warm, and empathetic and who show genuine interest in people, not just in their favorite techniques. The most effective teachers and trainers offer steadfast acceptance and positive regard. They create an atmosphere of safety and trust while fostering independence and acknowledging students' strengths and capacities.

Just as national guidelines recommend 30 to 60 minutes daily of physical exercise to maintain physical health, recommendations for meditation practice typically range from just a few minutes for young children to 10 minutes twice daily for school-age children to 40 to 60 minutes daily for older adolescents and adults.

Biofeedback

EEG biofeedback (neurofeedback) can significantly improve behavior, attention, and intelligence quotient (IQ) scores.[83–91] In fact, neurofeedback is as effective as standard therapies, even for children with Asperger's syndrome and those with mental retardation.[88,92–96] Most studies provided at least 20 EEG biofeedback training sessions with a professional trainer. EEG biofeedback training develops a skill. Unlike medications, whose effects stop when the pills stop, EEG biofeedback training benefits can be expected to persist if the skill is mastered and practice continues.

Typical costs range from $75 to $200 per session; insurance reimbursement for neurofeedback varies. Most professionals who offer EEG biofeedback are psychologists, however, and as such their professional services may be covered by insurance. Patients should check their insurance policies and ask clinicians to assess their unique situations.

Electroencephalographic frequencies correlated with levels of alertness and processing:
- Beta wave (>14 Hz) = Active processing
- Alpha wave (8–13 Hz) = Active alert
- Theta wave (4–7 Hz) = Transitional state (associated with meditation, relaxation, imagery, and hypnosis

Professional Counseling

Large studies suggest that, at least in the short term, the most effective treatment for children with ADHD is an integrated strategy including both behavioral therapy and stimulant medication.[97] Cognitive-behavioral therapy can be particularly useful in helping patients learn to question assumptions and thoughts underlying negative emotions. Given all the negative feedback patients with ADHD have received about their behavior and academic performance, it is not surprising that they have internalized many of these messages. Negative self-labels are sometimes projected onto others, thus leading to blaming and oppositional behavior. By recognizing, questioning, and transforming negative self-talk, one can build confidence and problem-solving capacities. Professional counseling may be particularly helpful for those who have coexisting conditions such as anxiety or depression or for families whose parents were not fortunate enough to have good role models for effective parenting skills. Psychological or neuropsychological testing and advice help identify and treat children with specific learning disabilities. For adults with ADHD, "metacognitive" therapy can help teach skills such as time management, organization, and planning. This training promotes significant improvements in daily living skills and job performance.[98]

Professional counseling takes a little longer to show a benefit than does medication. However, the skills learned in behavioral therapy can persist for years after the therapy officially ends.[99] Although it may appear to be more expensive in the short term, behavioral therapy can be an excellent cost-effective investment.

Social Relationships

Social support is useful for most families managing chronic conditions such as ADHD. National support groups usually have local chapters with ongoing support and local resources:

All Kinds of Minds (AKOM) is a nonprofit organization that aims to help individuals with learning differences achieve success in school and in life. Their Internet site has toolkits and other resources for parents, schools, and health professionals.

Children and Adults with Attention Deficit Hyperactivity Disorder (CHADD) is a national nonprofit organization that works to improve the lives of those affected by ADHD through education, advocacy, and support. Their home page offers links to local chapters, as well as international activities.

The National Federation of Families of Children's Mental Health is a parent-run organization to support families caring for children and youth with emotional, behavioral, or mental disorders. The Web site provides links to publications, research, and state chapters.

Learning Disabilities Association of America (LDA) was founded in 1963 to support people with learning disabilities and their families, teachers, and health professionals. It sponsors an annual conference. The Web site provides resources, legislative updates, and links to state chapters.

Mental Health America, formerly known as the National Mental Health Association, is the national's oldest and largest community-based network dedicated to promoting mental health, preventing mental disorders, and achieving victory over mental illness through advocacy, education, research, and delivering programs and services. The organization strongly supported the Mental Health Parity law that became effective in 2010 and continues to provide updates, action alerts, and advocacy to ensure effective implementation. The Web site provides links to local affiliates and a wealth of advocacy information.

Alliance With Schools

Clinicians should help teachers and school administrators recognize the child's unique gifts and challenges. Families should schedule regular meetings with their child's teachers to monitor progress and advocate for seating arrangements that put the child near the front of the classroom. Encourage families to advocate for the child to receive the public services to which he or she is legally entitled. According to the 1999 addendum to the U.S. Individuals with Disability Education Act (IDEA), children and youth whose disabilities adversely affect their educational performance should receive special services or accommodations that address their problem (e.g., ADHD) and its effects. Section 504 of the U.S. Vocational Rehabilitation Act prohibits discrimination against any person with a disability. Under Section 504, students may receive services such as a smaller class size, tutoring, modification of homework assignments, help with organizing, and other assistance.

If the patient has not received sufficient services or accommodation within 6 months of asking the teacher or principal, write to the school district's director or chairperson for special educational services. The letter should specifically request an evaluation for specific learning disabilities and a functional assessment to determine how the disabilities are affecting the child's classroom performance. These evaluations are required to develop an Individual Educational Plan (IEP) or a 504 Accommodation Plan. Middle school and high school students diagnosed with ADHD are also entitled to these evaluations and, if appropriate, an IEP or accommodation plans. With an IEP, the child may qualify for extra help, special classes, extra time for tests or projects, an extra set of books for home study, permission to take notes on a computer keyboard rather than by hand, extra breaks in the day, fewer classes, and other accommodations. Support teachers and administrators who offer creative, effective strategies to promote children's strengths.

Encourage parents to try other activities that explore the child's interests, talents, and possible life-long passions or vocations. When choosing activities, consider the adult-child ratio. Music, art, tutoring, and individual language lessons may offer more individual attention than soccer leagues. Look for consistency. A class that meets every Tuesday is easier to schedule and attend than a sports team that has inconsistent practice and game schedules requiring frequent changes in the family driving routine.

Environment

Increasing time in nature may help soothe irritable children and adults, allow room for exploratory and creative play, and build on innate strengths and skills. Encourage families to reduce electronic screen time to less than 2 hours daily. Ask, advise, and assist families in reducing or eliminating exposure to tobacco smoke and adults who model using alcohol and illicit drugs as primary stress management strategies. Remind families to use proper safety equipment (e.g., seat belts, helmets). Reduce the use of pesticides at home and in schools. Consider using music as a way of reinforcing positive behavior, a learning strategy (songs with rhymes to assist in memorization), and a way to influence the environment subtly to cue wake up times and bedtimes. Encourage families to use calendars and posted schedules to promote structure and predictability for the day, week, and month (Table 6-3).

Additional Therapies

Botanicals and Other Dietary Supplements

Melatonin

Melatonin does not improve daytime symptoms of ADHD, but it can help improve sleep, particularly for shift workers and those with delayed sleep phase syndrome.[100–103] The typical adult dose of melatonin is 0.3 to 5 mg 1 hour before the desired bedtime. Melatonin is not a substitute for a healthy sleep routine. One study followed children with ADHD who had started taking melatonin as part of a clinical trial on sleep; nearly 4 years later, more than two thirds of these children were still using melatonin because it was helpful and had no serious side effects.[104]

TABLE 6-3. Environmental Dos and Don'ts

Do
Spend more time in nature.
Be more mindful of use of music to calm, focus, and reinforce behavior.
Use clocks, calendars, and lists to organize time.
Post schedules, chore charts, and other tools to organize activities and expectations.
Use proper safety equipment (e.g., bike helmets and seat belts).
Don't
Spend more than 2 hours in front of electronic devices daily.
Spend time around tobacco smoke.
Model the use of alcohol or drugs as skillful stress management strategies.

Calming Herbs

Historically, some herbs have been used to promote calm and decrease agitation, but none can replace a healthy lifestyle. Calming herbs, such as chamomile, hops, kava, lavender, lemon balm, passionflower, and valerian, may promote sleep, but they are not usually helpful for calming daytime hyperactivity, inattentiveness, or impulsivity.[105]

Other Herbs

Coffee and tea containing caffeine are natural stimulants. Green tea also contains theanine, which can be calming, thereby offsetting some of the unpleasant side effects of caffeine.[106–108] Caffeine helps enhance attention and promote positive cognitive performance in both children and adults.[109–112] To minimize the risk of insomnia from caffeine, caffeinated beverages should not be consumed within 6 hours of planned bedtime. No controlled trials are available to show significant benefits for other commonly used stimulant herbs such as ginseng for ADHD. A pilot study from Italy indicated that ginkgo may help improve ADD symptoms.[113] A Canadian product (AD-fX) that combines ginseng and ginkgo benefitted patients with ADHD or dyslexia in one manufacturer-sponsored study.[114] Similarly, pycnogenol or European pine bark extract was significantly better than placebo in improving concentration and decreasing hyperactivity in children in several European studies funded in part by pycnogenol producers.[115–117] Neither evening primrose oil (which contains gamma-linoleic acid [GLA]) nor St. John's wort supplements have proved any more useful than placebo for ADHD. Variations in the quality of herbal products and the paucity of effectiveness research mean that routine recommendations for these products should await further study and standardization of products (Table 6-4).

TABLE 6-4. Herbs as Additional Therapy

Calming Herbs
Tea: chamomile, hops, lemon balm, passionflower
Valerian: tincture, glycerite, or capsule
Aromatherapy: chamomile, lavender
Avoid kava because of concerns about hepatotoxicity
Stimulant Herbs
Coffee
Tea: black and green
Ginseng or ginseng/ginkgo combination
Other Herbs
Pycnogenol (pine bark extract, also known as OPC): benefits shown in small, industry-funded studies
Evening primrose oil: ineffective in a randomized controlled trial
St. John's wort: ineffective in a randomized controlled trial

Pharmaceuticals

In the United States, stimulant medications combined with behavioral therapy comprise first-line treatment for youth, although the long-term effectiveness of this therapy is unclear.[118,119] The British National Institute for Health and Clinical Excellence (NICE) guidelines for treating ADHD recommend stimulant medications as a first-line therapy for adults with ADHD, but only for children with severe symptoms, not mild or moderate ADHD.[120] Initially, stimulants (which are classified as controlled substances) benefit approximately two thirds of patients. Stimulant medications do not generally improve oppositional or defiant behaviors or overall quality of life, however, and their adverse effects on appetite, sleep, and growth require ongoing monitoring. Research conducted by scientists without conflicts of interest (unlike previous studies, in which investigators sometimes received payments from pharmaceutical companies) showed that stimulants were little better than placebo.[121]

The National Institute of Clinical Excellence (NICE) recommends stimulant medications only for children with severe symptoms, not for children with mild to moderate ADHD.

Stimulant medications include short-acting (3 to 6 hours), medium-acting (4 to 8 hours) and long-acting (more than 8 hours) methylphenidate (Ritalin and Methylin) and amphetamines (Adderall, Dexedrine, Dextrostat, and Vyvanse). Related compounds include dexmethylphenidate (Focalin) and extended-release methylphenidate and amphetamine (Adderall, Metadate, and Concerta). A patch medication (Daytrana) provides controlled release of methylphenidate. Like coffee, most stimulants start working within approximately 20 minutes. Short-, medium-, and long-acting medications are available (Table 6-5).

Nonstimulant medications used to treat ADHD include atomoxetine (Strattera), modafinil (Provigil), clonidine (Catapres), guanfacine (Tenex and extended-release Intuniv), bupropion (Wellbutrin), and other antihypertensive, antidepressant, and antiseizure medications. Atomoxetine is the most commonly prescribed nonstimulant medication for ADHD. It is much better than placebo for improving the ability to focus, to be organized, and to regulate attention and emotions, as well as enhancing short-term memory in adults.[122] Atomoxetine has also been beneficial for children with ADHD, but side effects such as sleepiness and decreased appetite limit its appeal.[123] Many of the other medications are prescribed off label, that is, they have not been approved by the FDA for treatment of ADHD.

In addition to not working for some people, medications have several problems:

1. Side effects. The most common side effects of stimulant medications are decreased appetite, poor growth, and insomnia. Less common side effects include nausea, headaches, stomachaches, sweating, jitteriness, tics, dizziness, a racing heart, and, paradoxically, drowsiness. Of greater concern, stimulant use is linked to psychosis, hallucinations, heart arrhythmias, and sudden death.[124,125]
2. Failure to work when they are not taken. Medications are not a cure for ADHD. When a dose is missed, the

TABLE 6-5. Short-, Medium-, and Long-Acting Stimulant Medications for Attention Deficit Hyperactivity Disorder

SHORT (3–6 hr)	MEDIUM (4–8 hr)	LONG (> 8 hr)
Ritalin (methylphenidate) 5, 10, 20 mg bid or tid	Ritalin LA (methylphenidate long acting) 20, 30, 40 mg daily	Concerta (methylphenidate) 18, 36, 54 mg daily
Methylin (methylphenidate) 5, 10, 20 mg bid or tid	Ritalin SR (methylphenidate sustained release) 20 mg daily to bid	Focalin XR (dexmethylphenidate extended release) 5, 10, 20 mg daily
Focalin (dexmethylphenidate) 2.5 mg, 5, 10 mg bid	Metadate CD (methylphenidate extended release) 10, 20, 30, 40, 50, 60 mg daily	Daytrana (methylphenidate patch) 10, 15, 20, 30 mg daily
Metadate ER (methylphenidate extended release) 10–20 mg daily to bid	Methylin ER (methylphenidate extended release) 10, 20 mg daily to bid	Adderall XR (amphetamine/dexamphetamine extended release) 5, 10, 15, 20, 25, 30 mg daily
Adderall (amphetamine/dexamphetamine) 10, 20, 30 mg daily to bid		Vyvanse (lisdexamfetamine) 20, 30, 40, 50 mg daily

bid, twice daily; tid, three times daily.

medication cannot work. If someone stops taking it, it stops working. More than half the patients with ADHD stop taking stimulant medication without being advised to do so by their physician.[126,127]

3. Reliance on medications. Patients may rely on these agents instead of making healthy changes in lifestyle and environment.
4. Long-term costs. Continuous dependence on medications is costly for individuals and society. Stimulant use has increased from 0.6% of children less than 19 years old in 1987 to 3.4% in 2003. In terms of overall costs of medications, of the top five drugs prescribed for children, three were medications for ADHD.
5. Long-term effects. The effects of long-term medication use or of the concurrent use of multiple medications are unknown. Although stimulant medications have been used for decades, no long-term studies have evaluated the developmental impact of using these medications daily for 30 years. Short-term use has been evaluated for one drug at a time, but the impact of taking multiple medications simultaneously is unknown.
6. Misuse, diversion and abuse. As the number of prescriptions for stimulant medications has grown, so has the number of reports that these drugs are being diverted or sold to people who do not have ADHD. A 2009 study reported a 76% increase in the number of calls to Poison Control Centers related to adolescent abuse of prescription ADHD medications.[128]

Given these concerns about medications, many pediatricians do not write prescriptions for stimulant medications without first conducting *N*-of-1 trials to determine the short-term benefits and risks for individual patients. Such trials can be repeated annually to assess the ongoing need for medications.

Massage, Chiropractic, and Other Biomechanical Therapies

Scientific studies support the regular use of massage for improving ADHD symptoms.[129–131] Massage affects blood flow and neurotransmitters that influence focus and clarity.[132,133] Massage also reduces stress, improves mood, decreases pain, and alleviates anxiety, all of which can improve concentration, deliberation, and self-discipline.[132,134–136] Even a 15-minute chair massage can improve speed and accuracy on standard tests.[137] Additional studies would be useful to help determine the best type of massage, the duration and frequency of treatments, and whether massage provided by friends or family members is as helpful as care from a licensed professional.

Massage is safe when common sense precautions are used, such as avoiding massage over rashes, infections, bruises, or burns. Do not force massage therapy on someone who has suffered physical or sexual abuse or who is very shy. Respect adolescents' desires for privacy. In the United States, massage therapists are licensed or certified as health professionals in 40 states; elsewhere, cities or counties license them. Licensed professionals in the United States can be identified through the American Massage Therapy Association's Locator Service.

Prevention Prescription

- Advise pregnant women to stop smoking and avoid drinking alcohol.
- Advise parents not to smoke around their children and to limit exposure to television and pesticides.
- Encourage families to live a healthy lifestyle focusing on the following: a whole foods diet that limits intake of artificial colors, flavors, sweeteners, and preservatives and foods that cause sensitivity reactions and that avoids deficiencies of essential omega-3 fatty acids, amino acids, vitamins and minerals; daily physical activity, preferably outdoors in natural surroundings; adequate sleep; effective stress and emotional self-management; strength-based communication skills and participation in supportive community networks; and a safe, structured, well-organized environment.

Therapeutic Review

Accurate Diagnosis

- Use standard rating scales such as the Vanderbilt Parent and Teacher Rating Scales to assess ADHD symptoms and response to interventions. A1
- Rule out medical and neuropsychological conditions that impair attention and self-discipline such as hypothyroidism, vision, hearing, and specific learning deficits. Consider requesting a neuropsychological examination to assess IQ and learning difficulties. A1

Encouraging Healthy Habits in a Healthy Habitat

- Dietary
  - Assess diet and correct nutritional deficiencies with a better diet or dietary supplements. A1
  - Encourage patients to maintain a steady blood glucose level by eating regular meals with foods having a low glycemic index. Foods containing artificial colors, sweeteners, flavors, and preservatives should be avoided, as should foods with a heavy burden of pesticides. B1
  - Instruct patients to avoid dehydration. A1
  - Consider recommending coffee or tea as mild dietary stimulants and monitoring for insomnia and other common side effects. B2
- Sleep and activity
  - Promote adequate sleep with sleep hygiene. Consider melatonin (0.3 to 3 mg an hour before bed) or sedative herbal remedies (a cup of chamomile tea or lavender aromatherapy) as a first-line approach to improving sleep. C2
  - Encourage vigorous daily activity, at least 30 minutes daily of activity vigorous enough to break a sweat or make it difficult to talk and move at the same time. A1
- Stress management and emotional self-management skills
  - Assess stress management and emotional self-management skills.
  - Counsel families about stress management.
  - Consider referral for meditation training, including moving meditation practices such as yoga and tai chi. Consider referral for effective counseling and cognitive-behavioral therapy. C1
- Social support B1
  - Refer families to support networks of other families such as Children and Adults with Attention Deficit Hyperactivity Disorder (CHADD).
  - Encourage positive family communication, focusing on goals rather than problems. Help families view overall long-term goals in terms of short-term achievable objectives. Help families learn to make specific, measurable, achievable, relevant, time-specific (SMART) plans, including ways to celebrate success.
  - Consider referring families for additional support for parenting and discipline skills, as well as time management and organizational skill development.
- Healthy environment C1
  - Advocate for appropriate testing and learning accommodations at school.
- Referral for additional professional assistance
  - Consider referral to a psychologist for neurofeedback. C1
  - Consider a referral for massage therapy. C1
- Pharmaceutical management
  - Remember that 65% of people do respond to stimulant medication, at least initially.
  - Consider recommending an *N*-of-1 trial of a stimulant medication, comparing a low dose (e.g., 5 mg methylphenidate twice daily) with a middle dose (10 mg twice daily) with placebo for 1 week each.
  - If patient notes improvement, consider switching to a longer-acting medication to reduce the number of pills or doses required daily. B2
- Monitor and support families with regular follow-up every 3 to 4 months. A1

KEY WEB RESOURCES

Rating Scales

Vanderbilt Teacher Rating Scale. http://www.brightfutures.org/mentalhealth/pdf/professionals/bridges/adhd.pdf.
Vanderbilt Parent Rating Scale. http://www.vanderbiltchildrens.org/uploads/documents/DIAGNOSTIC_PARENT_RATING_SCALE(1).pdf.

Activity

U.S. Centers for Disease Control and Prevention. http://www.cdc.gov/healthyyouth/physicalactivity/.
ABC for Fitness. Activity bursts in the classroom. http://www.davidkatzmd.com/abcforfitness.aspx.

Diet

Feingold diet. www.feingold.org.
Nutrition information from the Center for Science in the Public Interest. http://www.cspinet.org/.
Food pesticide levels from Environmental Working Group. http://www.foodnews.org/.

Support Groups

All Kinds of Minds (AKOM). www.allkindsofminds.org.
Children and Adults with Attention Deficit Hyperactivity Disorder (CHADD). www.chadd.org.
The National Federation for Families of Children's Mental Health. www.ffcmh.org.
Learning Disabilities Association of America (LDA). www.ldanatl.org.
Mental Health America. www.nmha.org.

Environment

Collaborative on Health and the Environment. www.healthandenvironment.org/.
National Environmental Education Foundation's Children and Nature Initiative. www.neefusa.org/health/children_nature.htm.
Pesticide information from Environmental Working Group. www.ewg.org/chemindex.
U.S. Department of Education information on attention deficit hyperactivity disorder and schools. http://www2.ed.gov/rschstat/research/pubs/adhd/adhd-identifying.html.

Biofeedback

Association for Applied Psychophysiology and Biofeedback. www.aapb.org.

Massage

American Massage Therapy Association. www.amtamassage.org.

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Chapter 7

Autism Spectrum Disorder

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Autism is a neurodevelopmental disorder characterized by deficits in social interaction and language development and a restricted or stereotypical pattern of interests and activities. Formerly a relatively rare condition well out of the public eye, autism has increased in prevalence more than 10-fold since 1990, from an estimated prevalence of approximately 5 to 6 per 10,000 children to 110 per 10,000 according to the most recent estimate by the Centers for Disease Control and Prevention.[1] As a comparison, this disorder is now more than 5 times more prevalent than Down syndrome, which has a prevalence of approximately 20 per 10,000 (Fig. 7-1). No scientific agreement exists on the cause of this rapid increase in prevalence, often referred to as an "epidemic" in the media. The three most likely possibilities are the following:

1. A true increase in the prevalence of the disorder has occurred.
2. Case finding is increased because of heightened awareness of the disorder on the part of the public and medical and other professionals.
3. The definition of autism has been loosened so that more children are being included.

To complicate matters still further, other diagnostic categories such as autism spectrum disorder, pervasive developmental disorder, and Asperger syndrome have been added to the mix, including children with some features of autism but who do not meet strict criteria. Even so, the Brick Township, New Jersey study separated autism from autism spectrum disorder and Asperger syndrome and still recorded a prevalence of 40 per 10,000 for autism itself.[2] A study in Minnesota, in which autism was separated from these other categories, gave a striking picture of the rapidity of the increase in the prevalence of this disorder.[3]

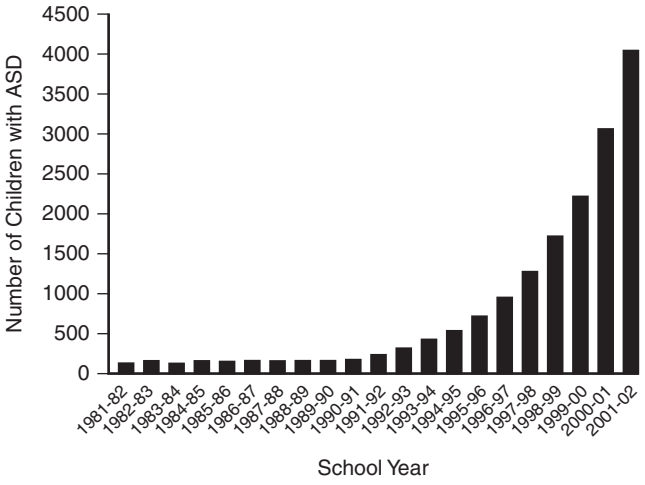
Regressive autism refers to children who have normal development until the age of 1 to 2 years, after which they lose language, social interaction, and other developmental milestones. This type of autism has mainly caused the widespread public concern over the influence of the measles-mumps-rubella (MMR) and mercury-containing vaccines on the development of autism. However, the available studies indicate that regressive autism accounts for only 30% to 40% of autism cases.[4, 5]

The origin of this disorder is basically unknown. Investigators currently believe that autism is a genetically based disorder requiring some environmental trigger to manifest. This belief is supported by the 90% concordance rate in identical twins, as opposed to the 30% concordance rate in fraternal twins. The siblings of an affected patient also have a much higher risk of autism. Many gene loci have been associated with autism, but no single gene or even group of genes has been shown to have a large impact contribution to this order.[6] The genetic aspect of this disorder likely consists of simultaneous genetic variations in multiple genes. In addition, even in the previously mentioned identical twins, when one twin has classic autism, the other twin has only a 60% incidence of also having classic autism. This finding emphasizes the role of environmental influence. From a conventional medical point of view, investigators have had little discussion of possible environmental factors that may trigger the expression of this disease. However, as discussed in greater detail later in this chapter, integrative physicians have examined the role of toxin exposure (especially including mercury), nutritional factors, infectious disease, and autoimmunity as contributing factors.

Pathophysiology

The pathophysiology of autism is not completely defined, but the use of functional magnetic resonance imaging and other imaging techniques has advanced our knowledge significantly. We do know that children with autism exhibit increased brain growth in the first year of life compared with neurologically normal children, followed by a period of decreasing growth rate. Investigators have theorized that this rapid growth is characterized by disjointed and disorderly growth resulting in abnormal neuronal connections. Intriguing neuropathologic evidence indicates that these

FIGURE 7-1
Number of children classified as having an autism spectrum disorder (ASD) special educational disability in Minnesota from 1981 to 1982 through 2001 to 2002.



abnormalities are associated with inflammation, thus raising the possibility that autism is, to some extent, a chronic inflammatory process. Patients have abnormalities of both gray and white matter. Evidence indicates that autism is, to a large degree, a problem of underconnectivity of cortical systems, especially interhemispheric communication, essentially a decreased ability of parts or systems of the brain to communicate with each other. This impairment results in difficulty with complex, higher-order functions, such as language and social skills. Autistic patients tend to have increased parietal and occipital activation, which is consistent with their greater reliance on visual-spatial as opposed to verbal skills. This feature also explains why autistic patients may have extremely high skills in areas not requiring this type of connectivity, such as mathematical calculation. Magnetic resonance imaging studies have shown abnormalities in the size of the cerebellum, amygdala, caudate, and various other parts of the brain, but the findings are not sufficiently reproducible to draw any definitive etiologic conclusions.[7]

Biomedical Approach

Some physicians and researchers have taken an alternative, or what is commonly referred to as a biomedical, approach to autism. The basis of this approach is that autism is a genetically based syndrome triggered by certain fetal, neonatal, and early childhood stimuli and that this syndrome results in a variety of nutritional, gastrointestinal, metabolic, and autoimmune abnormalities. Further, some of these abnormalities can be treated, and this treatment can improve the core symptoms of autism. Rather than thinking of autism as a brain disorder that has systemic effects, autism can be thought of a systemic disorder that affects the brain.[8]

Biomedical practitioners, including myself, have seen remarkable response to these treatments in some children with autism. The next sections discuss the strong evidence for the systemic nature of autism and the evidence for treatment efficacy.

Rather than thinking of autism as a brain disorder that has systemic effects, autism can be thought of as a systemic disorder that affects the brain.

Gastrointestinal System

One of the most common problems seen in children with autism is the wide variety of both gastrointestinal symptoms and clear gastrointestinal disease. The incidence of gastrointestinal problems in children with autism varies by study but seems to be in the range of 30% to 40%. Symptomatically, the most common reports are of chronic constipation or diarrhea and chronic abdominal pain; gastrointestinal disease is common and widespread. One study of children with autism and gastrointestinal symptoms showed that 69.4% of subjects had reflux esophagitis, 42% had chronic gastritis, and 67% had chronic duodenitis.[9] Because many of these children are nonverbal and cannot express gastrointestinal discomfort, many autistic children with these conditions may react to pain by exhibiting behaviors such as self-stimulation and temper tantrums that are not obviously referable to the gastrointestinal system.

Several studies have demonstrated definite disease of the small and large intestine. Torrente et al[10] performed biopsies on 25 children with autism and found duodenitis in almost all the children. These investigators described increased lymphocytic proliferation in both the epithelium and the lamina propria. This proliferation was associated with immunoglobulin G (IgG) and complement C1q deposition on the epithelial surface, indicating a possible autoimmune cause of the duodenitis. Horvath and Perman[11] also documented significant disaccharidase deficiencies in a population of children with autism and gastrointestinal symptoms.

The gut–immune system interface is an area of opportunity in developing a better understanding of how to treat autism most effectively.

Dysbiosis

Dysbiosis, or abnormalities of gastrointestinal microflora, is also thought to be a common problem. Rosseneu et al[12] analyzed 80 children with autism and gastrointestinal symptoms and found that 61% had growth of abnormal aerobic gram-negative endotoxin-producing bacteria. The endotoxin produced by these aerobic gram-negative bacteria could cause ongoing bowel damage; 55% had overgrowth of *Staphylococcus aureus,* and 95% had overgrowth of pathogenic *Escherichia coli.* No abnormal amounts of yeast were noted in this study. In a fascinating pilot study, 11 of these children were treated with a nonabsorbable antibiotic. Not only did the abnormal flora disappear, but also both gastrointestinal symptoms and autistic behaviors decreased significantly. This study did not have a control group, and unfortunately, after 2 months the abnormal bacteria returned to pretreatment levels.[12] In another study,[13] vancomycin treatment of children with regressive autism and diarrhea resulted in decreased autistic behaviors, as measured by blinded observers.

Yeast

An overgrowth of yeast is widely believed to be part of dysbiosis and responsible for many gastrointestinal and behavioral symptoms of autism. Many children are therefore treated with antifungal agents as part of their "bowel detoxification" protocol. Very little research evidence for this yeast overgrowth exists, however. As mentioned earlier, Rosseneu's study failed to identify any yeast among the abnormal bacteria, and no good controlled studies have evaluated yeast overgrowth in autism. Some research has shown the presence of urine organic acids suggestive of yeast overgrowth in children with autism, but the significance of these byproducts is unclear. Antifungals such as nystatin, fluconazole, and ketoconazole are widely used, with much anecdotal evidence of positive results, but no controlled studies.

Intestinal Permeability

Yet another gastrointestinal abnormality commonly attributed to children with autism is "leaky gut," or increased intestinal permeability. Although this issue is ignored by most conventional practitioners, studies have shown it to be a pervasive problem. In a study by D'Eufemia et al,[14] examination of 21 autistic children with no known intestinal disorders confirmed increased intestinal permeability in 43%, as opposed to 0% of controls. In addition, Horvath and Perman[15] examined 25 children with autism and gastrointestinal symptoms by using lactulose-mannitol testing and found that 76% of these children had altered intestinal permeability. Finally, in 2010, de Magistris et al[16] found increased intestinal permeability in 36.7% of autistic patients and in 21.2% of their relatives, as compared with 4.8% of neurologically normal subjects.

Food Sensitivities

Food sensitivities or allergies are also thought to play an important role in the pathophysiology of autism. The evidence for this connection is indirect but suggestive. In one study, 36 children with autism were compared with healthy controls and were found to have significantly higher levels of IgA, IgG, and IgM and antigen-specific antibodies for specific food proteins such as lactoglobulin, casein, and beta-lactoglobulin compared with controls.[17] Two studies by Jyonouchi et al[18] showed that children with autism had higher intestinal levels of inflammatory cytokines directed against specific dietary proteins than did controls. In 2002, as previously noted, Torrente et al[10] showed increased lymphocyte proliferation and epithelial IgG deposition in the small intestine of children with autism, a finding suggesting an autoimmune process.

Some researchers believe that gluten and casein pass through a leaky gut barrier and form gluteomorphins and caseomorphins, which then have important central nervous system effects. Research in this area has been inconsistent, however. These putative food protein sensitivities do not manifest as immediate hypersensitivity on standard skin testing or IgE radioallergosorbent testing (RAST). This finding leads investigators to question whether children with autism have true food allergies or food sensitivities that are not IgE mediated.

In summary, available evidence suggests that significant percentages of children with autism have gastrointestinal abnormalities, including gastroesophageal reflux, duodenitis, ileitis, colitis, dysbiosis, increased intestinal permeability, and immune reactions to specific dietary proteins. Whether one or more of these conditions is primary and others are secondary is not clear. For example, does food sensitivity or dysbiosis cause increased intestinal permeability and inflammation, or does the increased permeability cause the food sensitivity? Similarly, is dysbiosis primary, leading to chronic damage to gut epithelia, or is it secondary to other pathologic processes?

Autoimmunity

Some studies suggest that autoimmune abnormalities are common in children with autism. Some of these abnormalities can be directly linked to the central nervous system. Connolly et al[19] examined the sera of children with autism for antibrain antibodies. IgG antibrain antibodies were present in the sera of 27% of children and in only 2% of controls. IgM antibodies were present in 36% of the sera of autistic children and in 0% of controls.

Another study looked at the prevalence of antibodies to various brain structures in 68 autistic children and 30 controls.[20] Forty-nine percent of autistic children had serum antibodies to the caudate nucleus, as opposed to 0% of controls. Antibodies to the cerebral cortex and cerebellum were 18% and 9%, respectively, again with 0% of controls having these antibodies. The reason that autistic children have the abnormal presence of antibodies to the brain and central nervous system is certainly not clear, nor is it known whether these antibodies cause neurologic problems or are merely a byproduct of central nervous system damage caused by other factors. However, these studies do suggest a possible role for autoimmunity in the origin of the neurologic abnormalities found in autism.

An epidemiologic study supported the importance of autoimmunity in autism.[21] Three groups of 101 families were examined. The first set of families had a child with autism, the second had a child with a classic autoimmune disease, and the third were healthy families, without autoimmune disease or autism. Families were then evaluated to find the number of first- or second-degree relatives with an autoimmune disorder. The surprising results were that autistic families had 1.87 relatives with autoimmune disorders. Thus, a family containing an autistic child was significantly ($P = .03$) more likely to have another relative with an autoimmune disorder than a family already containing a child with an autoimmune disorder.

Mitochondrial Abnormalities

One of the more fascinating aspects of autism research is the discovery that children with autism have a higher percentage of mitochondrial abnormalities than do other children. This finding was confirmed in several studies. In one study, Olivieri measured plasma lactate in 69 patients with autism. Fourteen patients, or 20%, had elevated plasma lactate; 11 of these patients underwent muscle biopsy, and 5 showed definite mitochondrial respiratory chain abnormalities. Thus, a total of 5 of 69, or 7.2% of autistic patients, had mitochondrial disease.[22] A 2011 review and meta-analysis estimated

that the incidence of mitochondrial abnormalities is at least 5%, orders of magnitude higher than the general population.[23] Children with autism also demonstrated abnormalities in lactic acid, pyruvate, and carnitine levels compared with the general population.

Metabolic Disorders

Some studies demonstrated abnormalities in the metabolic functioning of children with autism, with defects in areas such as glutathione synthesis, sulfation deficits, and folate metabolism. For instance, a study reported in the *American Journal of Clinical Nutrition* demonstrated that relative to the control children, the children with autism had significantly lower baseline plasma concentrations of methionine, *S*-adenosylmethionine (SAMe), homocysteine, cystathionine, cysteine, and total glutathione and significantly higher concentrations of *S*-adenosylhomocysteine (SAH), adenosine, and oxidized glutathione.[24] This metabolic profile is consistent with impaired capacity for methylation (significantly lower ratio of SAMe to SAH) and increased oxidative stress.

In another study, activities of erythrocyte superoxide dismutase and erythrocyte and plasma glutathione peroxidase in autistic children were significantly lower than in neurologically normal children.[25] These results indicate that autistic children have low levels of activity of blood antioxidant enzyme systems.

An excellent review article by McGinnis[26] documented certain positive markers of oxidative stress in children with autism. Among other factors, he cited indirect markers for greater oxidative stress such as the following: (1) lower endogenous antioxidant enzymes and glutathione; (2) lower antioxidant nutrients; (3) higher organic toxins and heavy metals; (4) higher xanthine oxidase and cytokines; and (5) higher production of nitric oxide, a toxic free radical.

Heavy Metal Toxicity

Many clinicians and families involved in the alternative treatment of autism believe that increased body levels of heavy metals, especially mercury, are an important part of the pathophysiology of autism. This belief is related to the assumption that the thimerosal (ethylmercury) contained in, and later withdrawn from, infant immunizations, is a major factor in the autism "epidemic." Because children with autism are clearly not exposed to more mercury or other heavy metals than are other children, investigators have postulated that these children have impaired abilities to detoxify or excrete mercury and other heavy metals. This impairment is thought to result from the various methylation, sulfation, and antioxidant deficiencies discussed previously.

Little evidence supports the hypothesis that mercury is related to the development of autism. One of the problems in discussing heavy metal toxicity is that no simple tests are available for determining body levels of heavy metals. Blood tests for mercury are not useful because mercury remains in the tissues and not in the circulation. Hair analysis has been used, but whether low or high results correlate adequately with body levels is not clear. In conventional medicine, mercury toxicity is measured by giving a dose of a chelating agent, such as edetate disodium (EDTA) or dimercaptosuccinic acid (DMSA) and then measuring urine mercury levels. No published study exists in which this procedure has been done in autistic children. One study by Ip et al[27] compared blood and hair levels of autistic children with those of controls and found no significant differences; however, the investigators did not examine urine levels after chelation.

In another study, Holmes et al[28] compared the levels of mercury in the hair obtained during the first haircut of a set of babies with and without autism. These investigators found that hair mercury levels were significantly lower in autistic children than in controls, even though the exposure to mercury was the same or higher than that of controls. Because hair mercury level is a result of excretion of mercury, the investigators postulated that the toxic effect of mercury in autistic children could be caused by impaired excretion. In this article, hair mercury levels in controls were directly correlated with the number of mercury amalgams and with fish consumption in the mothers of these children, but no such correlation was noted in the autistic group.

If mercury is believed to be a cause of autism in some children, then why would these presumably neurologically normal children have impaired excretion resulting in higher than normal mercury levels? It would have to be postulated that the metabolic defects leading to impaired excretion were already present, perhaps on a genetic basis. This would explain why children genetically at risk for autism would react to mercury in a different way from nonautistic children to the same total mercury exposure. This hypothesis is plausible, but it has not yet been adequately investigated.

Finally, Bradstreet et al[29] performed a retrospective analysis of 221 children and 18 controls who had been treated with three doses of DMSA. Heavy metal concentrations in the urine were then analyzed. In this study, urinary concentrations of mercury were significantly higher in 221 autistic children than in the 18 controls. Moreover, vaccinated children showed a significantly higher urine mercury concentration than unvaccinated controls. No correlation was found between autism and urinary concentrations of lead or cadmium. The findings of this study implied that autistic children have significantly higher body burdens of mercury than controls, but the study had at least two significant limitations. First, it was a retrospective study with nonrandom selection of controls. Second, the imbalance between the number of cases and the control group was quite large.

In summary, although mercury is clearly a potent neurotoxin, especially in the developing brain, the idea that mercury exposure is a significant cause of autism is at this point largely unproven. To prove this association, a large study using postchelation urinary heavy metal levels in autistic children as compared with controls would be necessary.

Although it is clear that mercury is a potent neurotoxin, especially in the developing brain, the idea that mercury exposure is a significant cause of autism is at this point largely unproven.

Role of Thimerosal in Immunizations in the Causation of Autism

The role of thimerosal in autism is a topic of great controversy, and entire book chapters could be written about it. This issue has caused a remarkable rift between the

scientific mainstream and the "autism community" that seems to be completely impenetrable. This discussion is an attempt to describe the issue as succinctly as possible. First, even though mercury is a potent neurotoxin, it was used as a preservative in childhood vaccines until 1999. At that time, a review conducted by the U.S. Food and Drug Administration discovered that with the increased number of vaccines given in infancy, the amount of thimerosal, which is ethylmercury, received by infants in the first 6 months of life could exceed the U.S. Environmental Protection Agency guidelines for safe amounts of methylmercury. (The distinction between ethylmercury and methylmercury is important because safety standards are based on methylmercury.) Despite claims that thimerosal posed no danger or showed no evidence of harm, thimerosal was then withdrawn from all infant vaccines except the influenza vaccine. The autism community, however, aware of the huge increases in the diagnosis of autism, made the obvious connection and asserted that autism could in large part be caused by the thimerosal in childhood vaccines. This connection was supported by two analyses by Geier and Geier,[30,31] who claimed to link thimerosal-containing vaccines with autism through analyses of reports for the Vaccine Adverse Event Reporting System (VAERS) and through comparison of thimerosal vaccine rates and special education enrollment of children with autism. The authorities criticized reports on methodologic grounds, especially noting that VAERS is a passive reporting system and not suited to this type of analysis. Since then, several epidemiologic studies have failed to find a connection between thimerosal in vaccines and the incidence of autism, but opponents have refused to accept their statistics and have become suspicious of any report coming from government or medical "authorities."

Evidence that thimerosal in vaccines is responsible for a rise in autism is insufficient. The amount of mercury in vaccines since 2000 has been miniscule, yet we have not yet seen a corresponding drop in new cases of autism. Arguing that thimerosal was a major contributor to the so-called autism epidemic would be difficult without postulating that some "new" factor was causing the continued high incidence, now that thimerosal is no longer a factor.

This is not to say that environmental mercury or other toxins could not have a significant impact on the development of autism. A small study showed 287 environmental pollutants in the umbilical cord blood of newborn infants,[32] including mercury and a wide variety of organic and inorganic contaminants, such as polychlorinated biphenyls. Before their first breath, infants are already accumulating significant levels of mercury and other environmental toxins. Also true is that no levels of mercury exposure in the fetal brain are known to be "safe."

A study in Texas[33] showed a direct correlation between the incidence of autism and the amount of mercury expelled from industrial pollution. In fact, for each 1000 lb of environmentally released mercury, the investigators noted a 43% increase in the rate of special education services and a 61% increase in the rate of autism. Of course, this is a correlation only and does not prove causation, but it is nevertheless extremely concerning, especially as environmental mercury pollution continues to rise.

Low levels of environmental toxins can affect neurologic development in animal models. Although evidence is not yet available for a strong relationship with autism, the precautionary principle should be implemented and practiced.

Measles-Mumps-Rubella Vaccine and Autism

Because regressive autism occurs between the first and second year of life, which is when the MMR vaccine is usually given, many parents have suspected this live vaccine as a cause of autism in their children. This concept was reinforced when research by Dr. Andrew Wakefield asserted the presence of small bowel disease in children with autism that is often associated with the presence of the measles virus. This study, however, was retracted by the *Lancet* after very serious allegations of irregularities in the research.[34]

What is the evidence? Several epidemiologic studies have failed to find any link between measles immunization and autism.[35–37] Therefore, on a population-wide basis, I believe it is clear that the MMR vaccine is not a significant contributor to the increased incidence of autism. Also true, however, is that epidemiologic studies would have a difficult time teasing out a small subpopulation of genetically predisposed children who were susceptible to an autoimmune reaction to the measles virus. Therefore, the possibility certainly exists that the MMR vaccine is the triggering event for autism in a small subset of individual patients. One study did show increased levels of measles antibody in immunized children with autism versus controls, a finding indicating a possible hyperimmune response to measles in children with autism.[38]

On a personal level, I have met some parents who ascribed their child's development of regressive autism to the MMR vaccine, even if the regression occurred months after an uneventful vaccine reaction. These associations do not seem credible. However, I have also met a few parents whose neurologically normal child received the MMR vaccine, had a severe physical reaction, including mental status changes, and immediately began losing milestones. These reports are more difficult to dismiss, although coincidence is always possible.

No good evidence supports the potential relationship between the measles-mumps-rubella vaccine and the development of autism.

Nutritional Deficiencies

One tenet of the biomedical approach is that nutritional deficiencies are widespread and important in autism. These deficiencies are thought to be mainly linked to poor digestion and absorption of nutrients resulting from the aforementioned gastrointestinal problems, as well as abnormalities in the metabolic processing of nutrients. The evidence for these nutritional deficiencies, however, is somewhat uneven and rarely complete.

The beginning of the biomedical approach to the treatment of autism occurred when Bernard Rimland et al[39–41] began using supplements of vitamin B_6 in the early 1970s. These investigators reported controlled and uncontrolled studies of the effect of vitamin B_6 and magnesium on autistic symptoms, all of which were positive. However, many of these reports were not published in peer-reviewed journals, and they did not have a rigorous study design. In 2002, a Cochrane Review found only two articles of sufficient quality to analyze.[42] One was inconclusive, and the other showed no effect. A pilot study by Adams and Holloway[43] that evaluated the impact of a multivitamin and mineral study in a controlled double-blind fashion on a small group of children found statistically significant differences in sleep and gastrointestinal symptoms but not in the core symptoms of autism. The levels of vitamin B_6 were much higher in autistic children than in controls. This finding is postulated as reflecting the relatively poor conversion of pyridoxal to pyridoxal-5-phosphate, the enzymatically active form of the vitamin. This would explain why children with autism may need increased intake of vitamin B_6. A larger controlled study is currently under way.

Although no peer-reviewed studies have documented inadequate levels of vitamin C in children with autism, one study did show positive effects of up to 8 g/day of vitamin C in institutionalized autistic children.[44] This was a placebo-controlled double-blind crossover study, and total autism evaluation scores improved significantly in the treated group and worsened in the group going from vitamin C to placebo.

Omega-3 Fatty Acid Deficiency

A study by Vancassel et al[45] looked at levels of omega-3 fatty acids and other polyunsaturated fatty acids in the serum of children with autism compared with controls. Those children who had autism had 23% lower levels of omega-3 fatty acids in their plasma than did controls. They also had 20% lower levels of polyunsaturated fatty acids. This finding is in addition to two studies in the related diagnosis of attention deficit hyperactivity disorder (ADHD) that clearly showed lower levels of omega-3 fatty acids in both erythrocytes and serum in children with ADHD as compared with controls. The reason for this finding is unclear. Because no reason exists to assume that children with autism have different levels of omega-3 intake than control children, autistic children may have differences in how they use and metabolize these fats. This question is significant in that omega-3 fatty acids are a common supplement used in the integrative treatment of autism.

Integrative Therapy

Mind-Body Therapy

Conventional Behavioral Approaches

Intensive behavioral therapy is another common treatment for children with autism. With this therapy, direct behavioral intervention by trained facilitators occurs in home and school settings from 20 to 40 hours a week. Specific methods are used, such as Lovaas, Floortime, and applied behavior analysis. Intervention is directed at increasing appropriate social and language behavior while decreasing self-stimulatory activities. Overall, reasonable evidence indicates the effectiveness of this modality. A 2003 review in the *Canadian Journal of Psychiatry* concluded that "delivering interventions for more than 20 hours weekly that are individualized, well planned, and target language development and other areas of skill development significantly increases children's developmental rates, especially in language, compared with no or minimal treatment."[46]

Speech Therapy

Speech therapy is almost universally recommended to deal with the language deficits of children with autism. Most clinicians and parents, including myself, believe speech therapy to be helpful and effective in most children with autism. Very little convincing research supports the efficacy of speech therapy for autism, however. Although some showed specific areas of language improvement, all these involved a small number of subjects, and none of the studies were randomized or controlled. Considering the almost universal use of speech therapy in the treatment of autism, this is an area with surprisingly inadequate research.

Occupational Therapy

Occupational therapy is also commonly recommended for children with autism. As with speech therapy, anecdotal reports note improvement, but no convincing research evidence of efficacy exists.

Precautions

In general, the effectiveness of the therapy is highly practitioner dependent. Practitioners should find the excellent therapists in their area. The usefulness of the conventional behavioral approaches must be evaluated on an ongoing basis. Families have limits in both time and money in what they can do.

Alternative Behavioral Approaches

Another modality commonly employed with children with autism is sensory integration therapy. Children with autism clearly have significant sensory issues. They often do not enjoy touching, can be upset by noisy environments, and exhibit other sensory difficulties. To modify these deficits, sensory integration therapy is often recommended. This therapy usually involves a variety of sensory stimuli administered under controlled conditions. As with the other therapies discussed earlier, only anecdotal evidence indicates effectiveness. Small noncontrolled studies have been conducted, but any evidence of efficacy is preliminary at best.

A second behavioral modality is auditory integration therapy. This technique is based on the idea that hypersensitivity to certain sounds can cause behavioral and emotional difficulties in autistic children. Essentially, auditory integration therapy attempts to reprogram and "integrate" the auditory system by sending randomized sound frequencies through earphones worn by the autistic child. This is usually done in 20- to 30-minute sessions over a period of 10 days or so. Many anecdotal reports of efficacy exist, but studies so far are uncontrolled and limited to very small numbers, so any positive evidence must be judged as preliminary. Finally, a few small studies have indicated that music therapy may be beneficial for autism.

Nutrition

Dietary Interventions

The most common alternative or biomedical intervention employed with autistic children is the gluten-free, casein-free (GFCF) diet. This diet is based on the previously discussed theory that food sensitivities, especially to gluten and casein, can produce not only gastrointestinal symptoms but, in association with gut inflammation and increased gut permeability (leaky gut), can lead to many of the neurologic manifestations of autism. In general, parents are advised strictly to avoid all foods containing gluten or casein for a period of at least 60 days and sometimes several months.

The anecdotal evidence for efficacy is abundant. In various support groups, chat groups, and other situations bringing together parents of children with autism, the GFCF diet is often described as promoting significant and positive changes in gastrointestinal symptoms, language, socialization, and other autistic behaviors.

Two controlled studies concerning the efficacy of the GFCF diet in the treatment of autism showed positive results. In the first study, by Knivsberg et al,[47] 10 matched pairs of children with autism were randomized to a GFCF diet or a placebo control for 1 full year. Autistic behaviors were then evaluated by blinded observers using the DIPAB, a Danish instrument for measuring autistic traits. After the intervention, the diet group had a mean DIPAB rating of 5.60, significantly ($P = .001$) better than the control group rating of 11.20. Specifically, social contact increased in 10 of 15 of the treated children, whereas ritualistic behaviors in that group decreased in 8 of 11 children. In the second study, by Lucarelli et al,[17] autistic children were found to have decreased behavioral symptoms after 8 weeks on an elimination diet. A third double-blind study in 2006, with 15 children, showed no statistically significant differences between groups.[48]

The GFCF diet can be extremely stressful to maintain. Autistic children tend to be picky eaters, and using this diet often removes some of their main foodstuffs. The diet can also cause a financial hardship, because many of the GFCF substitutes can be significantly more expensive. The potential for nutritional deficiencies exists if the diet is not supervised by a dietitian or physician. Both protein and calcium intake should be watched, as well as overall caloric intake.

With willing families and adequate supervision, these concerns are minor and easily manageable. I believe it is important, however, to make no other changes when instituting the diet, so that any improvements will be clearly the result of the diet itself and not related to other factors. Too often, the GFCF diet is started in conjunction with several nutritional supplements and other interventions, thus making it difficult to know whether behavioral or other improvements can be clearly attributed to the diet.

If gluten and other proteins can cause gastrointestinal disease and other manifestations of autism, what about other dietary proteins? The answer is that no reason exists that other foods cannot cause problems, and anecdotal reports abound of children with autism who react to a variety of food proteins, as well as certain preservatives and artificial colors and flavors. No controlled trials support these observations, however. Deciding how to determine whether a child is sensitive to these foods is interesting. As with gluten and casein, results of IgE skin tests and RAST testing are mostly negative. Many practitioners use RAST testing specific for IgG or IgG-4, tests that are usually obtained from alternative laboratories that are not covered by insurance and are less strictly regulated. These IgG tests are thought to reflect delayed-type food allergy, but the actual evidence linking IgG results to clinical allergy is scant. Moreover, problems with the reliability and accuracy of some of these laboratories have been reported. Another alternative is single or multiple food elimination diets, in which one or more groups of foods are removed for a period and behavior is observed. These diets can be very illuminating, but they depend on subjective impressions of the observer (see Chapter 84, Food Intolerance and Elimination Diet).

Another dietary intervention is known as the specific carbohydrate diet, made popular by Elaine Gottschall in *Breaking the Vicious Cycle.* This diet, which eliminates almost all carbohydrates and sugars except monosaccharides, was originally intended for patients with inflammatory bowel disease, celiac disease, and other gastrointestinal problems. The diet has been used by families of children with autism, however, and many have claimed positive results. It is even stricter than the GFCF diet, and essentially no scientific evidence exists of its efficacy in autism. Finally low-phenol and low-oxalate diets have some anecdotal success, again without any substantiating research.

Dosage (Length of Trial)

Most practitioners believe that at least 60 days on a GFCF diet is necessary to evaluate its efficacy fully. Some practitioners recommend at least 6 months.

Precautions

Make sure that caloric intake is adequate, including protein, fat, and carbohydrate. Depending on the diet, calcium or a multivitamin supplementation may be indicated. Monitor the child's weight.

Pearls for Instituting a Gluten-Free Diet for Autism

1. Make sure that no other interventions are being started simultaneously.
2. Discuss carefully the need for strict adherence during the trial period.
3. Discuss the reading of labels and locations where gluten-free, casein-free products can be obtained.
4. I also recommend eliminating artificial colors and flavors.
5. Use a supportive nutritionist whenever feasible.
6. Do not substitute large amounts of soy for casein. Soy is also a significant player in childhood food allergies.
7. Following this diet is *hard*. Parents need support and guidance.

Omega-3 Essential Fatty Acids

Many nutritional supplements are used in the treatment of autism, including omega-3 fatty acids, probiotics, zinc, vitamin B_6, and other multivitamin and mineral supplements.

Omega-3 fatty acids, as discussed previously, have been shown to be decreased in the serum of children with autism. (Other studies, have shown similar deficiencies in children with ADHD.) Therefore, these supplements are widely used in the treatment of autism. In one pilot study by Patrick and Salik,[49] 18 children were given an omega-3 fatty acid supplement (247 mg of omega-3 and 40 mg of omega-6) for 3 months. The language skills of these children were measured at baseline and after the 3-month trial. The investigators found a highly significant increase in language skills over a wide variety of measures. A literature review rated the overall evidence for the efficacy of omega-3 fatty acids in autism as insufficient to draw conclusions.[50] This review noted that only one small randomized controlled study has been done, and this showed a trend toward improvement in hyperactivity and stereotypy that did not reach statistical signficance.[50]

Another study of relevance concerned the use of omega-3 fatty acids in developmental coordination disorder.[51] This is not part of the autistic spectrum but is relevant because children with this disorder can have elements of learning disabilities, ADHD, and autism. In this double-blind controlled trial, 117 children were given either an omega-3 supplement or placebo for 3 months. Although no coordination improvement was found, the treated children made startling gains in reading, spelling, and mathematical skills compared with the placebo group. As an example, the average reading scores in the treatment group advanced 9.5 months in 3 months, as opposed to an increase of 3.5 months in the placebo group ($P = .004$). No clearly accepted guidelines exist for the dosage of omega-3 fatty acids in autism, or the ideal ratio of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), the crucial omega-3 fatty acids.

Dosage

Dosage is an area of uncertainty. I usually begin with 15 mg/lb of omega-3 fatty acids. Some studies have used 1.5 g of omega-3 fatty acids for children 5 to 14 years of age.

Precautions

Too high a dose, or sometimes even low doses, can trigger hyperactivity in a small subset of children.

Experiential Pearls for Using Omega-3 Fatty Acids in Autism

1. I tend to use a fairly balanced dose of docosahexaenoic acid and eicosapentaenoic acid for a total dose of 15 mg/lb.
2. I use Nordic Naturals, Carlson Laboratories, or Genova Diagnostics products. These manufacturers have a good variety of products, including reasonable-tasting liquids and chewable capsules. However, the chewable capsules can become expensive for older or larger children.
3. Start slowly and move up the dose. Hyperactivity is an occasional side effect and disappears when the dose is lowered.
4. I like to start omega-3 fatty acids, multivitamins, zinc, and probiotics at the same time. This approach may be less scientific, but synergy may exist among some of these products.

Probiotics

Probiotics are used frequently in the biomedical treatment of autism. As discussed previously, many children with autism have abnormal gut flora, as well as increased intestinal permeability. It seems reasonable to treat this problem with probiotic therapy. Unfortunately, treatment with antibiotics seems to result in only temporary changes in bowel flora, thus leading to the conclusion that ongoing use of probiotics may be necessary to ensure normal bowel flora. In addition, despite the widespread use of probiotics and anecdotal reports of their efficacy, no well-designed studies have been conducted on the impact of probiotic use in the treatment of autism.

An interesting problem in the use of probiotics is that many different strains of beneficial bacteria exist. Controlled studies using probiotics in other areas of medicine tend to use single strains such as *Lactobacillus* GG (Culturelle). However, many of the commonly available probiotics used in the treatment of autism contain 1 billion or more colony-forming units of *Lactobacillus acidophilus, Lactobacillus bulgaricus, Bifidobacterium* of various species, and others. Because many of these strains of beneficial bacteria are commonly present in the colon, it would seem to make sense to use a product that includes them, but scientific evidence concerning this choice is absent. The correct dosage of probiotics is equally unclear (see Chapter 102, Prescribing Probiotics).

Dosage

Dosage varies greatly, depending on the type of preparation.

Precautions

Start slowly and gradually increase the dose; otherwise, diarrhea may occur.

Zinc

Zinc is the most widely recommended single mineral used in the treatment of autism. Much of this is related to research by Dr. William Walsh of the Pfeiffer Institute (Warrenville, Ill),[52] who found that copper-to-zinc ratios were increased in more than 85% of children with autism. He also found that a dysfunction of metallothionein, a protein involved in the regulation of these and other metals, was present in 99% of 503 autistic children. Unfortunately, this research was published by the Pfeiffer Institute only and not in a peer-reviewed journal. However, given the possibility of reduced zinc levels or increased copper-to-zinc levels in autistic children, many clinicians include increased zinc as part of autism therapy. However, no controlled studies have been conducted to indicate the efficacy of zinc in the treatment of autism. Some related evidence is available in the case of ADHD; two studies showed that children with ADHD tend to be deficient in zinc, and two studies showed improvement in these children when they were given zinc supplementation.

Dosage

20 to 25 mg/day.

Precautions

Zinc can inhibit the absorption of copper, thus leading to deficiency.

Carnosine

Carnosine is an antioxidant and may affect neurotransmitter function. It is one of the few metabolic supplements for which at least reasonable research evidence is available. One study showed carnosine levels in autistic children to be significantly lower than in controls. A double-blind placebo-controlled study by Chez et al[53] showed that autistic children had significant benefits from carnosine supplementation compared with placebo.

Dosage

The study by Chez et al[53] used 400 mg twice daily in 3- to 12-year-old children.

Precautions

Watch for hyperactivity or excitability.

Other Supplements

Many different metabolic and nutritional supplements have been used for the treatment of autism. These include trimethylglycine, dimethylglycine, glutathione, dipeptidases, digestive enzymes, methylcobalamin (methyl vitamin B_{12}), phosphatidylcholine, and others. All of these are recommended based on various metabolic and nutritional defects discussed earlier, and many come with glowing anecdotal reports of efficacy. None has been subject to any type of controlled study, so it is difficult to know which, if any, of these supplements are worth recommending. Methyl vitamin B_{12} injections, given every 3 days, are probably the most widely used of these therapies, and in my experience they elicit the most positive responses from parents. Some families have stated that methyl vitamin B_{12} was the most clearly effective of the entire range of biomedical interventions. The only double-blind study of methyl vitamin B_{12}, with 30 children, did not show any difference between experimental and control groups in either autistic symptoms or glutathione status, however.[54]

Hyperbaric Oxygen

One of the more interesting newer treatments for autism is the use of hyperbaric oxygen. Long used in deep sea diving, wound healing, and more recently cerebral palsy, hyperbaric oxygen use in autism is based on the finding that autism has been associated with hypoperfusion to various areas of the brain in several studies. Whether this association is primary or secondary to abnormal neurologic development is unknown. After a few case reports and unblinded studies, Rossignol[55] performed a randomized placebo-controlled trial with 62 children with autism. Subjects received either 40 sessions of either hyperbaric treatment or a placebo that involved being in a hyperbaric chamber with normal pressures and oxygen. The experimental group had statistically significant improvement in a range of autistic symptoms compared with controls.

Given early positive evidence and the knowledge that hyperbaric oxygen is a fairly safe procedure, practitioners are tempted to recommend it as a therapy. However, it is very expensive (usually at least $4000 dollars) for a set of 40 treatments and obviously time consuming. So far, no research is available on the permanence of any gains made with hyperbaric therapy.

Treating Mitochondrial Disorders

No direct research has specifically concerned the treatment of children with autism and mitochondrial disorders, outside of normal recommendations for mitochondrial issues. Clinically, many biomedical practitioners recommend testing of lactate, pyruvate, or carnitine levels to determine which children may be at increased risk. Treatment for children with elevated levels, with or without muscle biopsy confirmation, may consist of antioxidants such as coenzyme Q10, B vitamins, carnitine, and other antioxidants. Carnitine is known to be important in mitochondrial function, and antioxidants may decrease the oxidative stress associated with mitochondrial dysfunction. The somewhat speculative nature of this treatment may be reasonably countered by the high level of safety of these particular supplements.

Pharmaceuticals

Investigators generally believe that conventional psychotropic medication does not affect the core symptoms of autism but may help related comorbid behaviors that may be problematic. The main classes of drugs used are the following:

1. Mood-stabilizing medication, especially more recently the atypical antipsychotics such as risperidone (Risperdal), for explosive behavior and mood stabilization
2. Selective serotonin reuptake inhibitors (SSRIs) for anxiety, agitation, and depression
3. The psychostimulants such as methylphenidate (Ritalin) and combined amphetamine and dextroamphetamine (Adderall) for comorbid hyperactivity, lack of focus, and decreased attention span

Risperidone

Risperidone has had several good controlled trials and seems to be effective for the treatment of explosivity and irritability in children with autism, at least in the short term. In 2002, the results of a multisite trial of risperidone for the treatment of irritability, aggression, and explosiveness in autism showed a positive response in 56% of respondents as compared with 14% of the placebo group.[56] Increased appetite, fatigue, drowsiness, dizziness, and drooling were more common in the risperidone group than in the placebo group, however. The average weight gain in 8 weeks was 2.8 kg. Of the positive responders, two thirds still had a positive response after 6 months, a finding indicating that approximately 36% of the original group maintained improvement for 6 months. A follow-up study by these same investigators showed continued effectiveness without significant dose increases and a return to baseline when the risperidone was withdrawn.[57]

Although many integrative physicians would prefer not to use psychotropic medicines as first-line therapy in autism, one can imagine the difficulty of dealing with an explosive and noncommunicative adult-sized teenager to see how this type of treatment may have an important place.

Dosage

0.5 to 4 mg orally daily.

Precautions

Watch for tardive dyskinesia, anxiety, gastrointestinal disturbances, skin sensitivity, weight gain, and diabetes.

Selective Serotonin Reuptake Inhibitors

Theoretical reasons exist to believe the serotonin inhibitors could be effective in autism. First, some studies have established abnormalities of serotonin metabolism in children with autism. Second, the repetitive behaviors seen in autism have similarities to those seen in obsessive-compulsive disorder, which can be treated with SSRIs. A placebo-controlled trial by Hollander et al,[58] who used an 8-week course of low-dose fluoxetine (Prozac) (average 10 mg/day), showed significant improvement in repetitive behaviors compared with placebo but did not demonstrate any significant improvement in the Clinical Global Impressions score or global effectiveness.[58] The rate of adverse effects was no higher in the treatment than in the placebo group. This finding contrasted with an earlier study in which a 50-mg dose of fluoxetine was effective in only 1 of 18 subjects and caused significant adverse effects.[59] A Cochrane Review of SSRIs for autism stated that these drugs had no evidence of efficacy, could cause harm, and could not be recommended.[60]

Dosage

Dosage varies with the specific SSRI. Fluoxetine should be started at 5 mg and advanced slowly if necessary.

Precautions

Given the paucity of evidence, especially longer term, use SSRIs cautiously. Watch for decreased alertness, irritability, and dysphoria.

Psychostimulants

Although psychostimulants have been quite widely used in autism, the literature on their effectiveness is limited. Some studies, however, demonstrated a positive effect on those children with autism and hyperactivity symptoms. One double-blind study did show positive changes in some aspects of social interaction and self-regulation.[61] However, stimulants are associated with a significant incidence of negative side effects in children with autism, and in one study the drugs caused a variety of adverse effects, such as agitation, dysphoria, and irritability, in more than half of the subjects.[62] Clinically, however, some children with autism have hyperactivity and lack of ability to focus so severe that a careful trial of these medications is warranted.

Dosage

Dosage varies depending on the specific medication, beginning at low doses and working up slowly. Long- or short-acting preparations can be used (e.g., amphetamine plus dextroamphetamine [Adderall] 5 mg to 10 mg, one in AM, one in early PM).

Precautions

Watch for hypertension, weight loss, growth suppression, and insomnia if the drugs are given too close to bedtime.

Therapies to Consider

Complementary therapies such as homeopathy, craniosacral therapy, Reiki and other energy medicine modalities, and traditional Chinese medicine all may have a place in the integrative approach to autism. Scattered anecdotal reports of efficacy exist, but no research evidence. Certainly, any of these approaches would be safe for most children with autism.

Prevention Prescription

No definitive means exist to prevent autism. Some reasonable possibilities are the following:

- Have pregnant women avoid any unnecessary mercury intake. This would involve not eating certain fish and not having dental work done on amalgam fillings while pregnant.
- Encourage mothers to eat foods rich in omega-3 fatty acids during pregnancy and breast-feeding. If bottle-feeding, infants should use the omega-3–enriched formulas.
- Consider probiotics during pregnancy and infancy.
- If immunizations are a concern, the family could consider having fewer immunizations at once and separating immunizations when possible.
- Avoid exposure of pregnant mothers and infants to toxic household products of any kind.
- Avoid pesticide exposure wherever possible

Therapeutic Review

Nutrition

- Gluten-free, casein-free diet
- See Chapter 84, Food Intolerance and Elimination Diet

Supplements

- Omega-3 fatty acids: 15 mg/lb total eicosapentaenoic acid and docosahexaenoic acid to start
- See Chapter 86, The Antiinflammatory Diet
- Probiotics: 1 to 10 billion colonies daily (one or two capsules)
- Zinc: 20 to 25 mg daily; be careful of mineral (copper) malabsorption

Mind-Body Therapy

- Intensive behavioral therapy (Lovaas, applied behavior analysis, Floortime)
- Sensory integration therapy
- Auditory integration therapy

Other Therapy

- Speech therapy (for language development)
- Occupational therapy (for manual tasks and motor skill development)

KEY WEB RESOURCES	
Talk about Curing Autism. www.TACAnow.org.	This very good Web site contains information about both conventional and biomedical treatment for autism, as well as various types of support for families who have a child with autism.
http://www.talkaboutcuringautism.org/tag/gfcf/.	This useful Web site, associated with Talk about Curing Autism, has information about the gluten-free, casein-free diet.
Autism Research Institute. www.autism.com.	This Web site provides information about research on and application of the biomedical approach. It also notes DAN (Defeat Autism Now) Conferences, which are appropriate for both practitioners and parents.
MIND (Medical Investigation of Neurodevelopmental Disorders) Institute at the University of California, Davis. www.ucdmc.ucdavis.edu/mindinstitute/.	This institute is at the forefront of research into childhood neurodevelopmental diseases. At this Web site, physicians can find good information and parents can find research studies for which their child may be eligible.

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Chapter 8

Insomnia

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Insomnia is pervasive, associated with a broad range of illnesses, and presents a significant medical, social, and economic burden. Largely undiagnosed and untreated despite the existence of effective interventions, insomnia has been described as "unremitting, disabling, costly, pervasive, and pernicious."[1] Because it is strongly linked to lifestyle and body-mind dynamics and is resistant to conventional medical treatment, insomnia deserves much greater consideration from integrative medicine researchers and practitioners. In fact, a National Health Interview Survey reported that 1.6 million adults already use complementary and alternative medicine (CAM) to treat insomnia.[2]

The National Institutes of Health reports that 60 million adults in the United States struggle with insomnia annually.[3] Depending on definition, the prevalence of insomnia among adults ranges from 10% to 30% and increases with age and female gender, as well as with a broad range of medical and psychiatric comorbidities.[4]

Most patients with insomnia are at increased risk for comorbid medical disorders, including chronic pain, cardiovascular disease, cancer, neurologic and gastrointestinal disorders[5,6] obesity,[7] and diabetes.[8–10] Sleep loss has been associated with insulin dysregulation[9,10] disruptions of cortisol rhythms,[11,12] and immune function and inflammatory markers.[13–16]

Psychiatric illness, especially depression or anxiety,[17] is the most common comorbidity linked to insomnia.[18,19] Approximately 40% of adults with insomnia have a psychiatric illness—most commonly depression.[18,19] Persistent insomnia significantly raises the risk of clinical depression, anxiety disorders, and substance abuse.[20,21] The traditional presumption that insomnia is secondary to psychiatric illness has been challenged by several findings that suggest insomnia more often precedes and is likely a significant risk factor for mood disorders.[22–25]

Although psychiatric illness,[18] medical disorders,[26] and shift work[27] significantly increase the risk for insomnia, they are not causal but precipitating factors in patients already predisposed to the disorder.[28] Certain primary sleep and circadian rhythm disorders such as restless legs syndrome,[29] periodic limb movement disorders, delayed sleep phase, and sleep-related breathing disorders are also frequently associated with insomnia.[30]

Insomnia is associated with significant impairment in quality of life,[31–33] increased risk for accidents,[34] and decrements in work productivity.[35] The economic burden of insomnia has been estimated to be as high as $107 billion annually.[36]

Although conventional sleep medicine has clearly made advances in understanding and evaluating sleep and sleep disorders, one can argue that it lags in terms of developing effective treatment and prevention strategies for insomnia. Despite their serious limitations, hypnotic agents remain the primary focus of conventional insomnia treatment. Advances in cognitive-behavioral therapy for insomnia (CBT-I) challenge the conventional emphasis on medication and are associated with a growing chasm between conventional and behavioral sleep medicine. Among the most significant limitations of conventional approaches to insomnia is a widespread tendency to "treat the chart" that offers remarkably limited regard for subjective experiences of the patient. Among other consequences, this approach is associated with an unfortunate disregard for the role of rapid eye movement (REM) sleep and dreaming.

Because insomnia is so common and sleep is so vital a factor in general health, concern about the screening, evaluation, and treatment of insomnia should to be integral to primary health care. Along with nutrition, exercise, and stress management, sleep is clearly one of the four cornerstones of health. Because healthy sleep is associated with a broad range of biologic, psychological, behavioral, environmental, and lifestyle factors, the practitioner must approach insomnia from a comprehensive perspective.

Beyond bringing the best of conventional and CAM approaches together, integrative medicine takes the following approach to understanding and managing insomnia: (1) it restores the place of subjectivity, as is evident in CBT-I; (2) it emphasizes the restoration of sleep health, as

opposed to suppression of symptoms; (3) it acknowledges the important social and relational context of sleep; (4) it acknowledges the important role of natural rhythmic processes in life and health; and (5) it strongly emphasizes the role of lifestyle. An integrated approach to insomnia also calls for sensitive personalization of treatment based on a thorough evaluation.

Definitions

Insomnia disorder refers to difficulties with initiating or maintaining sleep, as well as nonrestorative sleep that is associated with excessive sleepiness or fatigue and with functional decrements for at least 4 weeks. Primary insomnia is not attributable to medical or psychiatric causes, whereas secondary insomnia has historically been viewed as a symptom of a primary disorder that would resolve with its treatment.[28] A National Institutes of Health (NIH) State of the Science Conference[5] recommended that secondary insomnia be considered *comorbid insomnia,* to encourage its direct treatment. Insomnia is frequently comorbid with other conditions, most commonly primary sleep disorders (Box 8-1), chronic pain syndromes, and psychiatric disorders, especially depression and substance abuse.

Etiology

The etiology of insomnia is commonly understood in terms of a "3 P" model,[37,38] consisting of predisposing, precipitating, and perpetuating factors. Predisposing factors comprise a broad range of biomedical, psychological, and lifestyle factors that increase the risk for developing insomnia. These include the following: (1) dependence on substances such as alcohol, caffeine, nicotine, and other drugs; (2) the long-term use of stimulant, sedating, or circadian rhythm–disrupting medications; (3) illnesses associated with nocturnal pain or discomfort; (4) primary sleep disorders such as restless legs syndrome, periodic limb movements in sleep, gastroesophageal reflux disease, and obstructive sleep apnea; and (5) circadian rhythm disorders associated with shift work, jet lag, and advanced or delayed sleep-phase syndromes.

Precipitating factors in insomnia commonly include stress associated with family, occupation, or health challenges. These factors are usually negative challenges such as divorce, death of a loved one, or illness, but they can also involve stress associated with positive events such as the birth of the child or retirement.[37,38]

BOX 8-1. Comorbid Primary Sleep Disorders

- Restless legs syndrome (RLS)
- Periodic limb movements in sleep (PLMS)
- Gastroesophageal reflux disease (GERD)
- Sleep-phase disorders
- Narcolepsy
- Obstructive sleep apnea (OSA)
- Nocturia

Perpetuating factors in insomnia are a range of behaviors that are intended to manage or compensate for insomnia but inadvertently exacerbate it. Examples include the following: (1) excessive waking time spent in bed; (2) an irregular sleep-wake schedule including napping and dozing; (3) excessive use of caffeine, alcohol, and other drugs; and (4) anxiety associated with attempts at controlling sleep, as well as the daytime consequences of sleeplessness. Dependence, habituation, and rebound effects associated with sedative-hypnotics, ironically, appear to be major perpetuating factors in insomnia.

Spending excessive time in bed in attempts to sleep or compensate for lost sleep results in conditioned insomnia, a negative association of the bed with wakefulness.

Conditioned insomnia is measured in terms of *sleep efficiency,* the ratio of total time spent asleep to the amount of time spent in bed. Sleep efficiency lower than 85% is considered problematic.[37,38]

Additional biomedical factors that can predispose to, precipitate, or perpetuate insomnia include iatrogenic influences of extended hospitalizations, as well as a broad range of medications that interfere with sleep such as analgesics, benzodiazepines, antidepressants, and anticholinergic medications. Beta blockers, calcium channel blockers, diuretics, and other medications may also suppress melatonin (MT) and interfere with sleep. Box 8-2 provides a more extensive listing of medications that can interfere with sleep.

Ordinary room light exposure before bedtime suppresses MT onset and duration in humans,[39] and it potentially disrupts circadian rhythms and sleep. Other sleep environmental

BOX 8-2. Medications That Can Interfere With Deep or Rapid Eye Movement Sleep

- Alcohol
- Antiarrhythmics
- Anticonvulsants
- Antihistamines
- Appetite suppressants
- Benzodiazepines
- Bronchodilators
- Caffeine
- Carbidopa/levodopa
- Corticosteroids
- Diuretics
- Decongestants
- Estrogen
- Lipophilic beta blockers
- Monoamine oxidase inhibitors
- Nicotine
- Pseudoephedrine
- Selective serotonin reuptake inhibitors
- Sedatives
- Statins
- Sympathomimetics
- Tetrahydrozoline
- Thyroid hormones
- Tricyclic antidepressants

factors such as sound, temperature, and air and bedding quality also appear to predispose to, precipitate, or perpetuate insomnia, although these factors have not received the research attention they warrant.

Pathophysiology

The most compelling pathophysiologic model for insomnia suggests a strong association with chronic cognitive-emotional hyperarousal, which may be a premorbid characteristic of the disorder.[40–42] Compared with controls, patients with insomnia have elevated heart rates,[43,44] increased body and brain metabolic rates,[45,46] elevated core body temperature,[47] increased beta and gamma electroencephalographic features, and neuroendocrine dysregulation including elevated nighttime cortisol and decreased serum MT.[48–51] Insomnia has also been linked to nocturnal sympathetic activation and overactivation of the hypothalamic-pituitary-adrenal axis.[52,53]

Chronic cognitive-emotional hyperarousal associated with elevated metabolic rate, sympathetic overactivation, and chronic inflammation is a common substrate of insomnia.

Insomnia appears to be bidirectionally associated with chronic inflammation. A single night of sleep deprivation in human subjects can alter cellular immune responses[54] and increase levels of inflammatory markers.[55–58] In contrast, inflammatory conditions have been shown to disrupt sleep by increasing pain, anxiety, and depression.[59,60] Chronic inflammation is fundamentally a process of immune system overactivation, which can be viewed as another expression of hyperarousal.

Sleepiness and sleep propensity appear to be strongly influenced by circadian core body temperature rhythms. Specific types of insomnia have been linked to specific patterns of body temperature rhythm disruption. Sleep onset difficulties have been associated with a delayed circadian temperature rhythm, early morning awakenings with an advanced circadian temperature rhythm, sleep maintenance insomnia with a nocturnally elevated core body temperature, and mixed insomnia with a 24-hour elevation of core body temperature, consistent with the hyperarousal model.[61]

Hyperarousal can be further elucidated by the widely accepted dual-process model of sleep regulation,[62] which views sleep in terms of a dynamic interaction between homeostatic and circadian processes. As the homeostatic sleep drive gradually increases through the waking day, the circadian pacemaker exerts an equal but opposite force to maintain alertness. The potential for sleep normally occurs with the nightly, rhythmic release of circadian alertness.

Although patients with insomnia are generally less sleepy during the day than normal sleepers, they appear to be significantly more fatigued (a construct independent of sleepiness).[63,64] Fatigue is very strongly associated with major depression.[65] Theoretically, fatigue, which draws one toward rest, and hyperarousal, which draws one toward activity, can result in a state of chronic isometric tension that characterizes the insomnia-depression complex. Suspended in a limbic zone between fatigue and hyperarousal, both a healthy descent into sleep and a passionate ascension into waking are inhibited.[66]

Anecdotal evidence strongly suggests that modern lifestyles are associated with widespread suppression of REM sleep. Excessive alcohol consumption, many sleep medications, and most psychiatric medications suppress REM sleep. Sleep maintenance insomnia, obstructive sleep apnea, and dream avoidance can further limit REM sleep and dreaming.[67]

Some human and animal studies confirmed that the selective deprivation of REM sleep results in its rebound in the form of reduced REM latency and disrupted deep sleep. The most common pattern of depression-related insomnia includes damaged REM sleep, most prominently reduced REM latency.[68] Could the classic psychodynamic notion that depression is "a loss of one's dreams" possibly have a literal underpinning?

Hyperarousal may be understood as circadian alertness (wakefulness) that has gone awry and overrides both normal sleep drive and the excessive daytime sleepiness one would expect with chronic insomnia.

Evaluating Insomnia

The scope of the insomnia evaluation should be comprehensive, including any and all biomedical, psychological, and environmental factors potentially affecting sleep. Box 8-3 provides a list of essential clinical interview and history topics.

Subjective measures, including the clinical interview and history, are the most critical components of the evaluation of insomnia.

The adage that as important as knowing which disease the patient has is knowing which patient has the disease is most pertinent here. It is critical to elicit each patient's personal sleep *and dream* story. Evidence from the study of bad

BOX 8-3. Clinical Interview and History

1. The presenting complaint
2. The sleep-wake routine
3. Daytime functioning and symptoms
4. Sleep conditions and routines
5. Previous treatment effects
6. Other sleep disorder symptoms
7. Comorbid medical conditions
8. Psychiatric conditions and stressors
9. Medication and substance use
10. Relevant family history

Adapted from Mai E, Buysse DJ. Insomnia: prevalence, impact, pathogenesis, differential diagnosis, and evaluation. *Sleep Med Clin.* 2008;3:167–174.

dreams and nightmares suggests that patients may respond to these dreams with sleep avoidant behaviors.[68] Eliciting the patient's basic posture toward sleep and dreams is a critical component of the insomnia evaluation. In addition to providing essential diagnostic information, doing so can engage the patient more deeply, strengthen the therapeutic alliance, and improve treatment adherence. The patient's story should be complemented with information gathered through personalized sleep logs or diaries, which should be recorded over a period of 1 to 2 weeks. Sleep logs and diaries (see Key Web Resources) provide data about sleep patterns, habits, and daytime effects, as well as related cognitive, affective, and behavior patterns. Interviewing available bed partners may also be helpful, to corroborate information about snoring and movement disorders.

Self-Report Scales

Self-report scales can be a useful adjunct to the interview for the general measurement of insomnia and specific assessment of sleepiness, fatigue, and hyperarousal. Self-report scales can be helpful in both the initial evaluation and treatment outcome measurements. The available empirically supported insomnia rating scales include the Pittsburgh Insomnia Rating Scale,[69] the Athens Insomnia Scale,[70] and the Bergen Insomnia Scale.[71] The Epworth Sleepiness Scale[72] is a brief, public domain questionnaire that provides an effective measure of current sleepiness (see Key Web Resources). Although the Epworth Sleepiness Scale is helpful as a screening device, it does not provide useful discriminative information for insomnia, although it may have value in screening for comorbid sleep apnea, narcolepsy, or other sleep disorders. Also in popular use, the Stanford Sleepiness Scale[73] offers sensitivity to patterns of daytime wakefulness. Finally, the Insomnia Severity Index[74] is a self-report scale that assesses insomnia type, severity, and impact on daily life.

Objective Measures

Polysomnography (PSG), as its name implies, measures multiple sleep parameters including indices of respiration, electroencephalography, and movement and muscle tone. Widely considered the gold standard of sleep evaluation, PSG is not, however, routinely indicated for insomnia because it provides little information useful for diagnosis or treatment.

PSG may be necessary to rule out periodic limb movements in sleep, obstructive sleep apnea, or other conditions underlying persistent insomnia.[75] With advances in remote monitoring technologies, home-based PSG is on the increase. Other home use devices such as actigraphy allow for longitudinal studies that can reveal useful information about circadian rhythms and other sleep parameters.[5]

Integrative Therapy

"The best cure for insomnia," said W.C. Fields, "is sleep." A common temptation among both patients and practitioners is to oversimplify the causes and treatment of insomnia. As suggested earlier, treatment of insomnia calls for lifestyle change. Promoting general health with proper nutrition, exercise, and psychological well-being provides an essential backdrop to the comprehensive integrative treatment of insomnia. No magic bullets exist. Treatment usually requires a comprehensive, multicomponent approach that addresses all 3 P factors contributing to the noise of hyperarousal, including comorbid medical and psychiatric conditions. Ongoing monitoring and evaluation using subjective reports, as well as the Epworth Sleepiness Scale and the Fatigue Severity Scale , should be an integral part of treatment.

> If there is a secret to a good night's sleep, it is a good day's waking.

From the patient's perspective, interventions for insomnia can be classified in terms of two basic approaches: *taking something to sleep* and *letting go of something to sleep.* Patients who struggle with insomnia are inclined to consume sleeping medication, alcohol, warm milk, herbal teas, MT, botanicals, nutraceuticals, a wide range of comfort foods, and more. The fundamental belief underlying this approach is that insomnia results from *insufficient sleepiness* that can be ramped up with sleep-promoting ingestibles.

Sleep Promotion: Principles of Taking Something to Sleep

That good general health practices, including adequate exercise, good nutrition, and effective stress management, would promote healthy sleep is a safe assumption. When challenged by insomnia, conventional and CAM approaches offer an array of options for *taking something to sleep*.

Situations certainly exist (e.g., personal or medical crises) for which taking something to sleep may be indicated. Short-term use of a safe alternative will minimize the risk of dependence and of erosion of sleep self-efficacy. With the possible exception of MT, which regulates circadian rhythms, both conventional and alternative sleep aids do little to address the underlying noise of hyperarousal.

> Most chronic insomnia results not from insufficient sleepiness, but from excessive wakefulness. *Letting go of something to sleep* refers to an approach concerned with reducing the noise of this excessive wakefulness.

Pharmaceuticals

Epidemiologic studies suggest that over-the-counter antihistamines, alcohol, and prescription medications are the most common treatments used by patients with insomnia. Data suggesting that sedative-hypnotics can be effective in ameliorating insomnia raise serious questions about pharmaceutical industry influence and bias. At best, positive outcomes found are negligible, and harmful side effects are substantial.[76]

Box 8-4 provides a list of the most common U.S. Food and Drug Administration–approved and off-label medications used to treat insomnia. Long-term use of most of these medications is associated with serious side effects (Box 8-5). Studies raised concerns that the use of hypnotic agents may increase the risk of cancer.[77,78] Additional findings revealed a 10% to 15% increase in mortality among occasional users of sleeping pills and a 25% increase in mortality among nightly users of these drugs.[79]

BOX 8-4. Common Medications for Insomnia

Over-the-Counter Agents
- Diphenhydramine
- Doxylamine

Benzodiazepines
- Estazolam
- Flurazepam
- Quazepam
- Temazepam
- Triazolam

Nonbenzodiazepine Hypnotics
- Eszopiclone
- Zaleplon
- Zolpidem

Melatonin Receptor Agonists
- Ramelteon

Antidepressants (Tricyclic or Tetracyclic Antidepressants)
- Amitriptyline
- Doxepin
- Trazodone
- Mirtazapine

Other Agents
- Clonidine
- Gabapentin
- Quetiapine
- Sodium oxybate (gamma-hydroxybutyric acid sodium salt [GHB])

BOX 8-5. Common Side Effects of Sedative-Hypnotics

- Dependence
- Tolerance
- Damaged sleep architecture
- Diminished deep sleep
- Rapid eye movement suppression
- Parasomnias
- Anterograde amnesia
- Morning hangover
- Undermined self-efficacy
- Rebound insomnia with discontinuation
- Increased risk of falls
- Cognitive impairment
- Symptom suppression
- Increased mortality

In the end, most sleep medications do little more than temporarily suppress the neurophysiologic symptoms of hyperarousal—and they do so with risk.

Despite these concerns, an unprecedented surge has occurred in the use of sleeping medications since 2000.[80] In addition are growing concerns about substantial increases in related polypharmaceutical practices.[81] Why is this the case? This approach is driven by two faulty presumptions: (1) the common belief that insomnia is primarily the result of insufficient sleepiness, rather than excessive noise; and (2) a culture-wide, naive conceptualization of healthy sleep that equates it with a knockout.

Supplements

Numerous botanical sleep aids have been in use around the globe for centuries. In contrast to conventional sleep medications, CAM sleep aids, including botanical medicines as well as nutraceuticals, provide less of a knockout and more of a gentle assist to sleep with significantly fewer adverse effects. Although L-tryptophan and 5-hydroxytryptophan (5-HTP), precursors to serotonin and MT, are widely used, reports about the effectiveness of these agents in treating insomnia are mixed. Kava has empirical support for use with insomnia, but findings have raised serious questions about its safety.[82] More rigorous research into such alternatives has been hindered by limited financial incentives, conventional sleep medicine biases, and the natural complexity of many botanicals. Of the many alternatives to conventional sleep medications available, MT, valerian, and hops, reviewed in greater detail, are in common use and are generally regarded as safe.

Melatonin

Synthesized from tryptophan via 5-HTP and serotonin, MT is a neurohormone found in most living organisms. MT production is normally inhibited during the day by exposure to the blue wavelength of light and is disinhibited by dim light and darkness.[83] In addition to regulating circadian rhythms, MT mediates sleep and dreaming, decreases nocturnal body temperature, and has antiinflammatory, immune-modulating, and free-radical scavenging effects.[84] The suppression of endogenous MT through overexposure to light at night,[85–87] in advancing age,[88] and by common substances and medications (e.g., caffeine, nicotine, alcohol, beta blockers, diuretics, calcium channel blockers, and over-the-counter analgesics[89]) may be a factor in insomnia, depression, and cancer. A growing number of animal, human, and population studies suggest that MT may have oncostatic properties.[90,91] Tetrahydrocannabinol (THC) has been shown to cause a 400-fold increase in endogenous MT.[92] Other findings suggest that high doses of MT may actually disrupt sleep.[93] Anecdotal reports suggest that MT may heighten awareness of dreams. Doses as high as 50 mg can dramatically increase REM sleep and dreams. Certain psychoactive drugs, including cannabis and lysergic acid diethylamide(LSD), increase MT synthesis and may emulate MT activity in the waking state as a "waking dream."[94] Although an Agency for Healthcare Research and Quality report suggested that MT had limited effectiveness in treating insomnia,[95] a more recent meta-analysis of the effects of exogenous MT confirmed its beneficial effects on sleep onset latency, total sleep time, and sleep efficiency.[96]

Preparations

MT is available in oral, sublingual, and transdermal immediate or sustained-release formulations. Sublingual MT can avoid first-pass liver metabolism, thereby likely resulting in more reliable serum levels. Given its short half-life

(approximately 0.5 to 2 hours) sustained-release forms are more likely to maintain effective levels throughout the sleep period.

Dosage
The dose is 0.3 to 0.5 mg for adults.[96]

Precautions
MT generally has a good safety profile. One meta-analysis found adverse effects uncommon and more likely with high doses.[97,98]

Valerian Root (Valeriana officinalis)
Valerian is a sedating botanical with purported anxiolytic and hypnotic properties. In contrast to prescription sedative-hypnotics, valerian does not impair psychomotor or cognitive performance.[99,100] One review concluded that valerian was safe but did not have significant effects on sleep.[101] A second study concluded that valerian appeared effective for mild to moderate insomnia.[102] Valerian is nonaddictive, resulting in no withdrawal symptoms on discontinuation. Valerian may sometimes require weeks of nightly use before producing an effect.[103]

Preparation
Valerian is available as whole powdered root and an aqueous or ethanolic extract standardized to 0.8% valerenic acids. High-quality products have an unpleasant odor, which confirms potency.

Dosage
For adults: 300 to 900 mg standardized extract of 0.8% valerenic acid or as a tea of 2 to 3 g of dried root steeped for 10 to 15 minutes and taken 30 to 120 minutes before bedtime for 2 to 4 weeks to assess effectiveness.

Precautions
Valerian has a good safety profile.[101] Possible herb-drug interactions can increase sedation or alter drug metabolism. Caution should be exercised during pregnancy or in patients with a history of liver disease.

Hops (Humulus lupulus)
Hops refers to the flower clusters atop the *Humulus lupulus*. Best known for its use in beer, hops has also been used in traditional preparations to treat a broad range of conditions, including insomnia. The German Commission E Monographs listed hops as an approved remedy for insomnia.[103] More recent findings showed a modest hypnotic effect for a valerian-hops combination for treating adult insomnia.[104] Hops is believed to have antispasmodic properties that can help reduce muscle tension and promote relaxation.[105] Additional evidence suggests that hops may be beneficial in alleviating hot flashes and other menopausal symptoms.[106]

Dosage
Prescribe 5:1 ethanolic extract, one-half to one dropper full, 30 to 60 minutes before bedtime.

Precautions
Although no evidence indicates toxicity in medicinal dosages, avoiding the use of hops in pregnancy may be advisable.

Noise Reduction Approach to Insomnia
The breadth of an integrative approach to insomnia treatment can overwhelm patients. Too often, the misguided temptation is to reduce sophisticated integrated strategies that support a shift in consciousness and lifestyle to a simple sleep hygiene checklist. The Noise Reduction Approach for Insomnia (NRAI)[107] provides a comprehensive and face valid framework for patients by organizing complex and numerous etiologic and therapeutic recommendations into an understandable and manageable system. More specifically, the NRAI uses a body, mind, and bed framework in which body refers to biomedical factors, mind refers to psychological factors, and bed refers to sleep environmental factors.

The NRAI conceptualizes healthy sleep in terms of a *sleepiness-to-noise ratio*, in which *sleepiness* refers to the propensity to sleep and *noise* refers to any kind of stimulation that interferes with sleep. Noise is used to denote the subjective experience of hyperarousal. Both sleepiness and noise can derive from body, mind, or bed factors. Insomnia can result from insufficient sleepiness caused by daytime sleep or dozing, inadequate activity, sedating medications, and circadian rhythm disorders. For the most part, however, insomnia results from excessive noise.

Noise resulting from body, mind, or bed factors is cumulative. For example, the stimulating effects of ordinary work stress or of 2 cups of coffee or minor reflux alone may not interfere with sleep, but their cumulative effect could well reach a threshold that does. Insomnia occurs when a person's noise levels exceed his or her sleepiness, whereas sleep occurs when noise levels fall to less than the threshold of sleepiness. Because the propensity to sleep is our natural default, the NRAI is less concerned with promoting sleepiness and more concerned with the identification and management of factors that produce noise.

Reducing Body Noise
The essential focus of body noise reduction is decreasing physiologic manifestations of hyperarousal. In addition to the importance of promoting basic health through exercise, nutrition, and stress management mentioned earlier, reducing body noise involves attending to a range of biomedical and lifestyle factors that commonly disrupt sleep. Box 8-6 summarizes the main components of reducing body noise.

Simultaneously addressing all comorbid disorders is essential. This is especially true for depression, primary sleep disorders, and disorders characterized by pain and discomfort. The reasonable assumption is that doing so may have a synergistic effect. For example, reducing pain will obviously improve sleep, but improving deep and REM sleep can raise pain thresholds by 60% and 200%, respectively.[108]

BOX 8-6. Reducing Body Noise

- Manage all comorbid conditions, especially other sleep disorders, depression, and chronic pain.
- Manage the sleep side effects of medications.
- Manage alcohol and caffeine use.
- Manage symptoms of women's health issues (e.g., premenstrual dysphoric disorder, menopause).

Managing the sleep disruptive side effects of medications (see Box 8-2) discussed earlier will help reduce body noise, as will managing caffeine and alcohol. Although considerable individual variation exists, the half-life of caffeine is approximately 5 hours and can range from 2 hours for tobacco smokers to more than 10 hours for women who are pregnant or using oral contraceptives. Consuming two 8-ounce cups of drip coffee within an hour of morning awakening will leave approximately 35 mg of caffeine, the amount found in a cola drink, in one's system near bedtime. "Energy drinks," which contain 2 to 500 mg of caffeine per serving, have soared in popularity. Because the depressant effects of alcohol can facilitate sleep onset, it is widely used as a sleep aid. Insomnia increases the risk of relapse in patients recovering from alcoholism.[109] Alcohol, especially if consumed without food or near bedtime, commonly compromises sleep quality and results in arousals early in the night.

Common women's health concerns, including premenstrual syndrome and premenstrual dysphoric disorder,[110] pregnancy,[111] and menopause,[112] are strongly linked to insomnia. These conditions and any associated insomnia are most effectively addressed independently. Additionally, MT may be helpful in managing premenstrual syndrome and premenstrual dysphoric disorder,[113,114] possibly through regulating rhythmic features of the disorder. Menopausal symptoms, particularly hot flashes, are commonly blamed for repeated awakenings. Disrupted sleep, however, is not an inevitable consequence of hot flashes.[115]

Menopausal symptoms likely function as precipitating factors of insomnia for women who were previously predisposed to it.

Reducing Mind Noise

The essential focus of mind noise reduction is decreasing psychological and behavioral expressions of hyperarousal. This approach is largely centered on the CBT-I set of strategies. CBT-I combines cognitive restructuring, which addresses insomnia-related dysfunctional thoughts and beliefs, with behavioral interventions including sleep hygiene education, stimulus control therapy (SCT), sleep restriction therapy (SRT), and relaxation practices. CBT-I also addresses common maladaptive coping reactions to insomnia that function as perpetuating factors. In addition to the treatment of individuals, CBT-I can be used in group settings, as well as through automated and Web-based formats. Box 8-7 provides a list of mind noise reduction therapies. This list primarily contains CBT-I components, but it is expanded to include dream health, which is not typically addressed in conventional treatment.

Compelling evidence indicates the effectiveness of CBT-I for primary insomnia,[5,116,117] and support for CBT-I in comorbid insomnia is growing.[22] CBT-I was shown to be at least as effective as prescription medications in the short-term treatment of chronic insomnia, with beneficial effects that extended well beyond the completion of treatment and no evidence of adverse effects.[118] Patients with insomnia who were treated with CBT-I experienced greater increases in deep sleep and decreases in wake time than those treated with zopiclone (Canadian hypnotic similar to eszopiclone). These benefits were still present at a 6-month follow-up, in contrast to patients treated with zopiclone, who showed no ongoing benefits of treatment.[119] CBT-I alone was also found to be no less effective than CBT-I paired with zolpidem.[120] CBT-I has also been shown to enhance depression outcomes for patients with comorbid insomnia.[121]

Sleep Hygiene

Sleep hygiene refers to a list of various behavioral and environmental recommendations that promote healthy sleep.[122] These can include most of the suggestions reviewed earlier, such as managing substances, regulating one's sleep-wake schedule, obtaining exercise, and creating an environment conducive to sleep. Sleep hygiene has not been demonstrated effective as a stand-alone intervention, **al**though most sleep specialists believe that it can be an effective aid to a multicomponent treatment approach.

Cognitive Restructuring

Cognitive restructuring techniques systematically review, reconsider, and replace thoughts and beliefs that trigger sleep disruptive anxiety and rumination. Box 8-8 provides examples of common dysfunctional thoughts about sleep. These thoughts are dysfunctional because they distort the truth, set up unrealistic expectations, and inevitably trigger anxiety. For example, the belief that "I can and must get myself to sleep" is nearly ubiquitous among patients with insomnia. Because it implies that falling asleep is under one's conscious control, this belief leads to excessive sleep effort, which then backfires by increasing arousal. Similarly, the common belief that "I should always sleep through the night" sets the stage for a reflexive reaction of frustration, disappointment, and even self-recrimination with wakefulness after sleep onset. In reality, what wakes one up is not necessarily what keeps one awake. Frequently, our strong reaction to the awakening, which is based on a dysfunctional belief, is the real problem. Similar cycles of disappointment, frustration, arousal, and anxiety can ensue from comparable dysfunctional thoughts and beliefs, and their effects can be cumulative.

BOX 8-7. Mind Noise Reduction (Cognitive-Behavioral Therapy for Insomnia)

- Sleep hygiene education
- Cognitive restructuring
- Stimulus control therapy
- Sleep restriction therapy
- Relaxation practices
- Restoring dream health

BOX 8-8. Dysfunctional Thoughts About Sleep

- I should sleep at least 8 hours every night.
- I should fall asleep quickly.
- I should always sleep through the night.
- I can and must get myself to sleep.
- I should just rest in bed if I cannot sleep.
- I will have a terrible day if I do not sleep well.

BOX 8-9. Stimulus Control Therapy Instructions

1. Get into bed with the intention to sleep only when sleepy.
2. Use the bed and bedroom only for sleep and sexual activity.
3. Do not watch the clock.
4. If awake after approximately 15 minutes, leave the bedroom, engage in restful activity, and return to bed when sleepy. Repeat as needed.
5. Keep a fixed morning rising time irrespective of the amount of sleep obtained.
6. Avoid napping until nighttime sleep is normal.

Stimulus Control and Sleep Restriction Therapies

Both SCT and SRT are effective behavioral interventions for managing conditioned insomnia and reducing sleep efficiency.[123,124] Both approaches systematically minimize the amount of waking time spent in bed in an effort to increase sleep efficiency. SCT does so through self-monitoring and staying out of bed when sleepless. Box 8-9 provides basic SCT instructions.

SRT requires patients to limit the amount of time in bed to their average total sleep time established at baseline. Time in bed is then gradually increased as sleep efficiency improves. The administration of SRT is challenging to both patients and clinicians and should be used only by professionals trained in this intervention. Both SCT and SRT may be contraindicated in patients with sleep apnea, mania, epilepsy, and parasomnias and those at risk of falling.

Relaxation Practices

Relaxation practices, which have been included under the rubric of CBT-I, are useful in reducing sympathetic tone, decreasing mind noise, and familiarizing patients with the waking state of rest that serves as a transition to sleep. A myriad of effective techniques are available (Box 8-10), and they should be matched to patients' interests and personalities. Breathing exercises are among the easiest and most portable practices.[125] Early research combining mindfulness meditation and CBT-I showed a reduction of sleep-related arousals.[126]

Restoring Dream Health

In contrast to conventional approaches, integrative therapies for insomnia are concerned with the restoration of dream health. From antiquity through recent times, dreams have been revered as rich sources of psychological insight, healing, and spirituality. Healthy REM sleep and dreaming are critical to the consolidation of procedural memory, as well as to the processing of emotion.[127]

BOX 8-10. Relaxation Practices

- Breathing exercises
- Mindfulness meditation
- Progressive muscular relaxation
- Gentle yoga/yoga nidra
- Self-hypnosis
- Guided imagery
- Biofeedback and neurofeedback
- Transcranial stimulation

BOX 8-11. Promoting Healthy Dreaming

- Identify and manage dream thieves.
- Arise slowly in the morning to enhance recall.
- Journal or talk about dreams.
- Join a dream circle or support group.
- Note dreamlike aspects of waking life.

Trying to promote healthy sleep without considering dreams is like trying to promote healthy nutrition without regard for the taste of food.

Given the frequency of bad dreams and the common belief that high-quality sleep is devoid of dreaming, it is not surprising when patients with insomnia state that they would prefer not to dream at all. Dream avoidance, evident in Hamlet's classic remark, "To sleep perchance to dream…," is clearly seen in patients with frequent nightmares and can result in sleep avoidance and arousals.[68]

Box 8-11 offers recommendations for promoting healthy dreaming. Simply asking patients whether they have dream recall can be an essential first step in sensitizing them to the importance of dreaming. In addition to avoiding dream thieves—REM-suppressant drugs, substances, and activities—it may be useful intentionally to recall and attend to one's dreams.[128] Because we usually awaken from dreams, arising slowly in the morning with a receptive attitude can improve recall. Bridging dream experiences to waking life through journaling, discussion, and noting the "waking dream," dreamlike aspects of ordinary waking life, can also be helpful.

Reducing Bed Noise

Although the sleep environment can have a critical impact on sleep, it has not yet received the attention it warrants. Recognizing the bedroom as not only a physical location, but also a temporal and psychological space, the goals of bed noise reduction include (1) minimizing the toxic burden of the physical environment, (2) regulating circadian rhythms through entrainment with light and darkness, and (3) creating a sense of sanctuary that is free of ordinary waking life stimulation.

A Healthy Sleep Environment

Sensitivities or allergies to bedroom irritants or toxins can be pronounced or subtle. Awareness is increasing, as reflected in the growth of the natural mattress industry, of the importance of an environmentally friendly and toxin-free bedroom. In addition to recommendations to keep the bedroom quiet and cool (no hotter than 68 °F), compelling arguments have been made on behalf of "green" (organic) beds and bedding and clean bedroom air.[128,129] Box 8-12 lists common sources of bedroom toxicity that should be evaluated and addressed to improve sleep. Bedroom air quality can be improved with

BOX 8-12. Common Sources of Bedroom Toxicity

- Pesticide-laden fabrics in bed and bedding
- Synthetic materials in mattresses and pillows
- Outgassing from furnishings, floors, walls, or carpeting
- Polluted indoor air
- Electromagnetic fields

high-efficiency particulate air (HEPA) filtration systems as well as with varieties of ordinary houseplants. Because electromagnetic fields can suppress endogenous MT,[130] it is advisable to clear them from the sleep area.

Regulation of Circadian Rhythms

Time can be conceptualized in two distinct ways. Ordinary waking life is structured by linear or clock time. Human biology, however, including sleep-wake cycles, operates on cyclic time, most evident in circadian rhythms. Nature's darkness may invite us to sleep, whereas culture, with its vast array of evening distractions, encourages us to stay awake.[70]

Sleep disorders, in part, are chronic skirmishes between nature and culture—between linear and cyclic time.

A factor that regulates circadian rhythms is called a Zeitgeber (from the German: "time giver"). Such factors include temporal patterns of feeding, exercise, and socialization, although the most potent ones are exposure to light and darkness. Bright light signals the start of morning, whereas dim light or darkness conveys a sense of night to the brain's circadian pacemaker. Sleep-phase disorders, most commonly advanced or delayed sleep-phase syndromes, are frequent predisposing factors in the origin of insomnia. These disorders are usually treated by systematically manipulating exposure to light and darkness to restructure the position of the patient's sleep phase within the circadian cycle.

Regulating circadian rhythms (Box 8-13) is a critical component of treating insomnia. Maintaining a regular sleep-wake pattern 7 days per week is essential to promoting a healthy sleep rhythm. Bright light exposure for approximately 30 to 45 minutes shortly after morning arising is a most potent Zeitgeber,[131] as well as a potential antidepressant.[132] When natural light is not an option, light boxes that provide comparable lux levels are commercially available. Exposure to higher lux levels of natural light throughout the waking day may also reduce daytime sleepiness.[133]

Given the relentless demands of daily living, dusk simulation practices—dimming lights for 2 to 3 hours before bedtime—are particularly challenging. Dim light diminishes the blue wavelength of light prominent in natural daylight, artificial lighting, and computer and television screens. The blue wavelength of light has been shown to signal the brain to suppress MT production, thus delaying the start of the sleep phase.[134] Newer blue light filtration technology in the form of goggles and light bulbs can provide illumination without suppressing MT (see Key Web Resources) and can minimize the negative impact of reading or watching television.

BOX 8-13. Regulating Circadian Rhythms

- Use phototherapy, with timed exposure to light and darkness.
- Maintain a regular sleep-wake pattern.
- Simulate dusk by dimming the lights or using blue blocker technology 1 to 2 hours before sleep.
- Supplement with melatonin.
- Sleep in total darkness.

BOX 8-14. Creating a Sense of Sanctuary

- Establish the bedroom as a stress-free and work-free zone.
- Limit exposure to stressful imagery from books, television, and radio.
- Conceal ready access to clocks.
- Establish a sense of personal safety.
- Maintain peace with your sleep partner.

Because even small amounts of light can trickle across closed eyelids and suppress melatonin, sleeping in total darkness or with a sleep mask is ideal.

Creating a Sense of Sanctuary

For many who struggle with insomnia, the bedroom is a place of work, entertainment, and other associations that may be antagonistic to sleep. Reimagining the bedroom as a sanctuary (Box 8-14), a place of retreat from the world of waking, is helpful. To do so, the bedroom should be a work-free, stress-free, and clock-free zone. Exposure to stressful imagery from reading material, television, or radio should be avoided. Clock watching is a common compulsion among patients with insomnia and serves only to exacerbate sleeplessness by tethering them to the waking world of linear time. Establishing a deep sense of personal or psychological safety in the bedroom is also important. For some patients, this may mean installing a security system, whereas for others it may mean keeping a religious icon on the bed stand.

The percentage of couples sleeping apart, largely as a result of sleep disorders, has increased dramatically and now stands at 23%.[135] Sleeping apart is associated with negative effects on the relationship.[136] Addressing sleep symptoms (e.g., snoring or periodic limb movements in sleep) that may provoke one's sleep partner is helpful. Differing sleep environment preferences can also be negotiated. Creating a sense of sanctuary in the bedroom encourages an essential shift from waking to *night consciousness*.[70]

Fundamentally, insomnia is associated with inadvertently smuggling waking consciousness into the world of night and sleep.

Behavioral Sleep Medicine Specialists

Although some components of CBT-I can be implemented by patients on their own, this complex therapy generally requires levels of specialized training. The stepped care model for CBT-I recommends a hierarchy of five increasing levels of interventions associated with clinician expertise and patients' needs (Fig. 8-1). Behavioral sleep medicine specialists, formally trained and certified in the use of CBT-I, are a small but steadily growing and key professional resource in this model (see Key Web Resources).

Spirituality

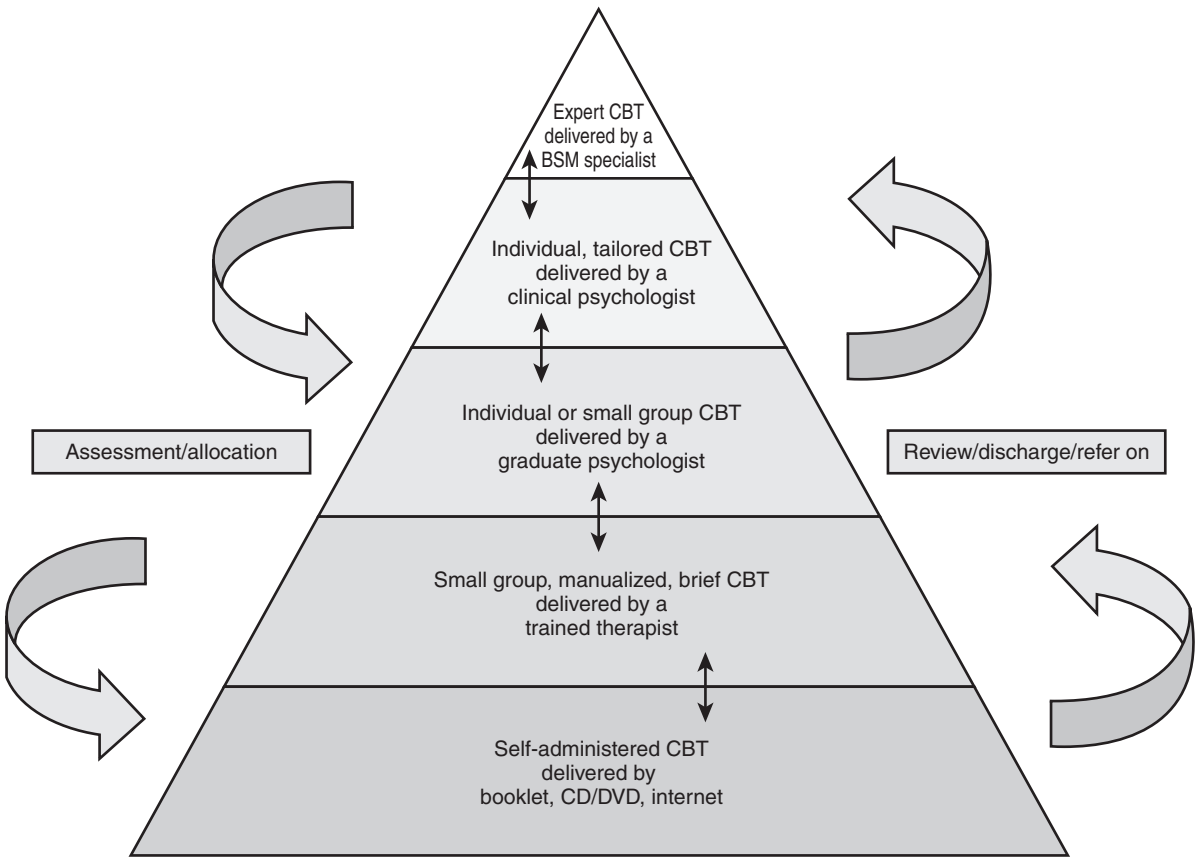
Sleep has historically been viewed as a deeply personal and even spiritual experience.[70] World sacred traditions have typically viewed dreaming as a portal to spirituality. Some traditions have established elaborate spiritual practices around sleep and dreams. One of the central themes found in spiritual perspectives of sleep is an emphasis on the need to let go or surrender to sleep. At their core, most CBT-I techniques reflect sensitivity to this central process of letting go. With this recognition, the place of a personal evening ritual in healing insomnia becomes evident. The many recommendations commonly offered the patient with insomnia can be best organized and implemented in the context of such ritual. Slowing down, dimming the lights, practicing relaxation techniques, journaling with a cup of soporific tea, and surrendering to sleep are much more than clinical recommendations. They are practices that will facilitate a shift not only in lifestyle, but also in consciousness.

Prevention Prescription

Preventing insomnia by intentionally maintaining healthy sleep is considerably less daunting than treating it.

- Recognize the value and joy of sleep.
- Attend to and journal dreams.
- Engage in relaxation practices daily.
- Obtain adequate regular exercise.
- Obtain daily exposure to morning light.
- Limit the use of stimulants and sedatives.
- Maintain a regular sleep-wake schedule.
- Dim lights or use blue blocker tools 1 to 2 hours before sleep.
- Sleep in total darkness or use a sleep mask.
- Consider low-dose melatonin replacement therapy.

FIGURE 8-1
A stepped care model for cognitive-behavioral therapy for insomnia (CBT-I). This evidence-based model for CBT illustrates how patients may be allocated to resources. *Arrows* represent referral movements. BSM, behavioral sleep medicine. (From Espie CA. "Stepped care": a health technology solution for delivering cognitive behavioral therapy as a first line insomnia treatment. *Sleep*. 2009;32:1549–1558.)



Therapeutic Review

Reduce Body Noise

- Directly address all comorbid conditions, especially primary sleep disorders, depression, chronic pain, and women's health issues. Evaluate and manage sleep side effects of all medications (see Box 8-2). Evaluate and manage alcohol, caffeine, and other stimulant use. B1
- Melatonin: 0.3 to 0.5 mg at bedtime, especially if the patient may have an associated circadian rhythm disorder A1
- Avoid sedative-hypnotics , and use complementary and alternative medicine sleep aids as needed, preferably on a short-term (2- to 4-week) basis. Consider one or a combination of the following: A2
  - Valerian, for adults: 300 to 900 mg standardized extract of 0.8% valerenic acid or as a tea of 2 to 3 g of dried root steeped for 10 to 15 minutes and taken 30 to 120 minutes before bedtime for 2 to 4 weeks to assess effectiveness B2
  - Hops: in a 5:1 ethanolic extract, ½ to 1 dropper full, 30 to 60 minutes before bedtime C1

Reduce Mind Noise

- Encourage patients to select and engage in a daily relaxation practice. The 4-7-8 relaxing breath exercise (Box 8-15) is an easy and effective option. A1
- Use stimulus control therapy for sleep efficiency lower than 85%. A1
- Evaluate and discuss basic dysfunctional beliefs and thoughts about sleep. Refer the patient to a behavioral sleep medicine specialist for more elaborate cognitive restructuring therapy as needed. A1

BOX 8-15. 4:7:8 Relaxing Breath Exercise

1. Place the tip of your tongue against the ridge behind your front teeth and exhale completely through your mouth.
2. Inhale through your nose for a count of 4.
3. Hold your breath for a count of 7.
4. Exhale through your mouth with a swooshing sound to the count of 8.
5. Repeat this cycle three more times for a total of four breaths.

The ratio of 4:7:8 is key, not the actual time spent on each breath cycle. Practice at least twice daily, beginning with no more than four breath cycles at one time for the first month and increasing to eight breath cycles afterward if desired. This exercise can be used to increase presleep relaxation and to facilitate sleep onset in bed.

- Encourage dream recall by limiting "dream thieves," and promote daily dream journaling and participation in dream support groups. Refer patients with chronic nightmares to a behavioral sleep specialist for image rehearsal therapy. A1

Reduce Bed Noise

- Recommend reduction of bedroom toxicity from beds, bedding, and furnishings, as well as air filtration with high-efficiency particulate air (HEPA) filters or houseplants. Encourage evaluation of and protection from electromagnetic fields. C1
- Urge the patient to maintain a regular sleep-wake schedule, including on weekends. The patient should simulate dusk by dimming lights or using blue blocker technology (see Key Web Resources) 1 to 2 hours before sleep, and sleep in total darkness. Exposure to morning light is important. B1
- Encourage patients to create a sense of sanctuary by establishing the bedroom as a stress-free and work-free zone, limiting exposure to stressful imagery and clocks, ensuring a sense of personal safety, and maintaining peace with bed partners. C1

KEY WEB RESOURCES

American Academy of Sleep Medicine: http://www.aasmnet.org/	This Web site provides professional information and resources for sleep medicine.
Society of Behavioral Sleep Medicine: http://www.behavioralsleep.org/	This official Web site includes links to lists of certified behavioral sleep medicine specialists.
Epworth Sleepiness Scale: http://epworthsleepinessscale.com/	This official Web site provides an overview of and access to the Epworth Sleepiness Scale.
Fatigue Severity Scale: http://www.medscape.org/viewarticle/472869	This Medscape Web site provides information about fatigue and the Fatigue Severity Scale.
Sleep diary forms: http://www.sleepeducation.com/pdf/sleepdiary.pdf or http://sleep.buffalo.edu/sleepdiary.pdf	These documents assist patients in collecting and monitoring data essential for initial and ongoing evaluation.

The Dark Side of Sleeping Pills: http://www.darksideofsleepingpills.com/all.html	Dr. Daniel Kripke's complementary e-book discusses the risks of sedative-hypnotics.
Low Blue Lights: https://www.lowbluelights.com/index.asp	This commercial Web site provides information, research, and products related to blue light filtering technology.
SHUTi (Sleep Health Using the Internet): http://www.shuti.net/	This is an automated Web-based program of cognitive-behavioral therapy for insomnia that was developed by the University of Virginia.
Dr. R. Naiman: http://www.drnaiman.com/	This Web site promotes the development of integrative sleep medicine.

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Chapter 9

Alzheimer Disease

Dharma Singh Khalsa, MD

Renowned gerontologist Ken Dychtwald, PhD,[1] has stated, "It's easy to overlook the remarkableness of aging." According to Dychtwald, throughout 99% of human history, the average life expectancy at birth was less than 18 years of age. In the past, people did not age; they died. Infectious diseases, accidents, violence, and other hazards often brought life to an early close. Until very recently, therefore, people were much more likely to die young than to live into old age.

Beginning in the last century, however, something unprecedented happened. Thanks to advances in sanitation, public health, food science, pharmacy, surgery, medicine, and, more recently, wellness-oriented lifestyles, the number of people in the United States who were more than 65 years old multiplied 11-fold during the twentieth century, from 3 million to 33 million. According to the U.S. Bureau of the Census, by the year 2035 some 70 million people—60 million of whom will be older baby boomers—will be 65 years old and older. Although we should applaud the increase in life span enjoyed by many people, a major problem is associated with it: with increasing longevity comes an increasing incidence of cognitive decline, dementia, and Alzheimer disease (AD).[2]

In 2009, 5.3 million people had AD in the United States. The costs were $148 billion a year, and more than 9.9 million people were unpaid caregivers. The 2010 report showed these figures to be increased to $172 billion in costs and 10.9 million unpaid caregivers. AD was the sixth leading cause of death in 2009, although more recently it was reported to be the seventh.

More telling however, is that AD is now the number one worry of aging baby boomers, thus surpassing cancer and heart disease. The integrative medical model is based on good science and good sense. Conventionalists, who focus narrowly on this gene or that neurotransmitter or a plaque or tangle, often overlook the fact that the brain is a flesh-and-blood organ. Because the brain is flesh and blood, like the heart, for example, it responds to health-promoting interventions such as improved blood flow, good nutrition, stress reduction, and exercise. An integrative approach brings surviving neurons to their optimal potential; therefore, using it can reverse many of the symptoms of AD and slow its progression.

Like many degenerative diseases associated with aging, memory loss spans a spectrum of signs, symptoms, causes, pathogenesis, and prognosis. Although the term memory loss does not imply a specific cause, it signifies a clinical syndrome characterized by the acquired loss of cognitive and emotional abilities that is severe enough to interfere with daily functioning and quality of life.

Pathophysiology

The term age-associated memory impairment was initially used to describe the minor memory difficulties that were previously believed to accompany the aging process. This impairment is now known to exist in patients as young as 50 years of age. An at-risk population with both subjective cognitive impairment (SCI) and mild cognitive impairment (MCI) that converts to AD at a rate of approximately 12% per year has been identified and is discussed later in the chapter.[3] Moreover, Lupien et al[4] noted a conversion to AD in subjects with cortisol-induced, stress-related memory loss. This chapter includes this emerging etiology for cognitive dysfunction in the discussion on chronic stress. Neuroscientists now agree that memory loss is a disease that begins to attack the brain 30 to 40 years before symptoms appear. Snowden et al[5] showed that nuns who displayed linguistic difficulties in their 20s had a higher incidence of AD later in life. Using positron emission tomographic scans, Reimen et al[6] noted that patients can have lesions consistent with severe cognitive decline years before symptoms are seen. It is becoming increasingly clear that AD is an insidious process similar to other chronic diseases such as heart disease, and therefore AD has lifestyle management implications.

Plaques or Tangles?

For a century, scientists have wondered which of the brain lesions associated with AD are more important—the plaques that litter the empty spaces between nerve cells or the stringy tangles that erupt from within the cell. An enzyme called

secretase on the surface of the brain cell makes a protein called beta amyloid. Patients with AD have too much amyloid, which forms the so-called plaques on the outside of brain cells. These plaques grow so dense that they trigger an inflammatory reaction from the brain's immune system that kills nerve cells. Among the powerful weapons the immune system brings to bear are oxygen free radicals, and this helps explain why antioxidants such as vitamin E are helpful.

A strong piece of evidence supporting the beta amyloid theory is that significant numbers of mice genetically engineered to develop plaques remained plaque free compared with controls after vaccination with a fragment of beta amyloid. Researchers then vaccinated 1-year-old mice whose brains were riddled with plaques. These mice became plaque free. Unfortunately, this vaccine has not been successful in tests on humans.

The second major school of thought among neuroscientists concerns tau, a molecule that acts much like the ties on a railroad track. Tau assembles microtubules that support the structure of the nerve cell. Chemical changes in the nerve cell cause the tau molecules to change shape so that they no longer hold the microtubule in place. The "railroad ties" begin to twist and tangle, causing neuronal cell death.

Many questions remain. Are the plaques and tangles seen in AD causative or simply tombstones? Does some still unknown biochemical event precede the formation of plaques and tangles and cause the inflammatory death knell? AD, no less than heart disease, certainly has multiple causes. As in aging itself, risk factors affect the development of AD. This means that lifestyle choices, especially relating to stress management, are critically important.

Risk Factors for Memory Loss

Hard Risk Factors

- *Increased age:* This is the most important risk factor. Ten percent of persons 65 years old develop AD. The incidence at age 85 years is as high as 50%.
- *Family history:* The risk of developing AD is increased threefold to fourfold if a first-degree relative has the disease.
- *Genetic factors:* Individuals with two *APOE4* genes on chromosome 19 are at least eight times more likely to develop AD. Gatz et al[7] noted that the *APOE4* gene exerts its maximal effect on people in their 60s and is a strong predictor of AD. The *APOE4* gene is also a strong predictor for heart disease. More recently, investigators have revealed that people with two *APOE4* genes begin developing cognitive decline perhaps as early as in their 20s.
- *Head injury:* AD risk doubles in patients who have suffered traumatic brain injuries early in life. Moderate head injury increases the risk of AD by two to three times, whereas severe head injury more than quadruples the risk of dementia.
- *Gender:* Because women have longer life spans than men, they have a higher incidence of AD. Lower estrogen levels may also play an important role in AD.[8]
- *Educational level:* The risk of developing AD decreases with the number of years of formal education. This finding highlights research suggesting that mental activity throughout life is neuroprotective.[9]

Warning signs of AD are shown in Table 9-1.

TABLE 9-1. Warning Signs of Alzheimer Disease

- Recent memory loss that affects job skill
- Difficulty performing familiar tasks
- Problems with language
- Disorientation to time and space
- Poor or decreased judgment
- Problems with abstract thinking
- Misplacement of important objects
- Changes in mood or behavior
- Changes in personality
- Loss of initiative

Lifestyle Risk Factors

Subjective Cognitive Impairment

Many specialists treating neurologic diseases once thought that complaints of benign senescent forgetfulness were insignificant because this condition had no potential to progress to true AD. However, a newer study revealed that, over a 7-year period, healthy adults who reported having the feeling that their memory was not functioning as well as it should progressed to MCI and AD at a higher rate than did those without SCI.[10]

In the study, researchers found that SCI in older persons without manifestation of symptoms is a common condition with a largely unclear prognosis. Patients were followed over a sufficient period by using conversion to MCI or to dementia to clarify SCI prognosis and determine whether the prognosis of patients with SCI would differ from that of demographically matched healthy subjects with no cognitive impairment (NCI).[10]

A consecutive series of healthy subjects, 40 years old or older, presenting with NCI or SCI to a brain aging and dementia research center during a 14-year interval, was studied and followed up during an 18-year observation window. The study population (60 NCI, 200 SCI, 60% female) had a mean age of 67.2 ± 9.1 years, was well educated (mean, 15.5 ± 2.7 years), and was cognitively normal based on scores of the Mini-Mental State Examination (MMSE 29.1 ± 1.2).[10]

In this study, 213 subjects were followed up over a mean period of 6.8 ± 3.4 years, and subjects had a mean of 2.9 ± 1.6 follow-up visits. Seven NCI (14.9%) and 90 SCI (54.2%) subjects had a decline in their cognitive function. Of NCI decliners, 5 declined to MCI, and 2 to probable AD. Of the 90 SCI decliners, 71 declined to MCI, and 19 to AD. Controlling for baseline demographic variables and follow-up time, SCI subjects had a higher likelihood of decline and declined more rapidly. The study also showed that mean time to decline was 3.5 years longer for NCI than for SCI subjects.[10]

Crucially, these results suggested that SCI in subjects with normal cognition was a possible indication of future decline in most subjects during a 7-year follow-up interval. Relevance for community populations and prevention studies in this at-risk population should be explored further.

Mild Cognitive Impairment

MCI is characterized primarily by recent memory loss. This is the transitional state from normal aging to SCI and dementia. People with MCI are at an increased risk of developing AD, at a rate of 12% to 15% per year. Symptoms of

MCI are distinguished from normal aging by recent memory loss. For example, people with MCI suffer frequently from forgetfulness and may visibly have difficulty learning new information and recalling previously learned information. The primary distinction between people with MCI and those with AD appears to be in the areas of cognition outside of memory. Unlike people with AD, those with MCI are able to function normally in daily activities requiring other cognitive abilities such as thinking, understanding, and decision making.[11]

Stress and the Brain

Stress is represented by a bell-shaped curve, with demand on the horizontal axis and performance on the vertical axis. As depicted on the graph, when a person's ability to perform is exceeded by the demand, stress ensues. At some point, however, a person's ability to perform is exceeded by the demand placed on him or her. That is when the chronic stress reaction comes into play, with the release of cortisol from the adrenal glands. Cortisol then flows throughout the bloodstream and has been shown to kill brain cells in the memory center of the brain, known as the hippocampus. Cortisol also suppresses immune system function.

Cortisol produces memory dysfunction by the following means:

1. Preventing the uptake of glucose by the hippocampus
2. Inhibiting synaptic transmission
3. Causing neuron injury and cellular death.[12]

For those skeptical about this notion, one simply has to look at the title of the book written by eminent brain researcher Professor Robert Sapolsky from Stanford University: *Stress, the Aging Brain, and the Mechanisms of Neuron Death*.[13] Beyond that, McEwen and Sapolsky, in their landmark article "Stress and Cognitive Function,"[14] also showed evidence suggesting that the glucocorticoid cortisol has a direct effect on synaptic plasticity and dendritic structures. Additionally, according to McEwen and Sapolsky, prolonged exposure to stress leads to loss of neurons, particularly in the hippocampus. Moreover, Stein-Behrins and Sapolsky, in their landmark article, "Stress, Glucocorticoids, and Aging,"[12] revealed that illness and aging are a time of decreased ability to handle stress.

As one reaches beyond the age of 46 up to more than 55 years, the amount of cortisol in the blood during chronic stress becomes elevated and drops more slowly. Part of the reason for this is that cortisol kills the same brain cells in the hippocampus that are responsible for the negative feedback loop in shutting off the release of cortisol from the adrenal glands in the first place. The mechanism of which Sapolsky wrote has been delineated in that the neurotoxic excitatory amino acid glutamate is usually taken up by the glial cells. With chronic stress, however, excess cortisol blocks this uptake by the glial cells in the synaptic cleft. High levels of free glutamate in the synapse therefore activate the *N*-methyl-D-aspartate (NMDA) receptors and cause an influx of calcium into the postsynaptic neuron. In addition, glutamate activation of the NMDA receptor blocks calcium efflux out of the postsynaptic neuron.[15] This excessive synaptic neuron calcium leads to free radical damage, inflammation, and cell death. Lupien et al[4] revealed that hippocampal volume was inversely related to cortisol levels in the serum.

Other work has revealed the effects of cortisol and stress on the development of dementia. For example, Crow et al[16] showed that greater reactivity to stress predicted a higher risk of dementia in individuals who reported a high incidence of work-related stress. The risk was not the work-related stress itself, but how the individual reacted to that stress. This 30-year longitudinal study included more than 2000 people. In addition, Newcomer et al[17] showed decreased memory performance in healthy humans who were injected with stress levels of cortisol intravenously. Wilson et al[18] revealed that unbalanced stress doubled the risk of AD. Moreover, Peavy et al[19] unveiled that stress produced more reactivity and higher levels of cortisol, with subsequent worse effects on memory function in older individuals who were *ApoE4* positive and therefore at greater risk for the development of AD.

More recently, work by Choi et al[20] at the University of California, Los Angeles (UCLA) School of Medicine revealed a reduction in telomerase activity in human T lymphocytes exposed to cortisol. This finding is significant because reduction in telomerase activity means that the telomeres in the DNA shortened precipitously, and shortened telomeres thereby accelerate aging and illness. This finding is especially important because the work of Lukens et al[21] showed that telomere length in peripheral blood was diminished in individuals with AD.

To summarize, chronic, unbalanced stress causes excessive cortisol release from the adrenal gland into the bloodstream. This cortisol then travels to the hippocampus, where it causes brain cell death and shuts off the inhibition of production of further cortisol from the adrenal gland. This excess of cortisol not only causes inflammation and hippocampal neuronal cell death, but also has an accelerated aging effect by decreasing telomere length in the stressed individual. Shortened telomeres may lead to accelerated aging, inflammation, cardiovascular disease, cancer, and AD.

Diagnosis

1. Patient history: Family history is important because of the correlation between AD in patients and their first-degree relatives. A personal history of illnesses, especially cardiovascular disease, and metabolic disorders such as diabetes mellitus is also useful. Other areas of concern include medication usage and a history of head trauma. In general, the diagnosis of MCI can be made if an individual has a memory complaint and an abnormal memory for his or her age and education. Moreover, the person demonstrates normal activities of daily living and a normal level of general cognitive function. The patient with MCI is not demented.
2. Cognitive assessment: I have found the MMSE to be valuable in an office setting. This test offers a relatively rapid and reliable means of assessing cognitive function, memory, and visual-spatial skills (Fig. 9-1). Individuals with low levels of education, however, tend to do more poorly on the test, independent of any effects of cognitive function. Moreover, the test is less sensitive in individuals with higher educational levels; they may have a normal score on the MMSE yet have early signs of dementia. Repeated MMSE testing offers a good means of tracking disease progression and monitoring the effects of treatment.

FIGURE 9-1
Mini-Mental State Examination.

One point for each answer.

1. Orientation

	Correct	Incorrect
What is the year we are in?	1	0
What season is it?	1	0
What is today's date?	1	0
What day of the week is today?	1	0
What month are we in?	1	0
What state are we in?	1	0
What country are we in?	1	0
What town are we in?	1	0
Can you tell me the name of this place?	1	0
What floor of the building are we on?	1	0
Subtotal Correct.		

2. Registration
Ask the patient if you may test his/her memory. Then say the names of 3 unrelated objects, clearly and slowly, about one second for each. After you have said all 3, ask him/her to repeat them. This first repetition determines his/her score (0-3), but keep saying them until he/she can repeat all 3, up to 6 trials. If he/she does not eventually learn all 3, recall cannot be meaningfully tested.

Score 0 1 2 3

3. Attention and Calculation
Ask the patient to begin with 100 and count backwards by 7. Stop after 5 subtractions (93, 86, 79, 72, 65). Score the total number of correct answers.
If the patient cannot perform this task, ask him/her to spell the word world backwards. The score is the number of letters in correct order (e.g., dlrow = 5, dlorw = 3)

Score 0 1 2 3 4

4. Recall
Ask the patient if he/she can recall the 3 words you previously asked him/her to remember. Score 0-3.

Score 0 1 2 3

5. Naming
a. Show the patient a wrist watch and ask him/her what it is.
b. Repeat for a pencil.

Score 0 1 2

6. Repetition
Ask the patient to repeat this sentence after you—"No If's, And's, or But's."

Score 0 1

7. 3-Stage Command
Have the patient follow this command—"Take a paper in your hand, fold it in half, and put it on the floor."

Score 0 1 2 3

8. Reacting
On a blank piece of paper print the sentence "Close your eyes" in letters large enough for the patient to see clearly. Ask him/her to read it and do what it says. Score 1 point only if he/she actually closes his/her eyes.

Score 0 1

9. Writing
Give the patient a blank piece of paper and ask him/her to write a sentence for you. Do not dictate a sentence; it is to be written spontaneously. It must contain a subject and a verb and be sensible. Correct grammar and punctuation are not necessary.

Score 0 1

10. Copying
On a clean piece of paper, draw intersecting pentagons, each side about one inch, and ask him/her to copy it exactly as it is. All 10 angles must be present and 2 must intersect to score 1 point. Tremor and rotation are ignored.

Score 0 1

Total Score

Total Possible Score = 30

Score suggesting dementia ≤ 23

* Using a cut-off score of 23, the MMSE has a sensitivity of 87% and a specificity of 82%.

3. Physical examination and laboratory tests: The physical examination and standard neurologic evaluation may reveal evidence of a stroke. Focal findings of hemiparesis, sensory loss, cranial nerve deficits, and ataxia are not consistent with a diagnosis of AD. Conventional laboratory testing should include a complete blood count, electrolyte and metabolic panels, a thyroid function test, vitamin B_{12} levels, and tests for syphilis and human immunodeficiency virus. Beyond that, the integrative medical practitioner also tests for certain hormone levels. Measuring dehydroepiandrosterone (DHEA) has proved clinically useful. In my experience, patients with AD have markedly low levels of DHEA. I also measure levels of free testosterone in men and estrogen in women. Although full hormone replacement therapy is not a regular part of my work, I do order an insulin-like growth factor-I level. Urinalysis, electrocardiogram, chest radiograph, and determination of folate levels are no longer recommended. Low folic acid levels, however, are a risk factor for the development of AD.
4. Neuroimaging: The Alzheimer's Association neuroimaging initiative has gained a large amount of support. The time to use neuroimaging is somewhat controversial, but I have found this modality useful in identifying lesions such as hippocampal and cerebral atrophy that are consistent with AD. I believe that neuroimaging can help in determining the stage of dementia and the patient's prognosis. Some experts suggest computed tomography or magnetic resonance imaging for all patients with suspected AD. Others consider positron emission tomography more

useful when the diagnosis is uncertain, and it can be used to identify a declining metabolic rate in the parietal-temporal lobe that is characteristic of AD.

5. Genetic testing: Determining *APOE4* gene status can contribute to diagnostic accuracy in patients who already have a clinical diagnosis of AD. This testing is most commonly used in academic medicine. Current controversy revolves around the routine use of genetic testing to offer information to people interested in knowing their genetic potential for developing AD. The concern is what can be offered to people who are *APOE4* positive. Some believe that nothing can be done. I disagree. My two decades of clinical experience has led me to believe that AD can be delayed or prevented and its progression slowed.

Integrative Therapy

A true integrative medical model combines evidence from therapies based on nutrition, stress reduction, exercise, and pharmaceuticals into a total synergistic program. Gould et al[22] showed that this type of program can reverse coronary artery disease, and I have had compelling success in my own practice involving patients with AD.

At this juncture, a large difference of opinion exists between the conventionalist who prescribes only a cholinesterase inhibitor such as donepezil (Aricept) and rarely vitamin E in the treatment of MCI or AD and the more forward-thinking clinician who practices integrative medicine. The integrative medicine practitioner understands, by virtue of experience and knowledge, that much can be done in patients with SCI, MCI, and AD to slow the progression and, in many cases, reverse the symptoms. What follows is an organized and scientific approach to the treatment of cognitive decline.

Lifestyle Factors

Physical Exercise

Aerobic conditioning has been shown to improve some aspects of mental function by 20% to 30%. Smith and Fredlund[23] demonstrated that physical exercise has a retardant effect on the development of AD. In a retrospective analysis of subjects aged 40 to 60 years, those with a regular exercise program did not develop AD as frequently as those who followed no exercise program. Exercise increases cerebral blood flow and the production of nerve growth factors. A more recent study on this topic by Jedrziewski et al[24] revealed results from the National Long-Term Care Study that provided evidence supporting an exercise-related lowering of risk for cognitive decline. In this 10-year study, the amount of exercise was inversely associated with the onset of cognitive impairment.[24]

Cognitive Exercise

Based on research by Diamond et al,[25] an integrative medical program that includes cognitive stimulation such as headline discussion, crossword puzzles, music, or art could help to maintain cognitive ability. Mental training increases dendritic sprouting and enhances central nervous system plasticity.[26] In addition to inducing positive medical benefits, cognitive exercise allows patients and their spouses to spend quality time together. In my view, computerized cognitive training is neither necessary nor cost effective.

Nutrition

The key points in nutrition are to reduce dietary fat and cholesterol, add omega-3–rich foods such as salmon and tuna, and lower caloric consumption.

Some studies have shown that a diet restricted in calories and consisting of 15% to 20% fat can help prevent and treat AD. This approach extends the life expectancy of animals and enhances health and cognitive ability of humans. U.S. citizens, who consume a high-calorie, high-fat diet, have a much higher incidence of AD than people living in countries where a relatively low-fat diet is eaten. High-fat and high-calorie intake leads to oxidative stress, which contributes to the onset and progression of cognitive decline.

Researchers at New York University's Nathan Kline Institute put transgenic mice on high-fat diets and then observed an increase in the rate at which beta amyloid built up in their brains. Cholesterol-lowering medication slowed the rate of plaque formation.[27,28] The studies using statins to prevent dementia, however, have been equivocal.

The dietary consumption of fish—especially salmon and tuna, which contain docosahexaenoic acid (DHA), an omega-3, long-chain, polyunsaturated fatty acid—is considered beneficial to cognitive health. Although supplementation with DHA was not found to reduce functional decline in AD in a large randomized trial,[29] a study by Yurko-Mauro et al,[30] published in *Alzheimer's and Dementia* in 2010, did, in fact, show beneficial effects of DHA on cognition in age-related cognitive decline.

In my consultation practice, the nutritionist works to create a 15% to 20% fat diet based on patient preferences. This has proved beneficial.[31–33]

Results of the Biosphere II experiment on caloric restriction and reduced fat showed reductions in triglyceride and cholesterol levels, which are important in the treatment of AD.[34]

Mind-Body Therapy

Stress-relieving techniques such as meditation have been shown to reduce cortisol levels and enhance cognitive function in patients with MCI and AD.[35] Moreover, I have seen that an innovative mind-body exercise called kirtan kriya (KK) activates the posterior cingulate gyrus, the first area to decline in patients with AD.[36]

Meditation

Because of the effects of chronic, unbalanced stress and cortisol secretion on memory, it is beneficial to suppress elevated glucocorticoid levels or normalize their release. Given that age increases the vulnerability to stress and cortisol-induced hippocampal damage, stress-relieving meditation is highly recommended for patients of all ages to reduce cortisol and limit the loss of hippocampal neurons.

Meditation has consistently been found to decrease cortisol levels and promote normalization of adaptive mechanisms.[37] Practitioners of meditation also display lower levels of lipid peroxidase, a marker of free radical production, and higher levels of the hormone DHEA, which is considered

important for optimal brain function. Wallace[38] reviewed studies that noted the positive health benefits of meditation on cognition. In a landmark study in older adults, investigators found that meditators had a greater life expectancy than nonmeditators[39] (see Chapter 98, Recommending Meditation).

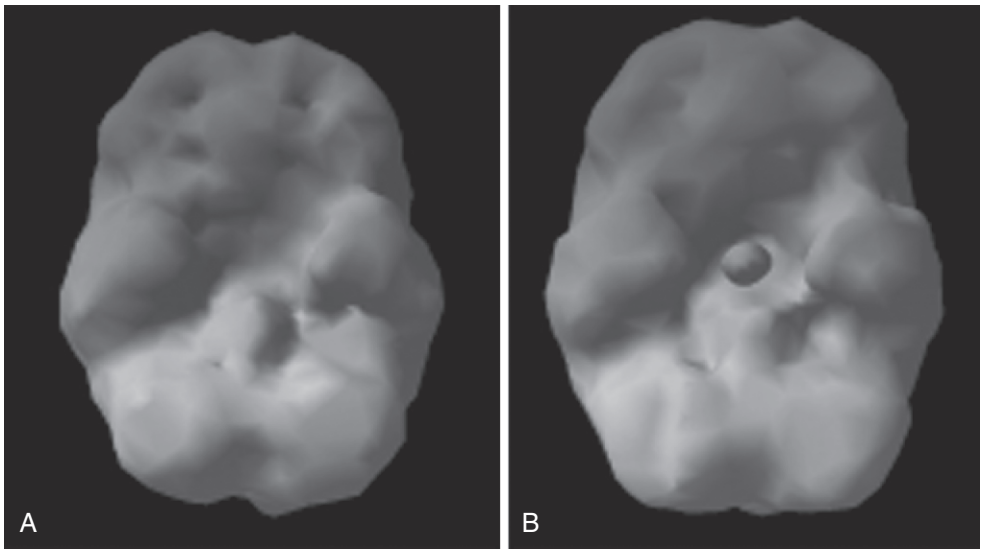
Physiology of Meditation

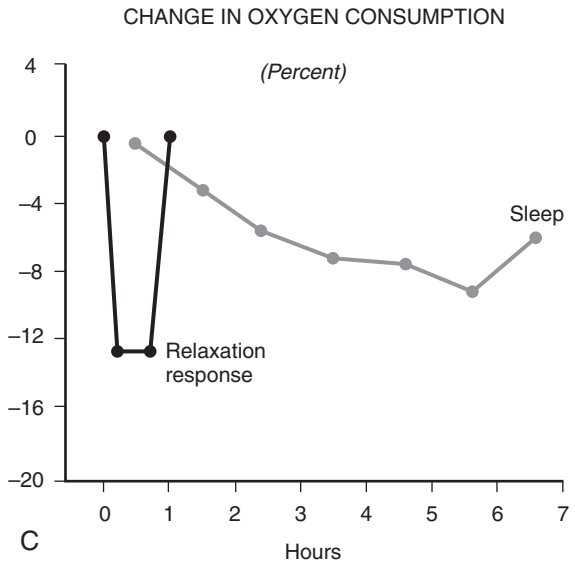
The most significant physiologic change induced by meditation is a drop in oxygen consumption (MVO_2). This effect was described by Herbert Benson in the late 1960s.[40] As seen in the graph in Figure 9-2, Benson showed that when one elicits the relaxation response, MVO_2 drops approximately 14% over the control or waking state. This finding is in contrast to sleep, in which MVO_2 has been shown to decrease 10% after 5 or 6 hours. To summarize, when one elicits the relaxation response or practices basic meditation for as little as 10 or 20 minutes, MVO_2 drops by as much as 14%.

At least 11 forms of basic meditation are recognized:

1. The relaxation response
2. Transcendental meditation
3. Mindfulness or Zen Buddhist meditation
4. Many types of yoga
5. Autogenic training
6. Progressive muscle relaxation
7. Affirmations
8. Visualization
9. Listening to music
10. Receiving a therapeutic massage, which is a passive activity in which the relaxation response is induced
11. Prayer, when the requirements previously described are followed

FIGURE 9-2
Before (**A**) and after (**B**) kirtan kriya. **C**, The key physiologic effect of the antistress response. (**A** and **B**, From Khalsa D, Amen D, Hanks C, et al. Cerebral blood flow changes during chanting meditation. *Nucl Med Commun.* 2009;30:956–961; **C**, from Benson H. *The Relaxation Response.* New York: HarperTorch; 1976.)





Moreover, at least 13 different physiologic effects of basic meditation have been observed[41]:

1. Decrease in pulse and increased heart rate variability
2. Decrease in respiratory rate
3. Decrease in blood pressure
4. Decrease in total peripheral resistance
5. Decrease in MVO_2
6. Decrease in stress hormones epinephrine and norepinephrine
7. Decrease in cortisol
8. Decrease in lactic acid, signifying a decrease in anxiety levels
9. Decrease in lipid peroxidase, which reveals a decrease in free radical formation
10. An increase in the hormone DHEA
11. Increase in the sleep and antiaging hormone melatonin
12. Enhanced immune system function
13. Reduction in inflammatory molecules

Even the most basic form of the relaxation response or meditation has a very high benefit at a very low cost. Generally, it has no side effects. However, sometimes people do become frustrated when they struggle to meditate. Very rarely, people have had idiosyncratic reactions, such as uncomfortable out of body experiences.

Almost 300 articles have been published on the many benefits of the regular elicitation of the relaxation response and various forms of meditation, going all the way back to the late 1960s. Although many of these studies were not well executed, the overwhelming data showed beneficial effects.

With regard to the prevention of AD and maximizing cognitive function in aging baby boomers, blood pressure regulation is critically important. Benson et al[42] demonstrated that the relaxation response decreased blood pressure in pharmacologically treated hypertensive patients. The hypometabolic state elicited by the response seems to represent an integrated hypothalamic mechanism. Benson et al[43] also showed that the relaxation response helped patients decrease the number of premature ventricular contractions, a finding demonstrating a salubrious effect on stable ischemic heart disease. In a similar study, Peters and Benson[44] showed that daily relaxation response breaks in a working population had a positive effect on self-reported measures of well-being after 12 weeks. This finding is highly significant because telomeres, as mentioned previously, are found to be shortened in patients with AD. As discussed later, self-reported measures of well-being either decreased the rate of shortening of telomeres or, in fact, lengthened them. This information may have profound significance for enhancing cognitive function as people age.

Kirtan Kriya

Specific brain exercises called kriyas are derived from the science of Kundalini yoga as taught by Yogi Bhajan. They combine breathing, finger movements, and regenerating sound currents. The practice of these exercises serves a dual purpose because they induce a meditative state and stimulate the central nervous system. Kriyas have been clinically shown to be useful in increasing global brain energy. Positron emission tomography scans demonstrate that these types of exercises enhance regional cerebral blood flow, oxygen delivery, and glucose use. Beyond that, research at Harvard University in Cambridge, Massachusetts, proved that what I call medical meditation, based on kriyas, is quite specific in increasing activity to the hippocampus compared with basic meditation. Moreover, this same research group is studying the effect of meditation on cortisol levels and grades in school-age children.[45]

In advanced meditative work, these five attributes—breath, posture or position, mantra or sound, fingertips or mudras, and focus of concentration—may be different, depending on the meditation that is chosen for a specific effect. Advanced meditations, such as KK, are therefore prescriptive or medical meditations. I described this in detail in the book *Meditation as Medicine* in 2001.[46]

Method of Kirtan Kriya

This exercise is called Kirtan Kriya and involves the chanting of the primal sounds. Say each of these words repeatedly, in order: Saa Taa Naa Maa. The "a" in these words is pronounced as a soft a, or ah. Repeat this mantra while sitting with your spine straight and your mental energy focused on the area of your brow, or forebrain. Yogis believe that this stimulates your pituitary. You can find this spot by rolling your eyes to the top, or root, of your nose. The mudras, or finger positions, are important in this kriya. On Saa, touch the index fingers of each hand to your thumbs. On Taa, touch your middle fingers to your thumbs. On Naa, touch your ring fingers to your thumbs. On Maa, touch your little fingers to your thumbs. For 2 minutes, chant in your normal voice. For the next 2 minutes, chant in a whisper. For the middle 4 minutes, chant silently, while still touching the fingertips. Then reverse the order, whispering for 2 minutes and chanting the mantra out loud for the last 2 minutes. The total time is 12 minutes. At the end, inhale deeply, stretch your hands above your head, and then bring them down in a sweeping motion as you exhale.

KK is thought to operate by several mechanisms. According to Yogi Bhajan, PhD, Master of Kundalini and White Tantric Yoga, the use of the tongue in KK during the chanting, or saying of the sounds, stimulates the 84 acupuncture meridian points on the roof of the mouth in a certain permutation and combination that sends a signal to the hypothalamus, as well as to the brain itself.

How this works on a chemical level is theoretical, but I postulate that practicing KK may rejuvenate the brain synapses by increasing important brain chemicals such as acetylcholine. This concept needs further evaluation. What we do know, however, is that meditation does increase levels of dopamine, serotonin, and melatonin.

What is not theoretical is the map of the brain, known as the homunculus, shown in *Gray's Anatomy*, as well as Penfield and Rasmussen's *The Cerebral Cortex of Man: A Clinical Study of Localization of Function.* The fingertips, hands, lips, tongue, and other aspects of vocalization are highly represented in the motor and sensory areas of the brain. Therefore, when the practitioner uses the fingertips in conjunction with the sound, specific areas in the brain, as seen on single photon emission computed tomography (SPECT) scans, are activated.

In a SPECT study published in *Nuclear Medicine Communications*, my colleagues and I[36] showed particular cerebral blood flow changes during the practice of KK. Perhaps most significantly, as seen in Figure 9-3, the frontal lobes of the brain showed increased cerebral blood flow, as did the whole brain itself. Beyond that, the posterior cingulate gyrus was activated. This finding is significant because the posterior cingulate gyrus is one of the first areas that demonstrate decreased activity on a scan when one develops AD.

One could therefore postulate that if an individual practiced KK meditation on a consistent basis, and activated the posterior cingulate gyrus, that person could decrease the risk of developing cognitive decline or even frank AD. This is also important because we know that AD may take as long as 20 to 40 years to develop.

In a follow-up to that study, Newberg et al[47] described positive effects of KK on cognitive function and cerebral blood flow in subjects with memory loss. In this preliminary study involving 15 experimental subjects and 5 subjects in a control group who listened to music, the participants in the experimental group kept a practice log revealing a high degree of compliance. When they returned to the university study area after 8 weeks of practice, the participants were scanned in the baseline state and after the meditation. They also had their neuropsychological tests repeated. The testing revealed a significant improvement in scores on tests of verbal fluency, animal naming, and attention. These neuropsychological tests tap into executive functioning skills.

Subjectively, the study subjects also reported improvement in their overall memory functioning. Given the findings of Reisberg et al about SCI,[10] this may be significant, because individuals with SCI were at higher risk for progression to MCI and later AD.

Of greatest significance is that this was the first study to explore meditation in people diagnosed with memory impairment. Also noteworthy, KK was revealed to have a positive effect in enhancing cerebral blood flow and improving cognitive functioning.

As can be seen in the scans in Figures 9-3, 9-4, and 9-5, a difference was evident in activation in the frontal lobe, posterior cingulate gyrus, and anterior cingulate gyrus, both the

FIGURE 9-3
Enhanced cerebral blood flow in the frontal lobe.

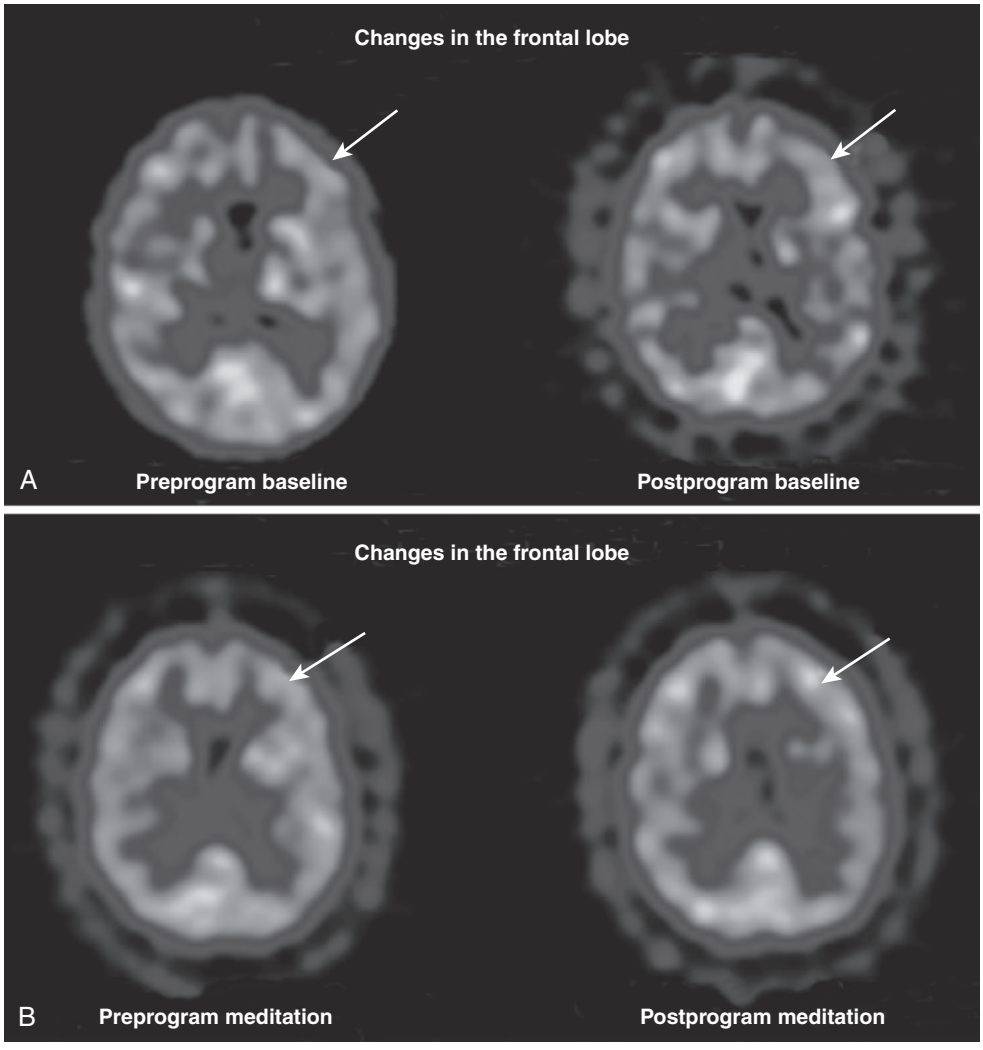


FIGURE 9-4
Enhanced cerebral blood flow in the posterior cingulate gyrus.

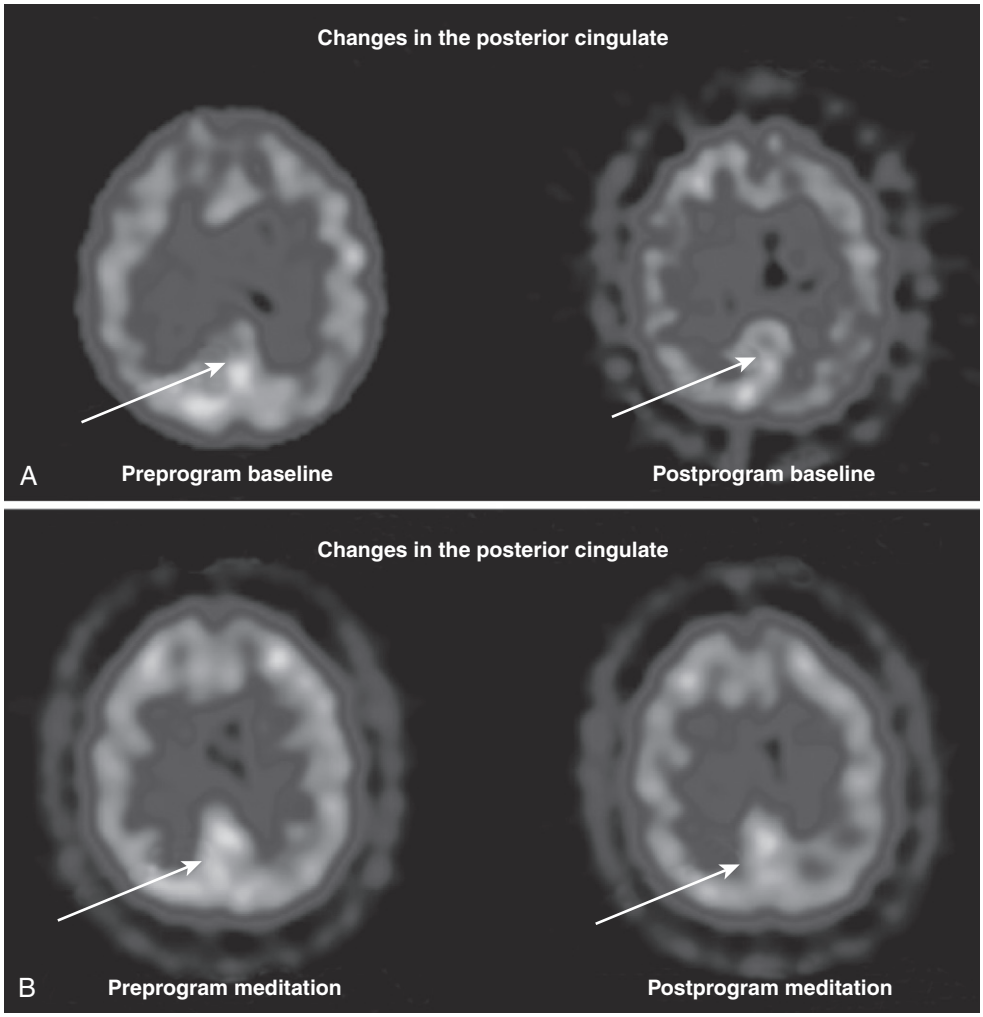
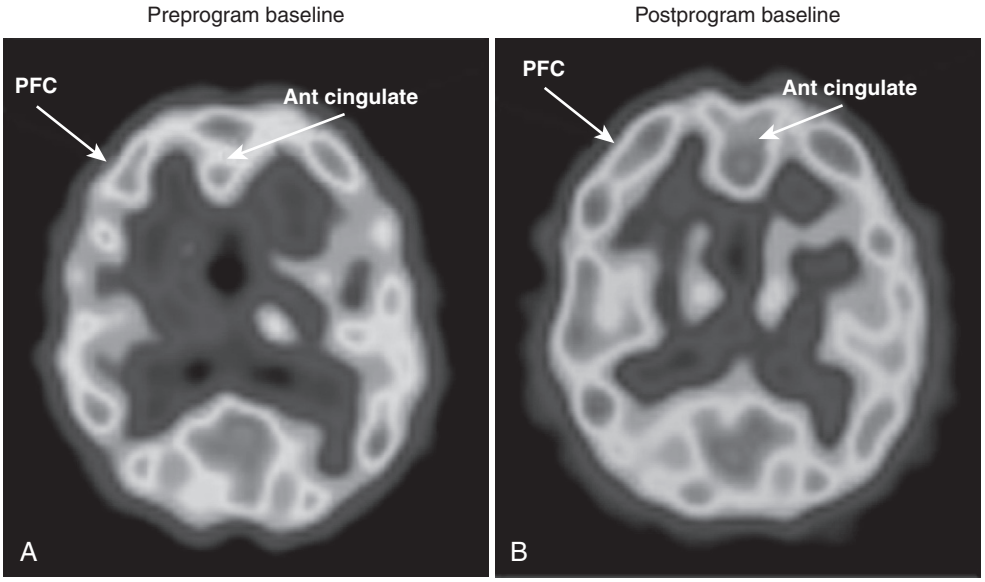


FIGURE 9-5
Enhanced cerebral blood flow in the anterior (Ant) cingulate gyrus. PFC, prefrontal cortex.



first time the subjects practiced the meditation and, more prominently, after 8 weeks of meditating only 12 minutes a day. MacLullich et al[48] showed that a smaller anterior cingulate cortex is associated with impaired hypothalamic-pituitary-adrenal axis regulation in healthy older men. In my view, enhancing activity and size of the anterior cingulate gyrus could improve hypothalamic-pituitary-adrenal axis function and normalize the stress response so that not as much cortisol bathes the hippocampus.

Kirtan Kriya, Telomeres, and Prevention of Alzheimer Disease

Telomeres are the cap on the DNA. When they shorten, a person ages, and when they elongate, a person is healthier and longer lived. Shortened telomeres have been associated with cancer, heart disease, and AD.

Although Dusek, Benson, and their colleagues[49] showed that stress reduction through meditation and yoga actually improved a person's genetic response to stress, Ornish et al[50] also revealed that improved diet, meditation, and other integrative medical interventions could actually turn off the disease-promoting process in men with prostate cancer. This work by Ornish et al, published in *The Lancet Oncology,* also showed increased telomerase activity with these comprehensive changes.[51]

The enzyme telomerase decreases the rate at which telomeres are shortened, and perhaps increases their length, which is an indicator of enhanced health and longevity. According to Ornish et al,[51] the telomeres increased 29% with meditation as part of this lifestyle program. Other aspects of the stress management program included, yoga, breathing, and imagery.

In July 2009, at the Conference of the International Society of Psycho-Neuro Immunology, Jacobs et al[52] presented work from the Samantha Meditation Project. This work showed that subjects taken to a retreat center who practiced mindfulness meditation for 5 hours a day for 3 months increased their psychological well-being, as well as their telomere length.

The following six facets of psychological well-being were thought to play a significant part in the enhanced telomere length:

1. Self-confidence
2. Self-acceptance
3. Personal growth
4. Purpose and meaning
5. Positive relationships
6. Sense of independence

Our preliminary research showed that KK meditation also appears to improve several aspects of psychological well-being. Noteworthy is that the amount of time necessary was only 12 minutes a day for 8 weeks, rather than 5 hours a day for 3 months. In a second study with Wang et al,[53] we also revealed that KK decreased stress, increased spiritual connection, and improved psychological well-being. In a study at UCLA, investigators revealed a positive relationship among KK, cognitive enhancement, well-being, and telomerase activation. This study had 44 subjects, 39 of whom completed the study (23 meditated, and 16 listened to relaxation tapes for 25 minutes a day for 8 weeks). Both groups demonstrated improvement in depression and anxiety, resilience, and perceived burden. The KK group improved significantly more compared with the relaxation tape group on measures of perceived support, physical suffering, energy, emotional well-being, and cognitive tests of memory and executive function. A subgroup also showed improvement in inflammatory processes.

Supplements

The following brain-specific nutrients play a part in the prevention and treatment of AD: B-vitamins; vitamin E in the form of mixed tocopherols; phosphatidylserine (PS), with an intake of up to 300 mg/day; coenzyme Q10 (ubiquinone), up to 100 mg/day; ginkgo *(Ginkgo biloba),* at a dose up to 240 mg/day; and the omega-3 fatty acid DHA, at 1500 mg/day. Other nutrients that hold promise are huperzine A, at 100 to 200 mg/day, and vinpocetine, at 2.5 to 10 mg/day.

B Vitamins

The B-complex vitamins are critical for neurotransmitter control and carbohydrate energy metabolism. Niacin itself (vitamin B_3) has been shown to have memory-improving benefits.[54] Folate reduces homocysteine, high levels of which have been implicated in heart disease and AD. A high intake of folate was found to be associated with a reduced risk of AD in the Baltimore Longitudinal Study of Aging.[55] An integrative brain program should also contain adequate antioxidants and vitamin C in the diet, as well as through supplementation.[56]

Vitamin E

Vitamin E, at a dose of 2000 units/day, has been shown to slow the progression of midstage AD primarily because it protects cell membranes from oxidative damage.[57] Combining vitamin E, at 1000 units daily, with donepezil (Aricept), at 5 mg daily, may help slow cognitive decline in AD.[58] Vitamin E does not appear to have a significant effect in preventing the progression from MCI to AD, however.[59] Moreover, the Baltimore Longitudinal Study of Aging did not show that dietary sources or supplemental vitamin E reduced the risk of AD.[55]

Phosphatidylserine

PS is a negatively charged phospholipid that is almost exclusively located in cell membranes. It has a set of unique physiologic properties that are important to neuronal functions, including stimulation of neurotransmitter release, activation of ion transport mechanisms, and augmentation in glucose and cyclic adenosine monophosphate levels in the brain. In the aging brain, a decline in these functions is associated with memory impairment and deficits in cognitive abilities.

PS has been the subject of 23 studies, 12 of which were double-blind trials. The findings indicate that PS improves short-term memory, mood, concentration, and activities of daily living.[60] Although early research used bovine PS, concern over possible slow viral infection prompted the search for an alternative, plant source. A novel PS product made by enzymatic conversion of soy lecithin has been developed and has been shown to be beneficial in patients with memory loss, including those with AD.[61] In my experience, PS is highly effective, especially at improving the recall of names and objects, both of which are symptoms of AD. For some reason, conventionalists have decided not to include PS in their armamentarium against AD.

Dosage
The dose is 100 to 300 mg/day.

Precautions
None are known.

Coenzyme Q10
Coenzyme Q10, a powerful neuroprotective agent, works as a dynamic antioxidant. It is present throughout the brain cell membrane and mitochondria, where it is involved in the production of high-energy phosphate compounds.[62]

Dosage
The dose is 100 mg/day.

Precautions
Coenzyme Q10 can lead to gastritis, loss of appetite, nausea, and diarrhea when taken in doses greater than 300 mg/day. It can also elevate serum aminotransferase levels.

Botanicals

Ginkgo biloba *Extract*
Although *Ginkgo biloba* enjoys a continuous, old stellar reputation for effectiveness among practitioners and patients alike, a more recent spate of controversial articles has reported negative outcomes.[63–65] In my view, these negative reports are flawed because the subject population was older, and most people who take ginkgo, especially for prevention, fall into younger groups. I personally still do employ ginkgo in my practice, and my patients benefit from it.

Ginkgo increases microvascular circulation, scavenges free radicals, and helps improve concentration and short-term memory in patients with SCI, MCI, and AD. A 52-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter study showed modest but significant improvements in 309 patients with mild to severe AD or multiinfarct dementia. These changes were equal to those induced by drugs with a higher side effect profile and were of a sufficient magnitude to be recognized by the patients' caregivers.[66]

Dosage
The dose is up to 240 mg/day.

Precautions
Reports in the medical and lay media have emphasized the need to exercise caution when combining vitamin E and ginkgo, especially in patients taking anticoagulants. In patients taking warfarin (Coumadin), for example, I measure the appropriate coagulation parameters and perhaps lower the dose of all the compounds. I believe it is a disservice to the patient with MCI or AD, however, automatically to withhold compounds with a proven benefit in fighting AD because of a purely theoretical concern. If the patient is not taking warfarin, I do not believe that the patient is in danger of excessive bleeding; in my clinical experience I have not seen it, nor have I heard of it from any practitioner of integrative medicine.

Huperzine A
Huperzine A is a natural anticholinesterase inhibitor derived from Chinese club moss. Many studies, most of which were done in China, showed that huperzine A surpassed donepezil in reversing memory deficits in aging animals. Huperzine's activity is also reportedly long lasting. What makes huperzine attractive is its apparent lack of serious side effects and low toxicity.

Dosage
I use 50 mg once or twice daily, depending on the severity of symptoms.

Precautions
Huperzine A can cause nausea, sweating, blurred vision, and fasciculations, but less often than prescription anticholinesterase inhibitors.

Vinpocetine
Vinpocetine, a nutrient derived from the periwinkle plant, has been shown to increase cerebral blood flow and enhance neuronal metabolism. A Cochrane Review reported evidence of beneficial effects on cognitive function, but most of the studies reviewed were of short duration.[67]

Dosage
I find the dose of 2.5 to 5 mg twice daily to be less stimulating and hence more effective than higher doses recommended by others.

Precautions
Gastrointestinal distress, dry mouth, low blood pressure, and rash are rare. Vinpocetine should be avoided in pregnancy.

Pharmaceuticals

Acetylcholinesterase Inhibitors
Currently, five drugs are approved by the U.S. Food and Drug Administration to treat early AD. These are acetylcholinesterase inhibitors, which increase the level of the neurotransmitter acetylcholine. Acetylcholine is critically important for memory formation and retrieval.

The first, tacrine (Cognex), was minimally effective and had poor patient compliance because of its side effects; it is no longer used. The second, donepezil (Aricept), is moderately effective in improving short-term memory in patients with early AD. Neither drug has any effect on the progression of the disease. Rivastigmine (Exelon) is slightly more effective than the others and has the best side effect profile of the available cholinesterase-inhibiting drugs.[68]

The other drugs are galantamine (Razadyne), which affects neurotransmitter function, and memantine (Namenda), which inhibits the toxic compound glutamate. Memantine has been shown to be effective in the moderate to later stages of AD.

Hormones
DHEA and pregnenolone, both neurospecific hormones and precursors to estrogen, are also useful. An animal study demonstrated that DHEA affected excitability in the hippocampus, thereby enhancing memory function at doses of 50 mg/day. Another study showed that DHEA enhanced

acetylcholine release from hippocampal neurons in the rat brain. DHEA levels have been shown to be consistently low in patients with AD.[69] Alternatively, an article by Grimley et al in 2006,[70] which reviewed four studies on DHEA supplementation while showing epidemiologic evidence that DHEA may protect against heart disease and AD risk factors, nevertheless concluded that little support exists for a beneficial effect of DHEA in prevention or treatment of AD. Individual integrative medical practitioners must decide whether DHEA is useful in their practice. I do prescribe it.

Pregnenolone has been the subject of research in both animals and humans. This hormone has been found to be a powerful memory enhancer. One study demonstrated improved memory with pregnenolone use in older adults.[71]

Estrogen deficiency in postmenopausal women is a factor in the development of AD. Observational studies indicated that estrogen replacement delays the expression of AD by 40% to 70%, enhances hippocampal plasticity, and increases nerve growth factor. Estrogen has antioxidant properties that protect the neuron from oxidative stress. Estrogen also enhances glucose transport in neuronal tissue, which may be impaired in AD. Finally, estrogen stimulates the production of several neurotransmitters whose deficiency characterizes AD.[72]

The hormone melatonin is a reasonable alternative to benzodiazepines in patients with AD for sleep. Melatonin restores circadian rhythm and may help prevent wandering.

Dosage

A good starting dose for melatonin is 1 to 3 mg at bedtime.

Spirituality

Beyond reported improvements in memory, concentration, learning ability, and activities of daily living, patients enrolled in an integrative medical program for cognitive enhancement also note positive changes in what can be described as personal awareness. This awareness sometimes appears as a sense of increased self-knowledge or what many people call spirituality and leads to a feeling of connectedness. Some patients report that this spiritual connection leads to a profound level of wisdom: the combination of age, intelligence, and experience. This wisdom, or maturity, brings greater life satisfaction. These changes are consistent with the work of Benson, Larson, and Matthews, who established that an integrative medical program, including mind-body interactions, enhances spirituality.[73] Spirituality was expressed as experiencing the close presence of a higher power. Furthermore, spirituality, faith, belief, and religion are now well known to be associated with fewer medical symptoms and better outcomes when medical interventions are needed. A preliminary study presented by Dr. Yaku Kaufmann at the 2005 American Academy of Neurology meeting demonstrated that patients with AD who lived a rewarding spiritual lifestyle had slower progression of their illness. This lifestyle was defined as being connected with a spiritual presence in the life, whether it took the shape of a family member, close friend, support network, meditation, yoga, or prayer. I have seen this in my patients as well.

As the population ages, cognitive decline, including SMI, MCI, and AD, is expected to rise. An integrative medical program can have a powerful impact on these diseases.

Prevention Prescription

- Recommend a low-fat diet (15% to 20%). Most of the fat should be rich in omega-3 fatty acids (see Chapter 86, The Antiinflammatory Diet).
- Encourage stress management. Meditation, deep breathing, prayer, and various other relaxation techniques are shown to lower cortisol levels, improve memory, and lower blood pressure.
- Exercise. Physical, mental and mind-body exercises all are essential for a healthy body and a healthy mind.
- Consider measuring hormone levels (dehydroepiandrosterone, estrogen, pregnenolone) and replace hormones to keep at optimal levels.

Therapeutic Review

Nutrition

- Recommend a diet containing 15% to 20% fat based on patients' preferences. Include organic fruits and vegetables, and fish or seeds rich in omega-3 fatty acids, such as salmon or flaxseed oil. A1

Supplements

- Vitamin E: 2000 units/day A2
- *Ginkgo biloba:* 240 mg/day B2
- Phosphatidylserine: 100 to 300 mg/day B1
- Fish oil (docosahexaenoic acid [DHA] and eicosapentaenoic acid): 500 to 1000 mg/day B2
- Huperzine A: 50 to 100 mcg/day B2
- Vinpocetine: 2.5 to 10 mg/day B2
- Coenzyme Q10: 100 to 300 mg/day C1

Be aware of the rare possibility of increased clotting time in patients taking maximum doses of ginkgo, vitamin E, and DHA, especially with warfarin and aspirin.

Mind-Body Therapy

- Control stress: Perform daily morning meditation for at least 12–20 minutes. A1

Continued

- Exercise: Physical, mental, and mind-body exercise should be part of the integrative prescription.

Pharmaceuticals

- Deprenyl, 5 mg twice daily, slows progression.

- Rivastigmine is the most effective acetylcholinesterase inhibitor available. Start with 2.5 mg twice daily and work up per package insert.

- Memantine is usually started with 5 mg in the morning for 2 weeks and then is often increased to a maximum of 40 mg/day slowly over a 2-week period.

Caution: Do not use deprenyl with antidepressant medication because fatal reactions can occur. Deprenyl can be used in conjunction with anticholinesterase drugs.

Hormone Replacement Therapy

- Dehydroepiandrosterone (DHEA): 25 to 100 mg/day, depending on blood level

- Pregnenolone: 10 to 100 mg/day

- Melatonin (for sleep): 3 mg/day at bedtime. A proper dose allows a complete night's sleep without morning grogginess.

When using DHEA in men, measure and follow the prostate-specific antigen level. If it is elevated, do not use DHEA. Also consider using saw palmetto with DHEA.

KEY WEB RESOURCES

Alzheimer's Research & Prevention Foundation. www.alzheimers-prevention.org.	This Web site provides education on holistic and preventive medicine.
Alzheimer's Foundation of America. www.alzfdn.org.	This resource has information on local and national awareness events such as Free Memory Screening Day.
Alzheimer's Association. www.alz.org.	The focus is on caregiver support and education on the latest medical developments.
Alzheimer's Disease Education and Referral Center. www.nia.nih.gov/alzheimers.	This government-sponsored education site gives an overview of all the scientific research and has in-depth referral center.

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Chapter 10

Headache

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Headache is one of the most common complaints that brings a patient to the attention of health care providers.[1] Ninety percent of all headaches are either migraine, with or without aura, tension-type headache (TTH), or a mixture of the two. Sixteen percent of women and 6% of men suffer from migraine.[2] The remaining 10% of headaches seen by caregivers are secondary to disorders of the tissues of the head and neck including the cervical spine, sinuses, temporomandibular joints, dental structures, soft tissue trauma and posttraumatic conditions, with primary tumors, infection, and metastatic cancers constituting a small fraction of possible causes.

"Red flag" symptoms of life-threatening disorders include the following: early morning headaches that awaken the patient, a suggestion of increased intracranial pressure; visual dimming or double vision; headaches that are increasing in frequency or severity over weeks to months; headaches made significantly worse by postural changes; explosive onset of new, severe head pain; and headaches associated with mental status changes, focal motor or sensory deficits, syncope, seizures, fever, or stiff neck. Headaches in the setting of systemic illness, weight loss, human immunodeficiency virus infection, or known malignant disease clearly require thorough investigation. Findings on examination that prompt further diagnostic workup include focal neurologic signs, evidence of head or neck trauma, temporal artery tenderness, papilledema, stiff neck, fever, and physical evidence of local or systemic infection or malignant disease.

The emphasis in this chapter is on complementary and conventional therapies that are effective in the treatment of the primary headaches, migraine and TTH.

Migraine

Pathophysiology

Characteristics typical of migraine include subacute onset of throbbing head pain (unilateral or bilateral) associated with nausea and vomiting, photophobia, or sonophobia. Headaches are heralded by visual or other painless premonitory symptoms in approximately 20% of those with migraine. The duration is usually more than 6 hours, and headaches may last several days with fluctuating intensity. Precipitating factors can include menses, specific foods, stress or letdown following stress, changes in the weather, infection, fatigue, and bright sunlight.

Although the origin of the pain of migraine is not fully understood, evidence points to a role for potent vasodilators such as substance P and calcitonin gene–related peptide, released by peripheral nerve endings of cranial nerve V on blood vessels in the scalp and meninges.[3] This process leads to sterile inflammation and edema of blood vessels, with increased sensitivity to mechanical stimulation that causes pain. Glutamate, nitric oxide, and vanilloid receptors are also implicated in migraine. Translation of this information to therapy is very active. For instance, calcitonin gene–related peptide receptor antagonists are currently in phase I and II clinical trials.[4] In the periphery, release of serotonin by platelets in the early stages seems to increase pain and prolong the headache. Centrally, the presence of a "headache generator" in the midbrain and pons is supported by findings from positron emission tomographic studies obtained during migraine attacks. Genetic influences are evident in most patients, who have one or more family members experiencing migraine. Although the individual attacks of migraine are often stereotypical, variation is not uncommon, and comorbid TTH is frequent.

Patients with migraine often suffer from tension-type headache and other forms of headache. A carefully recorded history of headache symptom characteristics helps establish criteria that lead to diagnoses and helps to highlight distinctions that guide specific therapies.

The following sections describe complementary approaches that are potentially useful for integration with conventional therapies in the treatment of migraine

TABLE 10-1. Summary of Migraine Therapies

TYPES OF THERAPY	SPECIFIC EXAMPLES/COMMENTS
Preventive	
Lifestyle	Sleep hygiene, exercise, stress management
Nutrition	Elimination of "food triggers," consideration of food allergy, maintenance of good hydration
Supplements	Magnesium, riboflavin, coenzyme Q10, omega-3 fatty acids, alpha-lipoic acid
Botanicals	Feverfew, petasites, melatonin, and valerian root (sleep); ginger root (nausea)
Pharmaceuticals	Tricyclic antidepressants, beta blockers, calcium channel blockers, anticonvulsants, NSAIDs, botulinum toxin; reduction of the risk of analgesic rebound headache by addressing analgesic polypharmacy
Mind-Body Techniques	
Biofeedback	Motivation required to practice and use as a life skill
Relaxation	Progressive muscle relaxation, focused breathing exercises, guided imagery
Cognitive-behavior therapy	Modification of maladaptive thoughts and reactions to feelings and sensations
Neurolinguistic programming	Alteration of the subjective experience of pain and modification of expectations
Self-hypnosis	Use for both headache prevention and pain control
Mindfulness meditation	Improvements in mood, coping, blood pressure, muscle tone, pain control, and pain perception
Body work	Craniosacral therapy and chiropractic
Bioenergetics	Effectiveness in both preventing and treating migraine
Abortive and Acute	
Pharmaceuticals	NSAIDS, ergot alkaloids, isometheptene, intranasal lidocaine, triptans, valproate, magnesium, narcotics, antiemetics (ginger)
Chiropractic, massage	Use especially for headaches associated with neck discomfort
Acupuncture	Use for severe acute attacks

NSAIDs, nonsteroidal antiinflammatory drugs.

(Table 10-1). Conventional approaches rely heavily on pharmaceutical interventions to prevent or abort headaches, and these agents are usually prescribed with analgesics and antiemetics. Although these measures by themselves are effective in the management of symptoms, they are often expensive, have significant side effects, and fail to address the underlying physical, psychological, and energetic issues that lead to headache. Patients with headache currently use a variety of alternative and complementary therapies,[5] many of which are reviewed in this chapter.

Integrative Therapy

Lifestyle

Effective management of migraine requires a careful assessment of lifestyle issues relating to sleep, nutrition, exercise, stress management, and relationships. Regularizing mealtimes, developing an exercise routine, and correcting poor sleep can significantly reduce the frequency of migraine. Sleep hygiene guidelines are readily available, easy to implement, and often lead to a decrease in both duration and frequency of migraine.[6] A 30-minute exercise program three times per week at aerobic levels has beneficial effects on headache intensity and variable effects on frequency.[7,8]

Nutrition

Dietary choices clearly influence migraine, and exploration of diet is an important therapeutic avenue for improving migraine outcomes.[9] Dietary triggers are found in 8% to 20% of patients with migraine.[10] Patients usually know which foods they need to avoid. Red wines, dark beers, aged cheeses, some nuts, onions, chocolate, aspartame, and processed meats containing nitrates such as hot dogs and pepperoni are common offenders. Caffeine withdrawal can temporarily exacerbate migraine or TTHs, whereas caffeine taken during a migraine can reduce pain in some patients, possibly because of its vasoconstrictive effects on scalp and meningeal vessels. Caffeine excess (more than 5 cups of coffee per day) can contribute to maintaining chronic daily headache. Raising the possibility of dietary triggers with patients is important because these triggers sometimes go unnoticed. Specific mechanisms may include direct effects of ingested substances on neuronal elements governing headache (e.g., tyramine in cheeses and wine) or allergic responses to foods such as wheat or dairy products. Diets containing large quantities of omega-6 fatty acids are usually proinflammatory and are likely to aggravate migraine and chronic TTH.

Supplements

Magnesium

Levels of ionized tissue magnesium are often low in patients with migraine, especially in those with menstrual migraine.[11–13] Oral supplementation with magnesium has been shown to be beneficial in preventing different types of migraine.[14–17] The mechanisms leading to improvement with magnesium supplementation may include reduction in cerebral cortical neuronal excitability or alteration in magnesium-dependent, circadian regulatory mechanisms that are frequently disturbed in migraine.[18–20] One study showed that oral magnesium dicitrate, 600 mg,

given once a day, significantly reduced the frequency of migraine compared with placebo.[6,21] In another study, oral administration of 360 mg of pyrrolidine carboxylic acid magnesium daily for 2 months was associated with greater pain relief than was placebo in women with menstrual migraine.[22] Patients with menstrual migraine should continue magnesium for at least 3 months to determine effectiveness because beneficial effects may be delayed for several cycles.

Preventive benefit can be achieved with oral potassium magnesium aspartate (500 to 1000 mg/day at bedtime). Magnesium oxide is more readily available and cheaper than other forms, but it is poorly absorbed, especially when combined with calcium, zinc, or iron. Magnesium may cause diarrhea, particularly in those with irritable bowel syndrome, a common comorbid condition. For acute treatment of migraine, 2 g in 100 mL of saline given intravenously over 30 minutes appears to be effective and safe in an outpatient setting.[23–25] Magnesium can be used safely for both prevention and acute therapy of migraine during pregnancy.

Dosage
For prevention: potassium magnesium aspartate, 500 to 1000 mg at bedtime

Precautions
Magnesium may cause diarrhea; consider magnesium gluconate as an alternate form.

Riboflavin (Vitamin B_2)
Patients with migraine have been shown to have reduced phosphorylation potential in brain and muscle, a finding suggesting a mitochondrial defect in electron transport.[26] Riboflavin is a precursor for two coenzymes involved in electron transfer for redox reactions. One hypothesis for the mechanism of action of riboflavin is that it improves mitochondrial energy reserves without changing neuronal excitability.[27] Several clinical studies of riboflavin as a supplement in migraineurs noted significant preventive effects.[28,29] Riboflavin may have synergistic preventive effects when it is used concurrently with a beta blocker.[27] No head-to-head studies have compared riboflavin with other preventive measures. Results in children with migraine are mixed.[30,31]

Dosage
Give 200 mg twice daily with meals.

Precautions
Riboflavin is well tolerated and does not influence the metabolism of other agents. Patients may notice that their urine turns an intense yellow with daily use. Riboflavin is safe in pregnancy.

Coenzyme Q10
The rationale for studying coenzyme Q10 relates to lower phosphorylation potentials found in patients with a variety of chronic disorders including migraine.[32] The findings of an open-label trial showing reduction in headache frequency at 3 months with daily doses of 150 mg of coenzyme Q10 were confirmed in a double-blind, placebo-controlled, randomized trial (RCT) in 42 patients with migraine.[33,34] Oral coenzyme Q10, 100 mg three times a day, resulted in a reduction in attack frequency of 47.6% compared with 14.4% in the control subjects at 3 months. Headache days were also significantly reduced. As with riboflavin, no change in headache intensity or duration was noted once a headache occurred. No major recent studies have been conducted.

Dosage
Prescribe 150 to 300 mg/day; minimum 3-month trial, based on the research of Sandor et al.[34]

Precautions
Coenzyme Q10 is well tolerated, with rare gastrointestinal side effects. It is relatively expensive and safe in pregnancy.

Fish Oil
Rationale for the use of omega-3 fatty acids in migraine includes their antiinflammatory properties, vascular relaxation effects, and inhibition of serotonin release from platelets. Reports include a crossover randomized trial in 27 adolescents with migraine, comparing daily omega-3 fatty acids with an olive oil control over 2 months. Both olive oil and omega-3 fatty acid were associated with a striking reduction in headache frequency compared with baseline and washout frequencies.[35] Results of a larger study in 96 adults with migraine were negative.[36] The dosing ranges studied were 2 to 6 g/day. Side effects included nausea and symptoms of gastric reflux. Fish oil is safe during pregnancy.

Alpha-Lipoic Acid
The rationale for use of alpha-lipoic acid in migraine is similar to that for riboflavin and coenzyme Q10, in that it is a mitochondrial cofactor directly involved in energy production while additionally being a potent antioxidant. One high-quality study found that daily use for 3 months was associated with reduced frequency of migraine and a significant decrease in headache severity and headache days.[37]

Dosage
The dose 200 mg three times a day.

Precautions
None are reported. It is safe in pregnancy.

Daily use of a compound containing 400 mg of riboflavin, 300 mg of magnesium, and 100 mg of feverfew has been shown to be effective in reducing the frequency of migraine in adults.[38]

Botanicals

*Feverfew (*Tanacetum parthenium *Leaf)*
Johnson et al[39] reported a significant increase in migraine severity and frequency when feverfew was stopped in a small group of migraineurs who were taking it for prevention. In one well-designed study, a 70% reduction in headache frequency and severity was shown in 270 patients with

migraine.[40] Variations in the standardization of the dried leaf constituents confound replication studies of this herb. A reproducibly manufactured extract of feverfew showed preventive efficacy in a double-blind RCT.[41] No long-term studies documenting safety and no head-to-head trials with other preventive medications have been conducted. The mechanism of action of feverfew in migraine may be related to its inhibiting effects on platelet aggregation and inflammatory promoters such as serotonin and prostaglandins or possibly its effect in dampening vascular reactivity to amine regulators of blood flow.

Dosage

Oral administration of up to 125 mg/day of the dried leaf standardized to a minimum of 0.2% parthenolide. Beneficial effects may take weeks to develop.

Precautions

Aphthous ulcers and gastrointestinal irritation develop in 5% to 15% of users. Abrupt cessation of feverfew occasionally results in agitation and increased headache. Feverfew is not recommended during pregnancy because it prolongs of bleeding times.

Butterbur (Petasites hybridus *Root)*

In a large, three-arm, dose-finding RCT of a standardized extract of the root of this perennial shrub, investigators found that migraine attack frequency was reduced by almost 50%. Of patients taking the highest dose, 68% had a 50% or greater reduction in headache frequency.[42] This effect continued for at least 4 months. One smaller study showed similar results,[43] and another study in 108 children and adolescents with migraine also had positive results.[44] One study that compared butterbur root extract with both music therapy and placebo in the prevention of migraine in children had mixed findings; butterbur demonstrated efficacy compared with placebo in long-term follow-up but not in short-term follow-up.[45]

A systematic review of the published literature on the effectiveness of *Petasites hybridus* revealed that higher-dose extracts (150 mg) were associated with a lower frequency of migraine attacks after 3 to 4 months, compared with a lower dose and placebo.[46] The extract is commonly standardized to 15% of the marker molecule (petasins), and known carcinogens are removed. Drug-herb interactions have not been studied.

Dosage

Start with 50 mg three times a day for a month, then 50 mg twice a day.

Precautions

The effects of butterbur in pregnancy are unknown. Excessive belching is a side effect.

Supplements for Sleep

Sleep management is a major therapeutic strategy in helping patients gain control over their headaches. Melatonin and valerian root can be used on a temporary basis to improve sleep.

Melatonin

Melatonin is used in management of migraine to improve sleep and circadian rhythms. Sleep maintenance, as opposed to sleep induction, is improved with melatonin. Melatonin is recommended nightly for 4 to 6 weeks and then is tapered. During that period, a sleep hygiene program can be put into place to reduce the need for the supplement. Melatonin has few side effects. Leone et al[47] demonstrated that a daily intake of 10 mg of melatonin for 14 days significantly reduced cluster headache frequency. Other investigators have shown beneficial effects of melatonin in migraine and other types of headache, including for migraine prevention in children[48–50] However, a more recent double-blind placebo-controlled crossover study comparing extended-release melatonin at a dose of 2 mg 1 hour before bedtime did not demonstrate improvement in migraine frequency compared with placebo.[51]

Dosage

Usual dose is 2 to 12 mg. Start at 2 mg and titrate up every 4 days as needed for sleep. Lower doses are needed if taken each evening for weeks. Higher doses (more than 15 mg) are needed to induce sleep acutely over several days (jet lag).

Precautions

Fatigue, drowsiness, dizziness, abdominal cramps, and irritability are all possible.

Valerian (Valeriana officinalis *Root)*

When taken at night for sleep, valerian rarely results in residual drowsiness on awakening. Valerian is nonaddictive and useful as an anxiolytic when it is given during the daytime (up to 250 mg three times per day). It generally does not impair psychomotor or cognitive performance.[52] The mechanism of action includes stimulation of central nervous system gamma-aminobutyric acid (GABA) receptors along with enhanced release, and inhibition of reuptake, of GABA. In clinical trials, including use for sleep and anxiety, valerian has been judged safe.[52–55] Gastrointestinal irritation is the most common side effect (15%).

Dosage

Prescribe 100 to 300 mg of the extract, standardized to 0.8% valerenate at bedtime or 250 mg every 6 hours for anxiety.

Precautions

Valerian has an extremely unpleasant smell that may aggravate nausea during migraine. It may cause worsening of TTH if taken regularly for more than 3 months. Valerian should not be used during pregnancy.

> Magnesium aspartate, in contrast to magnesium oxide, is easily absorbed and rarely causes diarrhea when used for migraine prevention. Avoid giving either preparation at the same time as calcium, zinc, or iron. Dose: 500 to 1000 mg each night.

Pharmaceuticals

The integration of conventional and complementary approaches in the treatment of headache has no inherent difficulty. Conventional pharmacologic therapy includes the

use of preventive and abortive medications. The pharmaceutical approaches discussed here are those with the greatest evidence of efficacy and clinical usefulness.[56–60]

Preventive Pharmaceutical Therapies

Application of preventive pharmacologic therapies in practice is typically organized around classes of medications, including tricyclic antidepressants, selective serotonin reuptake inhibitors, beta blockers, calcium channel blockers, anticonvulsants, and other miscellaneous agents. The goals are reduction in headache frequency and severity, improved function, and increased responsiveness to abortive and analgesic agents.

The decision to start preventive therapy is based on (1) headache frequency of more than two per month or more than 3 days per month lost to headache, (2) willingness of the patient to take a medication or supplement daily for at least 3 months, and (3) ability to keep a headache diary. Medications for prevention are administered according to the half-life and according to a schedule that minimizes side effects. Effectiveness is best measured by having the patient keep a headache diary, noting headache frequency and intensity, as well as significant life events such as stressful circumstances, menses, vacations, and major changes. Patients may respond to any of several beta blockers (e.g., propranolol, atenolol, metoprolol, or timolol), thus making the choice of an agent highly individualized. One cannot predict who will respond to a given agent in advance, although the history of a family member who achieved effective prevention with a given agent may guide initial choices. Comorbid depression, a history of active asthma, and thyroid disease limits the use of beta blockers, whereas obesity limits the use of tricyclic antidepressants and valproate.

Medications and supplements are prescribed one at a time and are tapered up to a maximum dose or until satisfactory benefit is realized at lower doses. Most drugs are started at less than half the predicted maximum dose. Often, patients achieve satisfactory results at doses much lower than the maximum, particularly with the tricyclic antidepressants. Conversely, verapamil usually must be given at doses of at least 320 mg/day for benefit to occur. Magnesium, vitamin B_2, coenzyme Q10, and daily aspirin mix well with conventional preventive agents.

Once improvement is achieved, the medication combination is continued for 3 to 6 months, with periodic gradual reductions in one or more agents to determine the minimum effective dose. Effective preventive agents allow time for patients to work on lifestyle issues including management of stress, sleep, nutrition, and exercise, as well as time to develop life skills such as relaxation, biofeedback, and self-hypnosis. Preventive agents are also chosen to facilitate treatment of comorbid depression and sleep dysfunction. As patients improve, diaries that focus attention on pain are discontinued.

Tricyclic Antidepressants

Amitriptyline, in doses of up to 150 mg at bedtime, starting as low as 10 mg, is effective for prevention. A few patients do well on very low doses such as 10 mg at night. Other useful medications in this group include nortriptyline, up to 100 mg at bedtime. Sleep is often improved, which reduces migraine frequency. Dry mouth, morning drowsiness, and constipation are significant side effects.

Beta Blockers

Medications in this class that have been shown to be effective for migraine include propranolol, nadolol, timolol, atenolol, and metoprolol. Long-acting formulations have not been formally studied. Side effects include fatigue, depression, insomnia, dizziness, and nausea. Rebound headaches may occur if beta blockers are withdrawn suddenly. Dosing regimens for propranolol for migraine prevention range between 80 and 240 mg/day in two or three divided doses.

Calcium Channel Blockers

Calcium channel blockers shown to be effective include verapamil, nimodipine, flunarizine, and nifedipine. Delayed onset (weeks) of effectiveness is typical, and side effects such as abdominal pain, bloating, weight gain, constipation, and even headache are not uncommon. A typical dose of verapamil is 180 to 360 mg once daily.

Anticonvulsants

The major members of this group prescribed for migraine are sodium valproate, gabapentin (Neurontin), topiramate (Topamax), zonisamide (Zonegran), and levetiracetam (Keppra).[57,58] A typical adult dose of sodium valproate for prevention is 1500 mg/day, with a starting dose of 250 mg twice daily. Side effects include weight gain, alopecia, tremor, and nausea. Sodium valproate is available in 125-, 250-, 500-mg and sustained-release formulations. Topiramate is the most consistently effective of the four most commonly used drugs in this class, but cognitive side effects and nausea can be limiting. Levetiracetam and zonisamide have the fewest side effects.

Nonsteroidal Antiinflammatory Drugs

Trends toward reduction in migraine frequency have been seen with daily use of aspirin, naproxen, ketoprofen, and tolfenamic acid. Gastric side effects are common, and patient compliance is poor. Dosages include the following: naproxen, 500 mg twice daily; aspirin, 350 to 975 mg/day; and ketoprofen, 150 mg/day. These drugs are not safe in pregnancy.

Abortive Pharmaceutical Therapies

The following are descriptions of medications that, when taken early in the course of migraine, can abort further development of the headache.

Nonsteroidal Antiinflammatory Drugs

Ibuprofen (800 mg) and naproxen sodium (200 to 400 mg) can block headache progression when they are given during the first few hours when the headache is building. Ibuprofen in liquid form (200 to 400 mg) is recommended when nausea occurs early in the headache. Individual variation in responsiveness to nonsteroidal antiinflammatory drugs (NSAIDs) is high so that it is worth trying several different agents in this class early in headache.

Ergot Alkaloids

Now largely supplanted by the triptans, ergot alkaloids can be useful in patients who cannot tolerate other abortive methods. A typical dose is ergotamine tartrate, 1 mg orally or 2 mg sublingually, or dihydroergotamine (DHE-45), 2 mg subcutaneously (self-injection) every 4 hours for up to three doses. A nasal inhalational form is also available.

Isometheptene

Isometheptene (Midrin) has a low side effect profile and modest cost. It is a weak vasoconstrictor of scalp vessels. The dose is two or three capsules at the start of a headache, then one every 45 minutes for three more doses as needed within 24 hours.

Intranasal Lidocaine

Intranasal lidocaine is effective for all forms of migraine and is particularly useful when it is given during an aura and when nausea and vomiting are prominent early in the headache. Lidocaine (4% liquid) is applied with a dropper, 0.25 to 0.50 mL up each nostril with the patient supine and the head hyperextended. Side effects include a transient burning sensation in the nose and numbness in the throat. Repeat dosing can be hourly for 4 to 6 hours.

Triptans (5-Hydroxytryptamine Receptor 1B/1D Agonists)

The triptans, on average, are the most effective agents available for aborting migraine.[61–65] They act by blocking the release of inflammatory cytokines from the distal nerve endings of the trigeminal system onto scalp and meningeal vessels, as well as by their vasoconstrictive effects on scalp vessels. Multiple products are available by prescription, including tablet or melt forms, self-injection kits, and nasal sprays. The efficacy of a single dose is 60% to 80% for pain and nausea relief, with a 25% to 30% recurrence rate necessitating a second dose. The choice of triptan depends on the patient's response, the side effect profile, and the preferred route of administration. Long-acting forms, including naratriptan (Amerge) and frovatriptan (Frova), can be effective when recurrence rates are noted with the more rapidly acting triptans. Oral melt formulations and nasal sprays are useful when nausea is prominent early in the headache.

Usual dosing is at 2-hour intervals if necessary for a maximum of three doses in 24 hours.

Sumatriptan (Imitrex): 25-, 50-, 100-mg tablets, 20-mg nasal spray, and injection kits of 6 and 4 mg/0.5 mL
Naratriptan (Amerge): 1- or 2.5-mg tablets
Rizatriptan (Maxalt): 5- or 10-mg tablets or melt tablets
Zolmitriptan (Zomig): 2.5- or 5-mg tablets or melt tablets
Almotriptan (Axert): 12.5-mg tablets
Frovatriptan (Frova): 2.5-mg tablets
Eletriptan (Relpax): 40-mg tablets

Triptans are contraindicated in pregnancy, cardiovascular disease, complex migraine, and poorly controlled hypertension. Cost is a major factor. Rebound headache can occur with daily use. Side effects include transient pressure sensations in the chest, neck, and head. These drugs are ineffective in TTH but occasionally effective in cluster headache. Insurance coverage varies widely.

Botulinum Toxin

Botulinum toxin has been found to prevent migraine when it is injected in small quantities at multiple sites into the muscles of the forehead, temples, and posterior neck, as well as the trapezius muscle.[66–68] Effects last an average of 2 to 4 months. That botulinum toxin has also been reported to be effective in TTH suggests a common pathophysiology.[69] The U.S. Food and Drug Administration has approved botulinum toxin for treatment of chronic daily headache (more than 15 headache days per month). Side effects can include transient weakness of injected muscles. Dosing is 100 to 200 units total, injected with a 27-gauge needle over 15 to 25 sites (approximately 2 to 10 units per site).

Mind-Body Techniques

Biofeedback

Biofeedback can provide significant benefit for patients with migraine and TTH without major side effects. Thermal biofeedback, in which patients learn to increase the temperature of their hands through guided imagery and relaxation, is a commonly employed technique. The combination of thermal biofeedback and relaxation training has been shown to improve migraine symptoms significantly.[70] Meta-analysis of 25 controlled studies revealed that biofeedback is comparable to preventive pharmacotherapy.[71] Another meta-analysis of five studies revealed a 37% improvement in headache symptoms associated with thermal biofeedback.[72] A systematic review of 94 studies concluded that biofeedback was effective for both migraine and TTH.[73] Biofeedback, however, did not appear to provide additional benefit in a study involving 64 patients randomized to relaxation training or relaxation training plus biofeedback.[74]

No criteria are available for predicting benefit from biofeedback, and training requires a significant time commitment (10 to 15 hour-long sessions in addition to home practice). Pharmacotherapy combined with biofeedback may have variable results. This is an important point because vascular reactivity (a major target in biofeedback training) may be modified by medications used for headache prevention (e.g., beta blockers), thus potentially limiting the effects of training. Conversely, biofeedback could be favorably synergistic with magnesium or topirimate.[75] Biofeedback is indicated for patients intolerant to medications, those oriented toward self-efficacy in pain management, and in pregnancy, and it is especially suited to patients willing to practice the techniques regularly.

Relaxation

The category of relaxation includes progressive muscular relaxation, focused breathing exercises, and guided imagery. Holroyd and Penzien[71] reported that these techniques are as effective as biofeedback. Treatment effects were enhanced by beta blockers and other preventive agents, thus making integration both feasible and effective. Some patients are able to identify the early stages of a headache in time to deploy focused relaxation or guided imagery to abort the full development of pain. D'Souza et al[76] demonstrated that relaxation training improved headache frequency and disability associated with migraines among college students, compared with written emotional disclosure or a neutral writing group

control. These techniques can be taught in groups and then practiced individually using audiotapes. Relaxation appeals to those with an internal locus of control and above-average motivation (see Chapter 93, Relaxation Techniques).

Cognitive-Behavioral Therapy

Cognitive-behavioral therapy is a stress management approach designed to help patients identify maladaptive thought patterns (e.g., self-blame, hopelessness, helplessness, worthlessness, and catastrophizing), as well as emotional states such as anger and anxiety, that can precipitate and amplify headache. Acknowledgment of present-moment and historical emotional states, shifting of habitual thought patterns, and modification of physiologic responses are the key steps in this approach. This type of therapy has been shown to be effective alone or in combination with other behavioral therapies for headache.[77] Combining cognitive-behavioral and biofeedback therapies is effective.

Neurolinguistic Programming

Neurolinguistic programming[78,79] relies on the following: establishing excellent rapport between provider and patient; developing an agreed-on, positively stated, and well-formed set of therapeutic goals; and skillfully applying a set of linguistic techniques that provide the patient with tools to deal with pain. Therapeutic approaches include reframing the meaning of headache, shifting the sensory coding of the pain, practicing dissociation techniques, modifying expectations, accessing coping resources, and anchoring effective resource states during and between episodes of pain. Patients respond favorably to the highly specific methods for pain management that are not medication based, are easily learned, and are readily applicable.

Hypnosis

Hypnosis has been shown to reduce the number of headache days and to decrease headache intensity among patients with chronic TTH.[80] For abortive therapy, hypnosis is useful in helping patients identify the early stages of migraine so that they can initiate relaxation or self-hypnosis routines. Patient motivation and regular practice are vital components of this strategy. Self-hypnosis can also be useful in resetting expectations about future successes with treatment, reducing rumination about past and future, and modifying patterns of negative thought (see Chapter 92, Self-Hypnosis Techniques).

Mindfulness Meditation

Meditation has been shown to have positive effects on mood, cardiac function, blood pressure, and muscle tone when it is practiced regularly. Effects are believed to be mediated by the development of nonjudgmental awareness of feelings, thoughts, and sensations, combined with a sense of gratitude while optimizing sympathetic and parasympathetic nervous system balance. Group instruction is based on the work of Jon Kabat-Zinn et al,[81,82] and this technique is taught as an 8-week course, including 2 to 3 hours of formal training each week, combined with daily practice of at least half an hour of meditation. Patients report improved sleep and less anticipatory anxiety relating to headache, as well as reduction in headache intensity.[83] Home practice is important in maintaining benefits.[84,85]

Biomechanical Techniques

Physical Therapy

Physical therapy alone does not appear to be effective in the treatment of migraine, but it can be useful as an adjunct to biofeedback and relaxation training when patients have significant reactive muscle tension in the upper body with limitation of head and neck movement.[70]

Chiropractic and Craniosacral Therapy

One published RCT of chiropractic spinal manipulative therapy for migraine revealed improvement in frequency, duration, disability, and medication use compared with a control group.[86] Another study revealed moderate improvement of symptoms among patients with migraine who received either chiropractic manipulation or mobilization (compared with medical care only). Chiropractic may serve as adjunctive therapy when guided by patient reports of significant neck discomfort during and between headaches. It may be especially useful when combined with biofeedback. Cost analysis has been favorable, and studies have supported its use in migraine, cervicogenic headache, and intractable headache during pregnancy, but not for TTH.[87–89]

Craniosacral therapy, derived from osteopathic theory and practice, is a gentle manipulative approach that is effective for both migraine and TTH.[90,91] Beneficial effects of four to six treatments can be long lasting.

Bioenergetics

Acupuncture

Findings from a systematic review and meta-analysis of acupuncture for migraine prophylaxis, involving 22 trials with 4419 participants, suggest that acupuncture is more effective than routine care only, but not more effective than sham acupuncture. Acupuncture was found to be associated with slightly better outcomes and fewer adverse effects than prophylactic drug treatment.[92] A systematic review and meta-analysis of acupuncture for the management of chronic headache (including chronic migraine) concluded that acupuncture is superior to sham acupuncture and medication therapy in decreasing headache intensity and frequency and in improving response rate to treatment.[93] In sum, current evidence clearly suggests that acupuncture is effective as an adjunct to usual care in the treatment of migraine, but the degree to which placebo effects contribute to this efficacy is unknown.

Homeopathy

One study of homeopathy in a group of 98 patients with mixed headaches found a 20% overall improvement rate, which was stable at 1 year. Half the patients continued homeopathic treatments with or without conventional therapy. The investigators concluded that the patients who had the most improvement suffered from both TTH and migraine and had an average disease history of 25 years.[94] Other reports are of poor quality or are inconclusive.[95] Side effects of homeopathic remedies are usually minimal, and any positive effects make integrative efforts worthwhile (see Chapter 111, Therapeutic Homeopathy).

Prevention Prescription: Migraine

- Identify and avoid environmental factors that consistently lead to headache (e.g., allergens, fluorescent lights, loud noises, fumes, and dust).
- Implement a sleep hygiene program, using a prebedtime routine that signals a time leading to restorative sleep. Avoid excessive sleep as well as inadequate sleep.
- Eliminate foods that lower the threshold for migraine (e.g., chocolate, aged and yellow cheeses, caffeine, red wine, dark beer, shellfish, and meats processed with nitrates).
- Water and fluid intake should be a minimum of 40 to 60 oz per day for an adult.
- Maintain an exercise program: aerobic level activity, for a minimum of 30 minutes, three times a week.
- Regularize meals, sleep, exercise, and use of medications for prevention.
- Keep a diary documenting headache frequency and intensity, response to medications, association with major life changes, stress, and changes in physiologic states, such as menses, pregnancy and illness. Share diary information with caregivers.

Therapeutic Review: Migraine

Migraine Prevention

Lifestyle

- Regular meals and sleep, sleep hygiene, aerobic exercise three times a week, headache calendar, stress management, avoidance of environmental triggers — A 1
- Consideration of discontinuation of hormonal birth control method if menstrual migraine is evident or the history suggests cause and effect

Nutrition

- Elimination of food triggers: wine, aged cheese, cashews, chocolate, processed meats, caffeine — A 1

Biochemical Supplements

- Magnesium aspartate: 500 to 1000 mg nightly — B 2
- Riboflavin: 200 mg twice daily — B 1
- Coenzyme Q10: 150 mg daily — B 1

Botanicals

- Feverfew: 125 mg up to three times daily — B 2
- Butterbur *(Petasites hybridus)*: 50 mg three times daily — A 1
- For sleep: valerian root extract: 100 to 300 mg nightly; melatonin: 6 to 10 mg nightly — B 2

Pharmaceuticals

- Aspirin: 325 mg daily — C 2
- Amitriptyline: 10 to 150 mg nightly — A 2
- Propranolol: 60 to 180 mg daily — A 2
- Gabapentin: 300 to 600 four times daily — C 2
- Topiramate: 100 to 200 mg nightly — A 2
- Verapamil: 180 to 480 mg daily — B 2
- Valproate: 500 mg three times daily — A 2
- Botulinum toxin: subcutaneous 100 units every 3 months — B 1

Mind-Body Therapy

- Biofeedback: 10 sessions — A 1
- Cognitive behavioral therapy — A 1
- Hypnosis — B 1
- Mindfulness meditation: 8-week course — B 1

Biomechanical Techniques

Consider in cases where muscle tension in the jaw, neck, or shoulder is prominent:

- Chiropractic — C 2
- Craniosacral therapy — C 1
- Massage — C 1

Bioenergetics

- Acupuncture: six to eight sessions over 8 weeks, repeated as needed — A 1

Acute Migraine Treatment

Use of specific abortive measures depending on efficacy, cost, side effects, and ease of administration; use of narcotics and antiemetics not covered

Lifestyle

- Darkened, quiet environment, maintenance of hydration, meals if possible, sleep

Biochemical Supplements and Herbals

- Magnesium sulfate: 2 g IV in 100 mL saline over 30 minutes
- Ginger tea for nausea: 8 oz every 3 hours
- Aromatherapy (peppermint)

Pharmaceuticals

- Naproxen sodium: 250 to 500 mg every 4 hours
- Ibuprofen liquid: 200 to 400 mg every 2 hours
- Lidocaine 4% liquid: 0.25 mL in each nostril every 1 hour
- Isometheptene (Midrin): two tablets at onset, then one tablet every 45 minutes × three
- Triptans: many available; dosing routines identical: initial dose at the onset of head pain, followed no sooner than 2 hr by a second dose if necessary; limit: three doses in 24 hr
- Valproate: 1 g IV over 1 hour
- DHE-45: 1.5 mg IV over 30 minutes preceded by promethazine (Phenergan) 20 mg IV

Mind-Body Therapy

- Self-hypnosis training
- Practiced biofeedback routine
- Relaxation

Biomechanical Techniques

- Craniosacral therapy
- Massage, slow stretch

Bioenergetics

- Acupuncture
- Reiki

IV, intravenously.

Tension-Type Headache

TTH may exist in a spectrum with migraine, as shown by positive responses to antimigraine agents in some patients, with or without coexisting migraine. History and physical examination suggest intermittent muscle traction of pain-sensitive tendons and connective tissues of the head and neck. Pain is typically bilateral, nonthrobbing, and bandlike, with trigger points at the base of the skull, the temples, the masseters, and the forehead. The pain is typically slow in onset and intermittent, with little or no nausea or sensory sensitivity. Positive responses to NSAIDs suggest that inflammatory and myofascial influences dominate, with modest secondary contributions from vascular structures.

Certain pericranial conditions (e.g., brain tumor and central nervous system infection) can manifest with features of TTH and little else. It is rare for a vascular headache pattern to be the presenting complaint for such conditions. Warning symptoms and signs that suggest the need for head imaging and other studies are reviewed in the first section of this chapter.

Integrative Therapy

An integrated treatment approach to TTH has considerable overlap with migraine treatment. Lifestyle issues surrounding stress, sleep, exercise, and diet are central to effective management, and all need to be reviewed carefully for both the work and home environments. Individuals with baseline TTH may develop conditions that abruptly amplify the pain. Examples include sinus and dental infections, head trauma, refractive errors, glaucoma, cervical disk disease, depression, and occult hypertension.

A thorough physical examination may lead to discovery of tender areas and trigger points in the head, the neck, or the shoulders that promote or sustain head pain. Observation of the patient while he or she is sitting, walking, and lying down can provide useful clues to musculoskeletal imbalances. Examination of temporomandibular joints is important in all patients because daytime clenching, nocturnal bruxism, and joint disease all can contribute to the pain of TTH.

Patient education in ergonomics, posture, and breathing is often useful in treating TTH. Mind-body approaches are equally effective in migraine and TTH and are usefully integrated with conventional therapies. The effectiveness of biofeedback, stress management, guided imagery, and self-hypnosis is documented in TTH.[96] Time-contingent and limited use of analgesics is needed to avoid analgesic rebound headache.

Chronic daily headache is often caused by excessive use of medications, including prescription and over-the-counter analgesics, decongestants, sleep aids, and even caffeine. Integrating nonpharmacologic approaches early in treatment, aimed at eliminating polypharmacy, can help prevent or reverse difficult-to-treat chronic analgesic rebound headache.

A combination of sleep hygiene and regularization of daily schedules is effective in reducing pain in motivated and compliant patients. The botanicals for sleep described previously for migraine can be equally effective for those with tension-type headache (TTH). Patients should be strongly encouraged to reduce consumption of sugar, caffeine, and red meat, along with increasing omega-3 fatty acids to reduce sympathetic nervous system activity and to enhance production of antiinflammatory prostaglandins (see Chapter 86, The Antiinflammatory Diet). Detoxification from unneeded drugs is part of effective TTH management. One often overlooked area is dehydration. Poorly hydrated muscles tend to cramp and contract painfully.

Pharmaceuticals have a limited role because of the risk of rebound headache and because they tend to reduce motivation to attend to needed lifestyle adjustments. NSAIDs should be medium to long acting and strictly limited to less than 20 doses per week. Muscle relaxants provide limited short-term benefit and tend to lead to psychological dependence and rebound headache. Triptans are rarely effective in TTH.

When TTH occurs daily or almost daily without evidence of an underlying organic condition, analgesic rebound headache is likely, especially when patients take more than a total of 20 doses of analgesics (NSAIDS and opiates), decongestants, muscle relaxants, and caffeine per week. Caffeine consumption, when more than three drinks a day, should be tapered slowly over 2 to 3 weeks, along with short-acting analgesics. Pain is managed with patient education, biofeedback, relaxation, slow-stretch exercises, massage, heat, long-acting NSAIDs, and low-dose tricyclic antidepressants given at night (10 to 50 mg amitriptyline, or equivalent).

Chiropractic

A few older studies investigated chiropractic or osteopathic manipulation in TTH. Hoyt et al[97] reported a 50% reduction in headache severity after a single 10-minute cervical manipulation session. In posttraumatic headache, patients had a 57% reduction in pain intensity and a 64% reduction in analgesic use over a 2-week period after two cervical spine manipulation treatments, compared with treatment with ice packs.[98] Another group found no difference between chiropractic manipulation and daily amitriptyline at the end of a 6-week course of treatment in patients with chronic TTH. However, patients who received chiropractic manipulation had fewer headaches on follow-up 6 weeks after the end of treatment.[99] Finally, an RCT comparing soft tissue therapy plus spinal manipulation with soft tissue therapy plus placebo laser treatment for episodic TTH did not show a statistical difference in outcomes between the two arms of the trial.[100] Credible more recent studies are lacking.

Acupuncture

A three-arm RCT involving 270 patients with TTH demonstrated that a course of up to 12 acupuncture treatments over 8 weeks was associated with significantly improved clinical outcomes compared with no acupuncture, but not when compared with a sham acupuncture comparison group.[101]

A systematic review and meta-analysis of acupuncture for the treatment of TTH included 11 trials with 2317 participants. Wide variability in comparison groups complicates interpretation of the findings among the trials collectively. The two large trials that included a no-treatment control demonstrated statistically significant and clinically relevant benefit associated with acupuncture. A meta-analysis with data from five trials that compared acupuncture with a sham acupuncture control demonstrated small but statistically significant benefits for treatment response and other clinical outcomes. The authors of the systematic review concluded "that acupuncture could be a valuable nonpharmacologic tool in patients with frequent episodic or chronic tension-type headaches."[102] Although further research is needed to differentiate placebo effects from purely physiologic responses to needling, available evidence suggests that patients with TTH may benefit from a course of acupuncture.

Prevention Prescription: Tension-Type Headache

- Notice physiologic reactions to stressful situations in the home and the workplace, especially muscle contraction in the neck and shoulders, breathing patterns, chest sensations, and gastrointestinal responses such as nausea, pain, and diarrhea.
- Develop a daily relaxation routine that focuses attention on posture and muscles of the head and neck.
- Maintain adequate sleep, regular aerobic exercise, and adequate hydration.
- Modify the diet to ensure regular consumption or supplementation of omega-3 fatty acids.
- Be alert to conditions that may contribute to, or intensify, muscular head pain, such as sinus or dental infection, jaw clenching, tooth grinding, head thrusting, anxiety, and depression.
- Be checked for hypertension at least twice a year.
- Consult a physician if symptoms of weakness, loss of sensation, poor coordination, difficulty with speech, fever, or syncope occur with TTH.

Therapeutic Review: Tension-Type Headache

Emphasis is placed on lifestyle and mind-body techniques and reduced reliance on medication.

Lifestyle

- Stress management, sleep hygiene, nutritional choices, ergonomic awareness, regular aerobic exercise

Nutrition

- Increased omega-3 fatty acid per diet or supplements; reduced sugar, caffeine, red meats, tobacco, and alcohol

Sleep and Exercise

- Sleep hygiene
- Aerobic exercise for 30 minutes, three times per week

Supplements and Herbals

- Melatonin: 6 to 10 mg nightly 
- Valerian root: 100 to 300 mg nightly 

Pharmaceuticals

- Time-contingent NSAIDs 
- Limit total of NSAIDS, decongestants, and caffeine to less than 20 doses per week to prevent rebound headaches 

Mind-Body Therapy

- Biofeedback and relaxation training 
- Stress management, cognitive-behavioral therapy, and mindfulness meditation 

Biomechanical Techniques

- Manipulative therapy, massage, and craniosacral therapy 

Bioenergetics

- Acupuncture: 6 to 10 weekly sessions with follow-up as needed 

NSAIDs, nonsteroidal antiinflammatory drugs.

KEY WEB RESOURCES

National Institutes of Health (NIH) National Center for Complementary and Alternative Medicine (NCCAM). http://nccam.nih.gov/health/acupuncture/acupuncture-for-pain.htm.
This Web site contains current practice guidelines, ongoing research, and research findings relating to acupuncture for pain, including headache. The NCCAM home page links to headache management using other complementary approaches.

NIH National Institute of Neurologic Disorders and Stroke (NINDS). http://www.ninds.nih.gov/disorders/migraine/migraine.htm.
This Web site contains diagnosis criteria, treatment information, and details of recently funded research on migraine headache and pain.

American Headache Society. http://www.achenet.org/education/patients/index.asp.
This Web site provides information for patient education and on research on headache.

National Headache Foundation. http://www.headaches.org/cms.
This Web site has information for patients with headache and professionals who treat headache.

National Headache Foundation Headache Diary. http://www.headaches.org/For_Professionals/Headache_Diary.

Migraine Disability Assessment Test (MIDAS). http://www.headaches.org/pdf/MIDAS.pdf.

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Chapter 11

Peripheral Neuropathy

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Pathophysiology

Peripheral neuropathy, or peripheral neuritis, is a common neurologic disorder resulting from damage to the peripheral nerves. It may be caused by diseases of the nerves or may be the result of systemic illnesses. It has various causes including toxic trauma (Table 11-1), certain prescription medications and chemotherapeutic agents (Table 11-2), and mechanical injury causing compression or entrapment, as with carpal tunnel syndrome (see Chapter 66, Carpal Tunnel Syndrome). Even simple pressure on superficial nerves, such as from prolonged use of crutches or sitting in the same position for too long, can lead to the disorder. Nutritional deficiencies can cause peripheral neuropathy, as seen in B-vitamin deficiency (i.e., from alcoholism, pernicious anemia, isoniazid-induced pyridoxine deficiency, malabsorption syndromes). Other causes include viral and bacterial infections and other infectious diseases (e.g., human immunodeficiency virus [HIV] infection, Lyme disease), autoimmune reactions (e.g., Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy), cancer (e.g., lymphoma, multiple myeloma), collagen-vascular disorders (e.g., systematic lupus erythematosus, rheumatoid arthritis, polyarteritis nodosa, Sjögren syndrome), endocrinopathies (e.g., hypothyroidism, acromegaly), and rare inherited genetic abnormalities (e.g., hereditary sensory neuropathy types I, II, III, and IV; Krabbe disease; Charcot-Marie-Tooth disease). Despite a thorough history and physical examination, the origin remains a mystery in approximately 50% of cases.[1]

One of the most common causes is diabetes; peripheral neuropathy is estimated to be present in approximately 40% to 60% of persons with diabetes of 25 years' duration.[2] Diabetic neuropathy is now thought to be the most common form of peripheral neuropathy that afflicts humans,[3] and the incidence increases significantly with age.[4] Although the exact pathophysiology of diabetic neuropathy has not yet been clearly identified, the origin is multifactorial. Persistent hyperglycemia and autoimmune and microvascular mechanisms are important factors.

Persistent hyperglycemia is the most common primary factor responsible for the development of diabetic neuropathy. Persistent hyperglycemia is thought to increase the activity of the polyol pathway, which results in the intraneural accumulation of fructose and sorbitol and thereby damages the nerves.[5] This form of hyperglycemia alone, however, cannot account for the development of nerve damage because diabetic neuropathy also occurs in patients with well-controlled disease, whereas other patients with poorly controlled disease have no evidence of neuropathy.[2]

In addition to accumulation of intraneural fructose and sorbitol, immunologic mechanisms have a role in the development of diabetic neuropathy. This damage is caused by antineural autoantibodies that circulate in the serum of some diabetic patients. Antiphospholipid antibodies may also be present and may contribute to nerve damage in combination with vascular abnormalities.[6]

Finally, endoneural vascular insufficiency resulting from decreased nitric oxide or impaired endothelial function, impaired sodium/potassium-adenosine triphosphatase (Na^+/K^+-ATPase) activity, and homocysteinemia has been found to be a primary cause of diabetic neuropathy.[6–9] Investigators have postulated that ischemia related to endoneural and epineural vascular changes causes nerve damage by thickening the blood vessel wall. Eventually, occlusion of the vessel may occur, leading to vascular permeability and compromise of endoneural blood flow (Fig. 11-1).

Other multifactorial mechanisms implicated in the development of diabetic neuropathy are body habitus, environmental factors (including alcohol, smoking, exposure to heavy metals), and genetic predisposition.

By these mechanisms, the sensory, autonomic, and motor nerves all may be affected, beginning with the distal lower extremities and spreading to involve the upper extremities as the diabetes continues.[3] Diabetic neuropathy usually manifests in a "stocking-and-glove" distribution, with sensory loss, dysesthesias, and painful paresthesias, most commonly in the lower

TABLE 11-1. Agents Causing Symptoms Associated With Toxic Neuropathy

Acrylamide (truncal ataxia)
Alcohol
Allyl chloride
Arsenic (sensory alterations, brown skin, Mees' lines)
Buckthorn toxin
Carbon disulfide
Cyanide
Dichlorophenoxyacetic acid
Dimethylaminopropionitrile (urinary complaints)
Biologic toxin in diphtheritic neuropathy (pharyngeal neuropathy)
Ethylene oxide
Germanium
Hexacarbon (n-hexane) (glue sniffing; occupational exposure to solvents, glue, or glue thinner)
Lead (wrist drop, abdominal colic)
Lucel-7 (cataracts)
Mercury
Methylbromide
Mold (in water-damaged buildings)
Nitrous oxide inhalation
Organophosphorus esters (triorthocresyl phosphate, leptophos, mipafox, trichlorphon) (cholinergic symptoms, neuropathy of delayed onset)
Polychlorinated biphenyls
Tetrachlorbiphenyl
Thallium (pain, alopecia, Mees' lines)
Trichloroethylene (trigeminal neuralgia)
Vacor

Modified from Wyngaarden JB, Smith LH Jr, Bennett JC, eds. *Cecil Textbook of Medicine*. 19th ed. Philadelphia: Saunders; 1992:2246.

extremities. Common symptoms include the following: tingling, prickling, or numbness; burning or freezing pain; sharp, stabbing, or electric pain; extreme sensitivity to touch; muscle weakness; and loss of balance and coordination.

Integrative Therapy

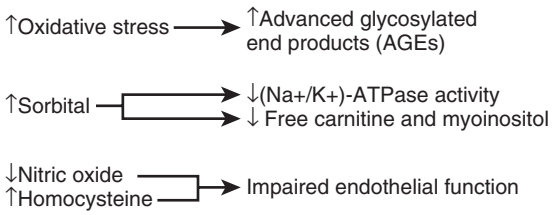
One survey showed that 43% of patients with peripheral neuropathy used complementary and alternative medicine (CAM) therapies. The most frequent were megavitamins

TABLE 11-2. Pharmaceutical Agents Associated With Generalized Neuropathy

5-Azacytidine
5-Fluorouracil
Amiodarone
Antiretrovirals (didanosine [ddI], zalcitabine [ddC], stavudine [d4T])
Aurothioglucose
Chloramphenicol
Clioquinol
Cytarabine
Dapsone*
Disulfiram
Ethambutol
Ethionamide
Etoposide
Gemcitabine
Gold
Glutethimide
Hexamethylmelamine
Hydralazine
Ifosfamide
Isoniazid†
Metronidazole, misonidazole
Nitrofurantoin*
Penicillamine
Perhexiline
Phenytoin
Pyridoxine† (in excessive amounts)
Platinum† (cisplatin, oxaliplatin)
Sodium cyanate
Statins (3-hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitors)
Stilbamidine
Suramin
Taxoids (paclitaxel, docetaxel)
Thalidomide†
Vinblastine
Vincristine
VM-26

Modified from Wyngaarden JB, Smith LH Jr, Bennett JC, eds. *Cecil Textbook of Medicine*. 19th ed. Philadelphia: Saunders; 1992:2247.
*Predominantly motor.
†Predominantly sensory.

FIGURE 11-1
Pathophysiologic factors in diabetic neuropathy. ATPase, adenosine triphosphatase; K^+, potassium; Na^+, sodium. (From Head K. Peripheral neuropathy: pathological mechanisms and alternative therapies. *Altern Med Rev.* 2006;11:295.)



(35%), magnets (30%), acupuncture (30%), herbal remedies (22%), and chiropractic manipulation (21%). Twenty-seven percent thought their neuropathy improved with these approaches. The most common reason (32%) for using CAM was inadequate pain control. Almost half the patients did not consult a physician before starting CAM.[10]

Because diabetic neuropathy is the most common peripheral neuropathy encountered in clinical practice, and its symptoms consist primarily of pain, the management of neuropathy involves not only prevention and control of underlying disease—in this case, diabetes—but also alleviation of the painful symptoms that result.

Lifestyle

Nutrition and Exercise

Good diabetic control can be one of the best preventive measures for peripheral neuropathy and must not be underestimated or overlooked. The benefits of near normoglycemia on nerve function in the Diabetes Control and Complications Trial adequately demonstrated that strict glycemic control may reduce the incidence of diabetic neuropathy by up to 64%.[11]

In addition, multiple studies have shown that following a whole foods, low-fat, high-fiber, plant-based diet along with exercise alone can decrease type 1 diabetic medications by up to 40%[12] or eliminate them completely for type 2 diabeties.[13–16] Therefore, strong emphasis should be placed on patient education about lifestyle changes, including a whole foods, low-fat, high-fiber, plant-based diet. Reduction of medications will help reduce health care costs and potential risk of side effects.[17] Maintaining diabetic control and avoiding environmental toxins such as heavy metals, cigarettes, alcohol, and pollution are of the utmost importance. Healthy eating habits should be established (see Chapter 32, Diabetes), and body habitus can play an important role in control of glycemia. Regular exercise of walking for a minimum of 30 minutes three times a week should be implemented. An optimal regimen would be daily walks for 30 minutes to 1 hour as tolerated (see Chapter 88, Writing an Exercise Prescription).

Although evidence is inadequate to evaluate the effect of exercise on the functional ability in people with peripheral neuropathy,[18] some evidence indicates that strengthening exercises improve muscle strength in peripheral neuropathy. Most of the studies involved conventional exercises such as cycling, running, and walking. However, patients may be fearful that exercise may exacerbate their symptoms, as well as increase the possibility of injury.[18] Physical limitations of their current state of health can lead to decreased compliance, and thus proper guidance and support must be given.

Yoga

In randomized controlled trials, nonrandomized trials, and uncontrolled trials, yoga was shown to improve glucose tolerance and insulin insensitivity, reduce body mass index, reduce lipid concentrations, reduce blood pressure, decrease stress and anxiety, increase energy levels, improve well-being and self-esteem, and control fluctuations of blood glucose better than oral hypoglycemic agents alone.[19–25] Yoga was shown to be helpful in children, adolescents, and adults with diabetes,[26–30] and it increased nerve conduction velocity in those patients with neuropathy.[31] Benefits can be seen in as little as 9 to 10 days.

Frequency

Benefits of yoga can be seen with a minimum of two to three sessions per week for a duration of 30 to 90 minutes. Daily practice is the most beneficial. Yoga asanas including Suryanamskar, Tadasana, Konasana, Paschimottansana Ardhmatsyendrasana, Shavasana, Pavanmukthasana, Sarpasana, Trikonasana, Sukhasana, Padmasana, Pawanmuktasana, Bhujangasana, Vajrasana, Dhanurasana, Bhastrika, and Padmasana Pranayama are beneficial for diabetes mellitus.

Precautions

Some asanas (postures) are contraindicated in patients with severe heart disease and retinopathy. Heated yoga should be avoided. A certified yoga instructor experienced in working with patients with chronic diseases should be recommended.

Tai Chi

Studies show that as little as 6 weeks to 6 months of performing tai chi can improve performance (6-minute walk, leg strength, time up-and-go), enhance balance (greatest improvements with those with large sensory losses), improve plantar sensation, decrease glycated hemoglobin (HbA1c), and improve peripheral nerve conduction velocities.[32–36] Tai chi can be used as a safe and effective intervention for patients with peripheral neuropathy.

Movement therapies such as yoga and tai chi are usually gentler and less strenuous and, as such, may lead to better compliance. With proper instruction and supervision, these techniques may be valuable lifestyle behaviors to help patients who may not be able to exercise using conventional modalities (see Chapter 90, Prescribing Movement Therapies).

Mind-Body Therapy

Biofeedback

Biofeedback may be used to reduce stress and improve coping skills, which may aid in improving compliance, thereby promoting better glycemic control and reducing pain associated with diabetic neuropathy.[37-38] Biofeedback has been shown to reduce HbA1c directly and to increase blood flow in the extremities, which, in turn, decreases neuropathic pain, reduces stress levels, improves psychological health, and enhances quality of life.[39–43] The patient should be referred to

a behavioral therapist or psychologist who teaches biofeedback techniques. Recommendation is for a minimum of six 1-hour biofeedback sessions at approximately 1-week intervals. Usually, treatments include sessions of guided imagery or relaxation techniques (see Chapter 95, Guided Imagery; Chapter 93, Relaxation Techniques). During these sessions, the patient wears a biofeedback device that indicates physiologic responses, such as electromyographic or electrodermal responses, and a vital sign monitor typically for blood pressure, pulse, or oxygen saturation. The monitoring enables patients to conceptualize how emotion, anxiety, stress, and pain can affect their physiologic status.

Once patients gain the ability to alter their physiologic state, they are taught to perform the relaxation biofeedback techniques at home with the use of a biofeedback home-use computer program[43] (e.g., emWave Desktop [Institute of HeartMath, Boulder Creek, Calif]), audio CDs, DVDs, or guided imagery exercises 10 to 20 minutes each day to attain the same result without the monitoring equipment (see Chapter 94, Enhancing Heart Rate Variability). Thus, biofeedback is a tool the patient can use to control certain physiologic parameters during times of stress or pain to help alleviate symptoms.

Bioenergetics

Infrared Therapy

The use of monochromatic near-infrared photo energy (MIRE) has been demonstrated to provide symptomatic reversal of peripheral neuropathy.[44,45] It provides a drug-free, noninvasive treatment for the consistent and predictable improvement of sensation in diabetic patients with peripheral neuropathy of the feet. Increasing foot sensitivity may substantially reduce the incidence of new foot wounds, and reversal of peripheral neuropathy is associated with a decrease in the absolute number of falls (78%), a reduced fear of falling (79%) and improved activities of daily living (72%).[46,47] Restoration of sensation, reduced pain, and improved balance in diabetic peripheral neuropathy was demonstrated in a double-blind, randomized, placebo-controlled study with MIRE.[48] This study used a medical device called the Anodyne Therapy System (ATS), which consists of therapy pads containing 60 near-infrared (890-nm) gallium aluminum arsenide diodes used three times a week for 40 minutes each visit.[48] In addition, a randomized clinical trial with photon stimulation reported significant improvements in pain quality, sensation, and quality of life outcomes for patients with severe peripheral neuropathy symptoms.[49] Photo stimulation is light emitted by light-emitting diode (LED) lights in the near-infrared wavelengths of 750 to 1500 nm.

Bioelectromagnetics

Static magnetic fields can penetrate up to 20 mm and appear to target the ectopic firing nociceptors in the epidermis and dermis. Although the exact mechanism of action is not well understood, investigators have speculated that magnets may lessen the sensation of pain by altering nerve C fiber firing frequency, possibly by stimulating K^+ internal rectifying channels to repolarize or hyperpolarize. A multicenter randomized, double-blind, placebo-controlled trial showed that subjects with diabetic peripheral neuropathy stage II or III who constantly wore static magnetic (450 G) shoe soles for 4 months showed statistically significant reductions in burning, numbness and tingling, and exercise-induced foot pain.[50] These results follow a previous study in which biomagnetic techniques were used in pain management. Positive outcomes were reported in 90% of patients suffering from diabetic neuropathy who used a magnetic footpad insole device (Magsteps [475 G], Nikku, Irvine, Calif) constantly for 4 months.[51] A systematic review of well-conducted controlled trials suggested that static magnetic fields are able to induce analgesia in all types of pain including neuropathy.[52] This included a double-blind, randomized controlled study that reported significant reductions in pain and increases in motor nerve conduction velocity by using frequency-modulated electromagnetic neural stimulation (FREMS).[53]

Acupuncture

Acupuncture and electroacupuncture have been found to be useful in neuropathic pain. Because beta endorphins have been found to be involved in the pathogenesis of both painful and painless neuropathy,[54] acupuncture may exert its well-known effect by stimulating the production of endorphins in the central nervous system.[55] Although acupuncture cannot be easily explained by known neurophysiologic mechanisms, several studies have examined the effect of acupuncture for the treatment of various types of peripheral neuropathy, including diabetic, HIV-associated, chemotherapy-induced, and neuropathy of mixed origin.[56] In randomized controlled studies, case series, and sham studies, acupuncture was shown to improve nerve conduction velocity, decrease numbness and pain (66% to 87%), and improve symptoms even more effectively than conventional medical treatment for peripheral neuropathy induced by chemotherapeutic drugs (66% versus 40%), especially for moderate and severe sensory nerve disorder.[57–63] In some cases (67%), patients were able to reduce or stop their pain medications.[64]

Acupuncture has a positive effect on neuropathic pain and often results in the ability to reduce or stop pain medications.

Patients can receive six courses of classical acupuncture analgesia[65,66] to both lower limbs over a 10-week period. In addition to classical acupuncture, electroacupuncture in a small clinical pilot study of biweekly treatments for 4 weeks demonstrated a reduction of continuous pain from 32.9% to 15.9% and a decreased intensity of pain attacks from 59% to 44%.[67] Electroacupuncture may have a positive influence on nerve conduction velocity and may also relieve neuropathic pain.[65] Electroacupuncture is performed in two cycles of five sittings each (10 sessions) at 2-day intervals.

A more comprehensive mixture of body acupuncture and scalp acupuncture (with or without electrical stimulation) can improve outcomes clinically by using the following protocol. Scalp points: upper one fifth sensory area, foot motor and sensory area; ear points: ShenMen, sympathic, foot; body points: GB-40, GB-34, SP-10, SP-6, ST-44, LR-3, and Bafeng (extra point). Electrical stimulation can be used for the ear and body points at a frequency of 100 Hz at low intensity for 10 to 15 minutes for enhanced response.[68]

Before such therapies can be recommended, a constitutional evaluation by a practitioner trained in acupuncture should be considered because each modality is prescribed on the basis of the unique symptoms and physical characteristics of the patient. A comprehensive review of medical acupuncture and scalp acupuncture for physicians may be found in the various texts by Dr. Joseph Helms[69] and Dr. Jason Hao.[68]

Botanical Medicine

Diabetes, like most diseases, is considered to be partly the result of inflammatory responses, especially when pain is involved. Many herbs are used for diabetes (see Chapter 32, Diabetes Mellitus), but a few Ayurvedic herbs, such as curcumin, [70–90] *Boswellia,*[91–105] and ginger,[106–116] are used to treat the pain of diabetic neuropathy and the other complications and comorbidities associated with diabetes.

Curcumin

Curcumin is the active ingredient in turmeric. It is widely used as a spice and food colorant throughout India. For more than 4000 years, curcumin has been used in traditional Ayurvedic medicine to treat a wide variety of ailments. It is one of the most researched natural medicines to date, with more than 5000 studies published.

Curcumin has shown to be beneficial in treating many different inflammatory diseases. It reduces inflammation in more than 97 biologic mechanisms including c-reactive protein, cyclooxygenase-2, 5-lipoxygenase, interleukin (IL)-1beta, IL-6, IL-12, tumor necrosis factor-alpha, interferon-gamma, activator protein-1, nuclear factor-kappaB, macrophage inflammatory protein, matrix metalloproteinase, human leukocyte elastase, several types of protein kinases, adhesion molecules, and genes involved with inflammation.[81–85] In addition, curcumin has been shown to improve endothelial function[86,87] and reduce vascular inflammation[88,89] and down-regulate adipokines, including resistin, leptin, and monocyte chemotactic protein-1.[81] Curcumin also shows antinociceptive activity by attenuating diabetic neuropathic pain[90] and provides other benefits for diabetic complications in in vitro, animal, and human studies.[83] Therefore, curcumin can be used as a safe analgesic for neuropathic pain while assisting in reversal of insulin resistance, hyperglycemia, hyperlipidemia, and obesity, which is common in diabetic patients as well as in the general population.[81]

Dosage

Dosing for curcumin C3 Complex: 500 to 1000 mg orally three times daily; or Bosmeric-SR (a sustained-release formulation that combines boswellia and ginger along with black pepper to enhance absorption), two caplets orally twice daily.*

Precautions

Although curcumin is nontoxic to human subjects at high doses,[82] many curcumin supplements may contain contaminants such as lead and are not standardized to the curcuminoids that provide the health benefits. Curcumin C3 Complex is a patented form of curcumin that is standardized to 95% curcuminoids, including curcumin (70% to 80%), bidemethoxycurcumin (2.5% to 6.5%), and demethoxycurcumin (15% to 25%). Curcumin C3 Complex has the most research in human studies at major hospitals and universities and thus is a safe and effective form to be recommended.

*Editor's Note: Dr. Pai has financial interests to the company that produces Bosmeric-SR.

Geranium Oil (Pelargonium *spp.)*

A patented formulation of geranium oil, Neuragen PN, has been clinically studied. It contains a proprietary blend of five essential oils and six homeopathic ingredients. A multicenter double-blind crossover trial and a randomized, double-blind, placebo-controlled clinical trial showed a significant reduction in neuropathic pain in 93% of patients of the patients within 30 minutes of application of Neuragen PN. In addition to the immediate reduction of neuropathic pain, 70% to 80% had lasting relief up to 8 hours.[117,118] Geranium oil provides significant pain relief in as little as 5 minutes and lasts up to 8 hours. Therefore, geranium oil can be used as monotherapy or used in conjunction with other treatments for diabetic neuropathy for breakthrough pain or immediate pain relief.

Dosage

Neuragen PN is highly concentrated, and thus one needs to apply one to two drops to the affected area, rub in, and allow to absorb. This can be applied several times a day but no more than five times daily. For efficient application to wider areas, or for extremely sensitive skin, it is recommended to dilute four or five drops in 1 tablespoon of carrier oil such as grapeseed oil or jojoba oil before application. Neuragen PN is now also available in a gel for easy application. Pain relief may be immediate but usually is noticed within 30 minutes. If relief is not experienced within the first application, repeat the application over a period of 3 days.

Precautions

As with any essential oil, only a few drops are needed because they can irritate the skin. For patients with sensitive skin, it is best mixed with carrier oil first before direct application is attempted. Wash hands after use; avoid contact with eyes and open sores. Discontinue if rash occurs.

Evening Primrose Oil

Evening primrose oil (EPO) is extracted from the seeds of *Oenothera biennis.* EPO is a rich source of omega-6 essential fatty acids, primarily gamma-linolenic acid (GLA) and linoleic acid, both essential components of myelin and the neuronal cell membrane.[119] GLA has provided positive results in the treatment of experimental diabetes and may be more beneficial than docosahexaenoic acid (DHA) in preventing diabetic neuropathy.[120–122] GLA is converted to prostaglandin E_1 (PGE_1) preferentially over PGE_2. PGE_1 has antiinflammatory, antiplatelet, and vasodilating properties. In patients with diabetes, however, levels of PGE_1 are decreased and levels of PGE_2 and thromboxane are increased[132] and thus tend to promote inflammation, vasoconstriction, and platelet aggregation.[124] Supplementing the diet with GLA has been shown to augment the production of PGE_1 (by bypassing the blocked enzymatic step delta-6-desaturase) seen in patients with hyperglycemia.[125–127]

Two of three randomized controlled trials showed positive effects of GLA in diabetic neuropathy.[119] Two of the trials demonstrated, with GLA at 360 mg/day for 6 months and 480 mg/day for 1 year, statistically significant improvements in neuropathy scores, nerve conduction velocities, and action

potentials. Therefore, EPO may be helpful for mild to moderate diabetic peripheral neuropathy.

Dosage

The dose is 360 mg/day of GLA from EPO (the most researched source of GLA, as opposed to borage oil or black currant oil), and it may be increased up to 480 mg/day. Obtain high-quality oil (preferably certified organic), packaged in light-resistant containers, refrigerated, and marked with a freshness date to avoid rancidity.

Precaution

EPO may increase the effectiveness of ceftazidime, chemotherapy agents, and cyclosporine and may interact with phenothiazines, thus causing an increase in seizures. Patients taking antiplatelet agents or anticoagulants should use EPO cautiously or not at all. Theoretically, the use of nonsteroidal antiinflammatory drugs (NSAIDs) may counteract the effect of EPO.

Supplements

Many supplements have been shown to be helpful for symptoms of diabetes (see Chapter 32, Diabetes) and specifically for peripheral neuropathy. Those supplements with the best results for peripheral neuropathy are discussed here.

Acetyl-L-carnitine

Acetyl-L-carnitine (ALC) is an acetylated form of L-carnitine, an amino acid responsible for transport of fatty acids into a cell's mitochondria. ALC is far superior to normal L-carnitine in terms of bioavailability in that it is absorbed by the gastrointestinal tract, enters cells, and crosses the blood-brain barrier more readily than does unacetylated carnitine.

Peripheral neuropathy is a common side effect of chemotherapy drugs belonging to platinum or taxane families. Animal studies showed the benefits of ALC as a specific protective agent when it was given concomitantly and also after treatment for chemotherapy-induced neuropathy after cisplatin, paclitaxel, and vincristine without showing any interference with the antitumor activity of the drugs.[128,129] Further studies in humans showed that ALC, given as a 1-g/day infusion over 1 to 2 hours for at least 10 days, improved chemotherapy-induced peripheral neuropathy in up to 73% of the patients.[130] Patients with chemotherapy-induced peripheral neuropathy treated with oral ALC (1 g three times a day) for 8 weeks showed sensory improvement (60%) and motor improvement (79%), and their total neuropathy scores that included neurophysiologic measures improved (92%), with symptomatic improvement persisting at median 13 months after treatment of ALC.[131] In addition to chemotherapy-induced peripheral neuropathy, multiple long-term (1-year) randomized, double-blind, placebo-controlled studies showed that ALC improves pain, nerve regeneration, and vibratory perception in patients with chronic diabetic neuropathy.[133,134] ALC appeared to work more effectively in patients with type 2 diabetes with a shorter duration of neuropathy than in patients with type 1 diabetes.[132]

Dosage

The recommended dose is 500 mg orally twice a day to 1000 mg orally three times a day. Better pain control is seen at the higher dose regimen.

Precautions

ALC may cause nausea, vomiting, diarrhea, headache, bladder irritation or infection, unusual body odor, stuffy nose, and rash. Other side effects associated with ALC include restlessness and difficulty sleeping.

Alpha-Lipoic Acid

Alpha-lipoic acid, also known as thiotic acid, is approved for clinical use in the management of diabetic neuropathy in Germany and has been used there extensively in medical practice since 1959.[134] Alpha-lipoic acid is a universal antioxidant, exerting direct (scavenges free radicals) and indirect (participates in the process of recycling other natural antioxidants, thereby increasing glutathione, vitamins C and E, and coenzyme Q10) antioxidant activity.[135–138] Alpha-lipoic acid chelates transition metal ions (e.g., iron and copper) and effectively mitigates toxicities associated with heavy metal poisoning.[139] Investigators have established that alpha-lipoic acid protects from lipid peroxidation and increases the activity of antioxidant enzymes—catalase and superoxide dismutase—in peripheral nerves. By decreasing oxidative stress, alpha-lipoic acid normalizes impaired endoneural blood flow and the impaired nerve conduction velocity.[140]

Several studies established the neurogenerative and neuroprotective effects of alpha-lipoic acid. The efficacy and safety of alpha-lipoic acid in peripheral and autonomic diabetic neuropathy were demonstrated in many randomized, double-blind, placebo-controlled trials.[141–145] A meta-analysis provided evidence that treatment with alpha-lipoic acid significantly improves both positive neuropathic symptoms and neuropathic deficits to a clinically meaningful degree in diabetic patients with symptomatic polyneuropathy.[146] Further studies showed the oral forms of alpha-lipoic acid to be effective on peripheral neuropathy.[147] Alpha-lipoic acid was shown effective for diabetic mononeuropathy of the cranial nerves, with full recovery of all the patients in the study.[148] The studies ranged from a minimum of 3 weeks to 2 years, and thus 3 weeks is likely to be the minimum amount of treatment time. Although greater improvements were seen with higher doses, so were adverse effects such as gastrointestinal upset and headaches.[146]

Most studies of alpha-lipoic acid used parenteral doses ranging from 600 to 1800 mg, which demonstrate more rapid response than oral doses of the same range, and found a continuous daily improvement in symptom scores beginning on the eighth day of treatment.[146] Unfortunately, the parenteral form of alpha-lipoic acid is not currently available as a prescribed therapy in the United States; only the oral form is available in various doses. In most studies, 600 mg seems to be the starting dose. To obtain similar results, patients should use high-quality products from manufacturers that source the alpha-lipoic acid from Europe (Germany or Italy).

Dosage

Alpha-lipoic acid is given orally at 600 to 1800 mg daily. Start with 600 mg daily, and increase up to 1800 mg daily in divided doses if needed.

Precautions

Although no evidence has indicated that alpha-lipoic acid affects glycemic control, case studies have shown improved glucose handling in diabetic patients.[139] As a precaution, patients predisposed to hypoglycemia, including those

receiving hypoglycemic agents, should have blood glucose levels monitored closely. In addition, because alpha-lipoic acid acts as a chelator, monitor for possible mineral deficiencies. Gastrointestinal upset may occur at higher doses. Rarely, this supplement may cause rash.

B Vitamins

Benfotiamine: Vitamin B_1

Benfotiamine, which is also known as *S*-benzoylthiamine-*O*-monophosphate, is a lipid-soluble derivative of vitamin B_1 (thiamine) and is absorbed up to 3.6 times more than water-soluble forms. Vitamin B_1 is associated with a 120-fold greater increase in the levels of metabolically active thiamine diphosphate. Its lipid solubility allows it to penetrate the nerves more readily. It has been found to give higher bioavailability of thiamine than its water-soluble counterparts.[149–151] Studies have shown benfotiamine to improve neuropathy scores significantly[152,153] and to increase nerve conduction velocity.[154–156] In a randomized, placebo-controlled, double-blind pilot study, investigators also demonstrated a pronounced effect on the decrease in pain[157] in conjunction with the earlier described benefits. Benfotiamine may also be beneficial in preventing diabetic nephropathy[158] and retinopathy.[159] Therapeutic benefits can be seen as early as 3 weeks, with the most significant improvement in patients taking the highest-dose benfotiamine.[160]

Dosage

The recommended dose of benfotiamine is 150 to 300 mg twice daily specifically for diabetic peripheral neuropathy.

Methylcobalamin: Vitamin B_{12}

Methylcobalamin is the active form of vitamin B_{12}. In a small double-blind, placebo-controlled trial of patients with type 1 and 2 diabetes with neuropathy, those given oral methylcobalamin at a dose of 500 mcg three times daily showed significant improvements of somatic and autonomic symptoms compared with placebo.[161] A review of several clinical trials of the use of methylcobalamin alone or combined with other B vitamins found overall symptomatic relief of neuropathy symptoms that was more pronounced than electrophysiologic findings.[162] Additionally, supplementation of 1500 mcg/day methylcobalamin for 2 months resulted in improved vibratory perception thresholds and heart rate variability (a sign of improvement in signs of autonomic neuropathy) in patients with diabetes.[163]

Dosage

The dose is 500 mcg three times daily or 1500 mcg daily of methylcobalamin or 5-adenosylcobalamin for best bioavailability and absorption. Most generic vitamins contain the cyanocobalamin, which may not be as effective or as beneficial.

B-Complex Multivitamin

Vitamins B_1 (thiamine), B_6 (pyridoxine), and B_{12} (cobalamin) play an important role in the pathogenesis of peripheral neuropathy in deficiency syndromes such as those resulting from alcoholism or pernicious anemia, from isoniazid-induced pyridoxine deficiency, and from malabsorption syndromes. If peripheral neuropathy is caused by deficiency syndromes, then use B-100 complex (a multivitamin that usually contains 25 to 100 mg of thiamine, riboflavin, niacin, pyridoxine, and pathothenic acid and also may include other vitamins such as folate) for ease of administration and intake of all B vitamins.

Dosage

B-complex multivitamin (B-100), one tablet once or twice daily is taken for peripheral neuropathy caused by deficiency syndromes. The B vitamins such as methylcobalamin and 5-adenosylcobalamin (vitamin B_{12}) and the 5-methyltetrahydrofolate (5-MTF) form of folate should be used in these formulas.

Precautions

Avoid excessive doses of vitamin B_6 (pyridoxine). Doses higher than 250 mg/day can cause reversible nerve damage.

> In prescribing B-complex vitamins, make sure that the patient is not already taking another vitamin supplement that may contain B vitamins. Vitamin B_3 (niacin) in doses greater than 300 mg/day may cause headache, nausea, skin tingling, and flushing. Vitamin B_6 in doses greater than 250 mg/day may cause reversible nerve damage.

Fish Oil: Omega-3 Fatty Acids

Similar to EPO (GLA), omega-3 fatty acids are also essential for healthy nerve cell membranes and blood flow.[164] Omega-3 fatty acids have been found to have neuroprotective effects against experimental diabetic neuropathy, to reduce proinflammatory cytokine production, and to benefit macrovascular and microvascular functioning in diabetics.[165–168] A clinical study of diabetic patients with neuropathy who consumed 1800 mg eicosapentaenoic acid (EPA) daily for 48 weeks reported significantly decreased cold and numb sensations, vibrational perception, and improved vibratory threshold in these patients. Circulation, measured in the dorsal is pedis artery, and lipid profiles also significantly improved.[169]

Dosage

Doses are EPA, 1000 to 2000 mg/day, and DHA, 500 to 1000 mg/day. The natural triglyceride form provides superior absorption and bioavailability up to 70% more than preparations with ethyl ester forms.[170] For patients who are vegetarian or allergic to fish, a plant-based form of EPA and DHA called NutraVege is available. It contains *Echium plantagineum* oil (stearidonic acid, a precursor of EPA) and algal DHA and GLA. High-potency fish oils should be used to obtain the clinical dose. They also should be independently tested for purity (e.g., no heavy metals), potency, and label claims. Sources that are sustainably harvested are preferred to preserve the ocean's ecosystem and reduce overfishing.

Precautions

Possible blood thinning effect may occur with higher doses. Patients taking anticoagulant medications should be closely monitored.

Pharmaceuticals

Capsaicin

Capsaicin, an extract of chili peppers, when applied topically, has been demonstrated to relieve neuropathic pain by affecting sensory fibers, especially C fibers,[171] and by depleting

endogenous neurotransmitter stores associated with pain transmission, such as substance P, vasoactive intestinal peptide, cholecystokinin, and somatostatin.[172] Capsaicin does not reverse, stabilize, or lessen neuropathy but decreases the pain that occurs from it. The result can be a burning sensation with the first few weeks of use. Successive application, however, results in a dose-dependent degeneration and desensitization of afferent fibers blocking further action potential conduction.[171] Patients should be advised to continue use, if the pain is tolerable, for at least 4 to 6 weeks before full benefits are appreciated.

A Cochrane Database Systematic Review showed that capsaicin, either as repeated application of a low-dose (0.075%) cream or a single application of a high-dose (8%) patch, may provide a significant degree of pain relief to some patients with painful neuropathic conditions.[173] In addition, patients with postherpetic neuralgia and painful HIV-associated distal sensory polyneuropathy were studied in randomized, double-blind, multicenter trials using a high-concentration capsaicin dermal patch successfully for up to 1 year; this patch is now available by prescription.[174–176]

Dosage

Capsaicin cream is available over the counter (Capzacin HP, Zostrix HP). Various strengths range from 0.025% to 0.1%, although clinical studies use the 0.075% strength. The cream is applied to the affected area up to three or four times daily for at least 4 to 6 weeks. Clinical trials show that application must take place three or four times a day for improvement.[173] Using daily, twice daily, or on an as-needed basis is likely ineffective.

Capsaicin 8% patch (Qutenza) is by prescription only and is applied in a physician's office. The painful area is pretreated with anesthetic, and the patch is applied for 1 hour and then removed. One patch provides relief for up to 3 months. Follow insert directions for specific application procedure.

Precautions

Application with gloves is recommended. Wash hands immediately after application, and avoid contact with eyes or mucous membranes. Local skin irritation, which is often mild and transient but may lead to withdrawal, is common. Systemic adverse effects are rare.

Antidepressants

The Neuropathic Pain Special Interest Group of the International Association developed evidence-based guidelines for pharmacologic treatment of neuropathic pain using first-line treatment options including tricyclic antidepressants (TCAs), dual reuptake inhibitors of serotonin and norepinephrine, and calcium channel α_2-δ ligands.[177] The results of a systematic review defined clinical success as a 50% reduction in pain. Investigators found that TCAs were the most effective analgesics, followed by traditional anticonvulsants, and then the newer-generation anticonvulsants.[178] However, the review concluded that the efficacy of most of these pharmacologic treatments is limited, because for any particular drug, only 30% of patients treated will experience analgesia.[49] With these low analgesic response rates and the risk of side effects, the use of integrative therapies and dietary supplements is therefore recommended as a trial of benefit before treatment with pharmaceuticals.

Tricyclic Antidepressants

TCAs such as amitriptyline (Elavil, Endep), nortriptyline (Aventyl, Pamelor), and desipramine (Norpramin) have been commonly used as the mainstays in the palliation of pain secondary to diabetic neuropathy.[179] Many placebo-controlled, randomized controlled trials found TCAs to be efficacious for several different types of neuropathy.[180] TCAs work by increasing the postsynaptic concentration of norepinephrine. Because the inhibitory pathways in the spinal cord use norepinephrine as a neurotransmitter, TCAs are believed to increase the inhibitory influence on nociceptive transmitting neurons.[181] The selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine and paroxetine have also been used; although they are better tolerated than the TCAs, they have little or no efficacy in relieving pain.[182–184]

Dosage

To minimize side effects and encourage compliance, start therapy with amitriptyline or nortriptyline at a dose of 10 mg at bedtime. Titrate this dose upward to 25 mg at bedtime as side effects allow, in 10-mg to 25-mg increments. Even at lower doses, patients generally report rapid improvement in sleeping and begin to experience some pain relief in 10 to 14 days. If no relief of pain is obtained with increased doses (usual range, 50 to 300 mg/day), the addition of gabapentin (Neurontin) alone or in combination with nerve blocks with local anesthetics is recommended.[185] The slow onset of action of TCAs and their potential side effects often require a gradual dose buildup (6 to 8 weeks) before maximum efficacy and tolerance are achieved.

Precautions

Significant anticholinergic side effects, including dry mouth, constipation, sedation, and urinary retention, are common. TCAs are contraindicated in patients who have significant ischemic heart disease, and these drugs may also cause arrhythmias and orthostatic hypotension (thus should be avoided in older persons because of the risk of falling). Limit doses to less than 100 mg/day when possible. Screening electrocardiography for patients older than 40 years is recommended. These agents are not to be used with monoamine oxidase inhibitors (MAOIs).

Serotonin Norepinephrine Reuptake Inhibitors

- Venlafaxine (Effexor)
- Duloxetine (Cymbalta)

Although both drugs have been used traditionally as antidepressants, studies on venlafaxine and duloxetine have demonstrated beneficial treatment for reduction of painful diabetic neuropathy with better tolerability and fewer side effects than TCAs.[186–190] Although these studies are positive and duloxetine has been granted U.S. Food and Drug Administration (FDA) approval for treatment of neuropathic pain, they were less than 12 weeks in duration, and thus the long-term efficacy and safety are unknown.

Dosage

For venlafaxine ER, the dose is 150 to 225 mg daily; start with 150 mg daily, and increase to 225 mg daily if a greater analgesic effect is needed. The maximum dose of duloxetine is 60 mg daily; start with 30 mg daily and increase to 60 mg

daily if an increase in analgesic effect is needed. With both medications, higher doses increase the risk of side effects.

Precautions

Nausea, dyspepsia, somnolence, and insomnia are possible. Venlafaxine may cause cardiac rhythm changes. Duloxetine may decrease sodium, uric acid, chloride, gamma-glutamyltransferase, and alanine aminotransferase. It may also increase bicarbonate and alkaline phosphatase levels.

Anticonvulsants

- Gabapentin: First-line choice
- Pregabalin (Lyrica): First-line choice
- Phenytoin (Dilantin)
- Carbamazepine (Tegretol)

Phenytoin and carbamazepine have been used with varying degrees of success, either alone or in combination with antidepressants.[191] Gabapentin has been shown to be highly efficacious in the treatment of various painful neuropathic conditions, including postherpetic neuralgia and diabetic neuropathy.[192] Based on the reviewed randomized controlled trials, gabapentin shows good efficacy, a favorable side effect profile (especially when compared with phenytoin and carbamazepine), and few drug interactions; therefore, it may be a first-choice treatment in painful diabetic neuropathy, especially in older adults.[193,194] The precise mechanism of action of anticonvulsants that accounts for their analgesic efficacy is unknown. Anticonvulsants modulate both peripheral and central mechanisms through sodium channel antagonism, inhibition of excitatory transmission (e.g., *N*-methyl-D-aspartate receptor), or enhancement of gamma-aminobutyric acid–mediated inhibition.[195]

Pregabalin is a selective high-affinity ligand for the α_2-δ subunit of voltage-gated calcium channel,[196] which plays a role in pathologic changes believed to be associated with neuropathic pain in humans.[197,198] Double-blind, placebo-controlled trials showed that pregabalin is effective in the treatment of diabetic peripheral neuropathy and postherpetic neuralgia, and it produces significant improvement of various pain scores as well as reduced sleep interference.[199,200] The FDA has approved pregabalin for the management of neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia. Pregabalin is structurally and mechanistically related to gabapentin but differs from gabapentin in exhibiting linear pharmacokinetics with increasing dose and low intersubject variability. These properties may make pregabalin easier to prescribe and could impart a more effective dose range with potentially fewer side effects. Although pregabalin has become a first-line agent in the treatment of diabetic peripheral neuropathy and postherpetic neuralgia, all studies were less than 13 weeks in duration, and thus the long-term durability of response and safety are unknown. Physicians should also consider the cost before prescribing this agent.

Gabapentin

Dosage

A single bedtime dose of 300 mg of gabapentin for 2 nights can be followed by 300 mg given twice daily for an additional 2 days. If the patient tolerates this twice-daily regimen, the dose can be increased to 300 mg three times a day. Additional titration upward can be carried out in 300-mg increments as side effects allow. Total daily doses greater than 3600 mg are not currently recommended.[185] A possible combination with 10 to 25 mg of TCAs (see earlier) can be added for patients with sleep disturbance.

Precautions

The most serious concern with gabapentin is leukopenia. This drug can also cause somnolence, dizziness, ataxia, and fatigue. Taper dose over 7 days or longer to discontinue.

Pregabalin (Lyrica)

Dosage

Pregabalin is taken at 50 to 150 mg daily, divided into two or three doses. After an initial daily dose of 150 mg, it should be titrated with patient's response and tolerability over 2 weeks to a maximum of 300 mg daily. Pregabalin dosage adjustment should be considered in case of renal impairment.[201]

Precautions

The most common side effects are dizziness, somnolence, headache, dry mouth, and peripheral edema.

Analgesics

Simple analgesics such as acetaminophen, aspirin, naproxen, and ibuprofen may be used in conjunction with anticonvulsants and antidepressants, but the response is very poor. Caution must be taken because many of these NSAIDs received black box warnings and can cause fatal cardiac and gastrointestinal events. Do not exceed the recommended daily dose because of the risk of renal and hepatic toxicity, particularly in diabetic patients.

Narcotic analgesics also are suboptimal agents for pain control. Owing to their significant central nervous system and gastrointestinal side effects, coupled with problems of tolerance, dependence, and addiction, these agents should rarely be used, if ever. If a narcotic analgesic is considered, the analgesic tramadol (Ultram), which binds weakly to opioid receptors, may provide some symptomatic relief.

Dosage

Tramadol, 50 to 100 mg, is taken every 6 hours as needed for pain; the maximum dose is 400 mg per day.

> Caution should be used with the combination of tramadol, antidepressants, and anticonvulsants, owing to increased seizure risk.

Biomechanical Modalities

Electrical Stimulation

Electrical stimulation modalities such as transcutaneous electrical nerve stimulation (TENS)[202] and application of spinal cord stimulators[203] have been used successfully to alleviate the pain and discomfort associated with peripheral neuropathy. TENS portable units that generate a biphasic, exponentially decaying wave form (pulse width 4 msec, 25 to 35 V, more than 2 Hz) should be used for 30 minutes daily for 4 weeks. A study showed that percutaneous electrical nerve stimulation

(PENS), in addition to decreasing pain, improves patients' capacity for physical activity, sense of well-being, and quality of sleep while reducing the need for oral nonopioid analgesic medication.[204] PENS is similar to electroacupuncture in that electrical stimulation is given by disposable acupuncture-type needles. It differs in that it is delivered along the peripheral nerves innervating the region of neuropathic pain, rather than being delivered at acupuncture points or along meridians. Although use of alternating low and high frequencies of 15 and 30 Hz at 30-minute intervals three times a week is recommended, the patient should be evaluated by a health care professional familiar with electrical stimulation techniques for adjustment of frequencies and time intervals as tolerated.

Neural Blockade

Local anesthetic peripheral and sympathetic blocks provide useful diagnostic information but tend to confer only temporary therapeutic benefit in patients with peripheral neuropathy.[205]

Surgery

Entrapment neuropathies such as carpal tunnel syndrome may be relieved by surgical decompression (see Chapter 66, Carpal Tunnel Syndrome). In addition, compression or entrapment from cancers may be addressed by removal of the tumor directly.

Therapies to Consider

Physiologic Regulating Medicine: Biotherapeutics.

Physiologic Regulating Medicine (PRM) is a safe and effective approach to treatment of neuropathic pain that has been used in Europe for many years and is gaining awareness in the United States. The GUNA Method (Guna, Whitehall, Pa) represents the most cutting-edge integration of conventional and homeopathic medicines. The GUNA Method includes the most up-to-date knowledge about homeopathy, homotoxicology, psychoneuroendocrine immunology, and nutrition.

PRM adds a new therapeutic concept to classical homeopathy by restoring physiology through communicating molecules such as hormones, neuropeptides, interleukins, and growth factors prepared in homeopathic dilutions at the same physiologic concentration as the biologic milieu. The unique homeopathic preparation method of dilution-dynamization or sequential kinetic activation makes these communicating molecules even more effective and provides a biofeedback mechanism capable of restoring the body's homeostatic balance.

Treatment is given through oral therapies (drops) as well as injectables specific for neural pain that includes classical homeopathic ingredients, beta endorphins, anti-interleukins 1α and 1β, and neurotrophin, all given in specific acupuncture and trigger points by using a mesodermal technique. These molecular microdoses are capable of reactivating the appropriate biologic immune response that work in synergistic coordination to reverse inflammatory processes and their resultant physiologic effects.[206] No known side effects have been reported with use, and thus PRM can be used along with the other recommendations in this chapter.

Prevention Prescription

- Eat a whole foods, low-fat, high-fiber, plant-based diet.
- Avoid environmental toxins such as heavy metals, cigarette smoke, alcohol, pesticides, and herbicides.
- Prevent adult-onset diabetes by maintaining ideal weight and staying physically fit and active.
- If possible, avoid specific toxins (see Table 11-1) and pharmaceutical agents known to cause neuropathy (see Table 11-2).
- Avoid doses of vitamin B_6 (pyridoxine) greater than 250 mg/day.
- If taking the chemotherapeutic medications cisplatin, paclitaxel (Taxol), or vincristine, consider acetyl-L-carnitine, 1 g three times daily for 8 weeks.

Therapeutic Review

Lifestyle and Nutrition

A1

- Daily exercise of walking at least 30 minutes per day three times per week should be implemented. If walking is not possible because of painful peripheral neuropathy, gentler forms of exercise such as yoga or tai chi three times a week for 30 to 90 minutes are therapeutic. A whole foods, low-fat, high-fiber, plant-based diet with strict glycemic control should be strongly advised. Environmental and other toxins such as heavy metals, cigarette smoke, alcohol, and pollution should be avoided.

Mind-Body Therapy

B1

- Biofeedback: Recommendation is for at least six 1-hr biofeedback sessions at approximately 1-week intervals. Thereafter, relaxation biofeedback techniques can be performed at home with the use of biofeedback home-use programs (e.g., emWave Desktop or emWave [Institute of HeartMath]), audio CDs, or guided imagery exercises (for 10 to 20 minutes each day).

Bioenergetics

B1

- Infrared: Monochromatic near-infrared photo energy (MIRE), that is, the Anodyne Therapy System (ATS), which consists of therapy pads containing 60 near-infrared (890 nm) gallium aluminum arsenide diodes used three times a week for 40 minutes each

Continued

visit. Four treatments of photostimulation using light-emitting diodes (LEDs) at wavelengths between 750 and 1500 nm may be beneficial.

- Bioelectromagnetics: Magnetic footpad insole devices (i.e., Magstep) with a range of 450 to 475 G steep field gradient can be worn for up to 24 hours of direct contact, and for up to 4 months, to obtain symptomatic relief. A1
- Acupuncture: Scalp points: upper one fifth sensory area, foot motor and sensory area; ear points: ShenMen, sympathic, foot; body points: GB-40, GB-34, SP-10, SP-6, ST-44, LR-3, and Bafeng (extra point). Electrical stimulation can be used for the ear and body points at a frequency of 100 Hz at low intensity for 10 to 15 minutes for enhanced response. Patients can receive 2 treatments per week for 10 weeks. A1
- Electroacupuncture: This treatment can be performed in two cycles of five sittings each (10 sessions) at 2-day intervals. B1

Botanicals

- *Curcumin longa, Boswellia serrata,* and ginger (e.g., Bosmeric-SR, two caplets twice daily) or Curcumin C3 Complex: 1000 mg three times daily. B1
- Geranium oil (*Pelargonium* spp.): For topical pain relief, apply a few drops (i.e., Neuragen PN) to the affected area several times a day. B1
- Evening primrose oil (EPO; *Oenothera biennis*): 360 mg orally daily of GLA from EPO. The dose may be increased up to 480 mg orally daily. A2

Supplements

- Acetyl-L-carnitine (ALC): 500 mg orally twice daily to 1000 mg orally three times daily. ALC is used for both chemotherapy-induced and diabetic peripheral neuropathy. A1
- Alpha-lipoic acid: 600 to 1800 mg orally daily; start with 600 mg orally daily and increase up to 1800 mg orally daily in divided doses if needed. A1
- Benfotiamine: Lipid-soluble vitamin B_1, 150 to 300 mg twice daily specifically for diabetic peripheral neuropathy. B1
- Methylcobalamin or 5-adenosylcobalamin: Better-absorbed vitamin B_{12}, 500 mcg three times daily or 1500 mcg daily. B1
- B-complex multivitamin (B-100): One tablet once or twice daily for peripheral neuropathy caused by deficiency syndromes. B2
- Fish oil (omega-3 fatty acids): Eicosapentaenoic acid (EPA), 1000 to 2000 mg/day, and docosahexaenoic acid (DHA), 500 to 1000 mg/day or a vegetarian plant-based option (i.e., NutraVege). B2

Pharmaceuticals

For topical relief:

- Capsaicin cream 0.075%: Apply to the affected area up to three or four times daily for at least 4 to 6 weeks. A2
- Capsaicin patch (8%): One patch to area for 1 hour (after preanesthetic applied) and then removed. It is applied in a doctor's office under supervision. A2

For acute pain management, consider:

- Analgesics: Nonsteroidal antiinflammatory drugs (NSAIDs) as usually prescribed for pain, as well as narcotics. All should be used very cautiously due to black box warnings. A2

For chronic pain management:

- Antidepressants
  - Amitriptyline or nortriptyline: 10 mg orally nightly; titrate the dose upward to 25 mg orally nightly as side effects allow (usual range: 50 to 300 mg/day). A2
- Anticonvulsants
  - Gabapentin (first-line choice): 300 mg orally nightly for 2 days, then 300 mg orally twice daily for 2 days; can be increased to 300 mg orally three times daily as tolerated, with increases in 300-mg increments as side effects allow; maximum daily dose, 3600 mg. A2
  - Pregabalin: 50 mg three times daily. After an initial daily dose of 150 mg, it should be titrated with the patient's response and tolerability over 2 weeks to a maximum of 300 mg daily. A2

Biomechanical Therapy

- Transcutaneous electrical nerve stimulation (TENS): Use of a TENS portable unit for 30 minutes daily for 4 weeks is recommended. B1
- Percutaneous electrical nerve stimulation (PENS): This modality can be used three times a week; stimulation is delivered along the peripheral nerves innervating the region of neuropathic pain. B1
- Neural blockade: This provides only temporary therapeutic benefit. B2
- Surgery: Surgical decompression may relieve symptoms in carpal tunnel syndrome; with neuronal entrapment from cancer, removal of the tumor itself may also be helpful. B2

KEY WEB RESOURCES

National Institute of Neurological Disorders and Stroke. www.ninds.nih.gov/disorders/peripheralneuropathy/peripheralneuropathy.htm.	This page has information about organizations that support neuropathic conditions, as well as up-to-date clinical trials.
MedlinePlus, National Library of Medicine. http://www.nlm.nih.gov/medlineplus/ency/article/000593.htm.	Simplified information is provided for patients about neuropathy and its associated conditions with definitions.
WebMD. www.webmd.com/brain/understanding-peripheral-neuropathy-basics.	This page on understanding peripheral neuropathy contains the basics for patients.
Neuropathy Association. http://www.neuropathy.org/site/PageServer.	This patient source describes neuropathic treatment centers and support groups.

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References are available online at expertconsult.com.

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Chapter 12

Multiple Sclerosis

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Pathophysiology

Multiple sclerosis (MS) is the most common cause of chronic neurologic disability in young adults, with a prevalence varying by geographic region from 1 to 2.5 per 1000.[1]

Although the origin and exact mechanisms remain uncertain, MS is a complex disorder characterized by axonal injury, inflammation, and demyelination. This demyelination impairs the transmission of nerve impulses and results in fatigue, weakness, numbness, locomotor difficulty, pain, loss of vision, and other health problems. MS is generally viewed as an autoimmune disorder that transpires when internal antibodies mistakenly direct their "attack" against the body's own nerve cells.

Research suggests that MS is more correctly thought of as one end of a spectrum of central nervous system (CNS) disorders resulting from a byproduct of the malfunctioning of a physiologic immune response whose purpose is protective. According to this view, all individuals are endowed with the potential ability to evoke an autoimmune response to CNS injuries (viral, bacterial, toxin, or direct injury). The inherent ability to control this response so that its beneficial effect will be expressed is limited and is correlated with the individual's inherent ability to resist autoimmune disease induction.[2]

Because of the wide variability of the disease presentation and of the development of treatment protocols, investigators have found it useful to categorize patients with MS into the following four groups[3]:

1. Relapsing-remitting (RR) disease occurs at onset in 80% of cases and is characterized by acute attacks followed by remissions with a steady baseline between attacks.
2. In 50% to 80% of patients with RR disease, progressive deterioration with less marked attacks occurs within 10 years of onset; the disease in these patients is called secondary progressive phase MS (SP-MS).
3. Primary progressive MS (PP-MS) occurs in 10% to 15% of patients and is characterized by progressive deterioration from the outset without superimposed relapses.
4. Approximately 6% of patients with PP-MS also experience relapses in parallel with their disease progression and are said to have progressive-relapsing MS (PR-MS).

Etiology

The search for the cause of MS is made difficult by the marked variation in disease expression. It is not clear whether MS is one disease with variable symptoms or whether the different subtypes represent unique causes.[4] At present, four major theories of the cause of MS are recognized: immunologic, environmental, infectious agent, and genetic factors.

Immunologic Factors

The theory that MS is an organ-specific autoimmune disease is, although unproven, widely accepted. Antibodies against antigens located on the surface of the myelin sheath cause demyelination either directly or by complement-mediated processes. Investigators have suggested that priming of myelin-reactive T cells occurs as part of the disease process in MS. Primed T cells reactive to myelin antigens may develop a phenotype making them more resistant to regulatory processes. The concept that autoantigens can drive B-cell clonal expansion and contribute to autoimmunity has been demonstrated in other autoimmune diseases. A role of B cells in the recovery from inflammatory demyelination has also been hypothesized.[5]

Environmental Factors

Several decades of research have documented that the incidence of MS increases with increasing distance from the Equator. Possible explanations for this finding include genetic predisposition in population groups, dietary factors, and levels of the active form of vitamin D. Evidence indicates that the timing of the exposure to an environmental agent plays a role, with exposure before puberty predisposing a person to develop MS later in life.[6] The dietary influence on MS was first reported by Swank et al in 1952.[7] Dr. Swank noted that people living in colder climates tend to consume diets higher

in fat compared with those living in more tropical regions, and this dietary difference was linked to a higher incidence of MS in colder regions.[7]

The relationship between mercury from dental fillings and MS is one of extreme controversy; some studies concluded a clear relationship between mercury and MS,[8] and other studies showed a relationship between the extent of dental caries and MS but no association between MS and the number of fillings.[9] At present, mercury toxicity and MS have too many similarities to be ignored.

The possible connection between viral vaccines and MS is another area of controversy. Although it appears that immunity to tetanus is protective against the development of MS,[10] even stronger evidence indicates that hepatitis B vaccination can induce autoimmune demyelinating diseases.[11]

Exposure to cigarette smoke has been demonstrated to be a clear risk factor for developing MS, as well as increasing the severity of illness.[12,13] These findings suggest the possibility of environmental toxins or pollutants in the pathogenesis of MS.

Infectious Agents

At least 16 different infectious agents have been implicated as causes of MS; however, none has been definitely associated with the disease. At present, three agents are receiving the most attention: human herpesvirus-6, *Chlamydia pneumoniae,* and Epstein-Barr virus.

Genetic Factors

Although most cases of MS are sporadic, susceptibility to MS is substantially affected by genetic factors. For example, clear associations exist between certain subtypes of the major histocompatibility human leukocyte antigen (HLA)-DRB1 gene and susceptibility and disease course in MS.[14] However, the aggregate contribution of germline genetic variants to the disease expression of a given patient with MS may be modest. This concept is highlighted by observations that the clinical expression of MS may be quite different between monozygotic twin siblings who both have the disease; it is therefore likely that several postgermline events influence the clinical expression of MS.[15]

Diagnosis

The hallmark for the clinical diagnosis of MS is neurologic dysfunction that is disseminated in space and time. Objective evaluation includes magnetic resonance imaging (MRI), evaluation of cerebrospinal fluid, and evoked potential tests (measuring the electrical activity of the brain in response to stimulation of sensory nerve pathways). The pathologic hallmark of MS is the presence of demyelinated plaques involving the periventricular white matter, optic nerves, brainstem, and cerebellum or spinal cord white matter (Figs. 12-1 and 12-2).

Integrative Therapy

Lifestyle

Smoking Cessation

As previously mentioned, tobacco smoke exposure is a risk factor for developing MS and is associated with a worse prognosis. Smokers with MS should be offered appropriate counseling and support measures to quit.

FIGURE 12-1
Multiple sclerosis. **A**, T2-weighted magnetic resonance imaging (MRI) scan of the brain demonstrates multiple lesions located in the white matter characteristic of multiple sclerosis *(arrow)*. **B**, T1-weighted MRI scan of the spine indicates a demyelinating plaque of multiple sclerosis in the midcervical region *(arrow)*. (From Johnson MV. Demyelinating disorders of the CNS. In: Kliegman RM, Behrman RE, Jenson HB, eds. *Nelson Textbook of Pediatrics.* 18th ed. Philadelphia: Elsevier; 2007.)

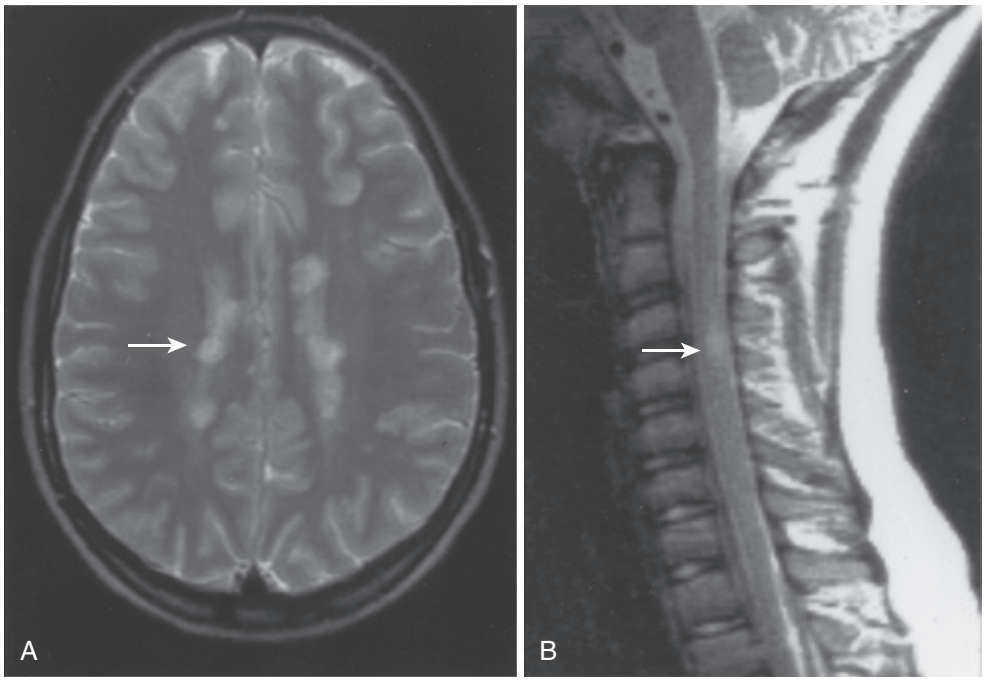
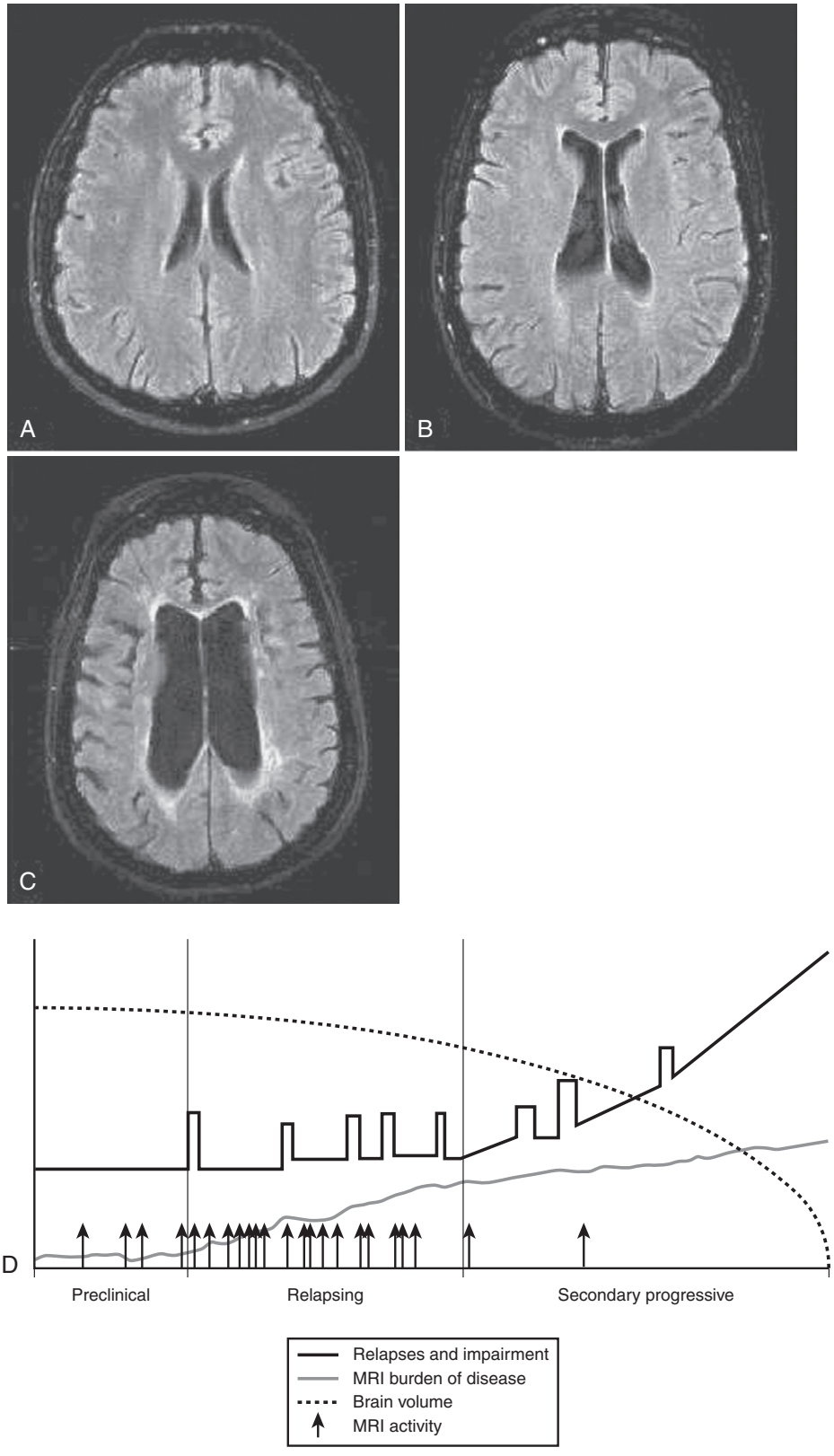


FIGURE 12-2
Changes in magnetic resonance imaging (MRI) scans with duration of disease. **A, B,** and **C,** Comparison of three scans from patients with different disease duration, indicating the appearance of atrophy and ventricular dilatation with time. **D,** As brain atrophy appears, it is common to observe that the number of gadolinium-enhancing lesions declines. (From Lublin FD, Miller AE. Multiple sclerosis and other inflammatory demyelinating diseases of the central nervous system. In: Bradley WG, Daroff RB, Fenichel GM, Jankovic J, eds. *Neurology in Clinical Practice.* 5th ed. Munich: Butterworth-Heinemann; 2008.)



In addition to affecting risks of other diseases, tobacco smoking is probably the most important disease-specific modifiable risk factor for patients with multiple sclerosis who smoke.

Exercise

Although physical fitness and exercise have been associated with better function for patients with MS,[16–18] the exact role of exercise in treating MS remains uncertain, likely because of the variability of the disease. The main question is which patients will benefit from which types of exercise. Accordingly, this is an active area of research.

A reasonable approach is to recommend exercise programs designed to activate working muscles but avoid overload that results in conduction block. Before recommendations are made, physical activity patterns and physical effects of MS should be assessed in individual patients.[19] Research shows that for people with MS, exercise capacity is reduced in response to a single bout of continuous exercise to maximal effort; however, minimally impaired people with MS often exhibit cardiorespiratory responses similar to those of healthy individuals during discontinuous exercise.[20]

Aquatic and other body weight–supported activities are generally considered the most appropriate form of exercise for the population with MS. Water can provide adequate support for patients with gait and balance problems, by allowing movement that may be difficult to achieve with full weight bearing. Modified yoga classes may also provide benefit to patients with MS (see Mind-Body Therapy, later).

Sunshine

Sunlight has been postulated as having a protective effect in the development of MS, which has a clear increase in incidence in extreme latitudes. Furthermore, exposure to sunlight is associated with improved vitamin D levels, decreased relapse rate, and lower mortality in MS.[21] Whether the association of sunlight is entirely attributable to vitamin D is unclear.

Alcohol

Minimal research suggests a dose-related association between modest alcohol consumption and decreased disability for patients with MS.[22] Further research is needed.

Mind-Body Therapy

Psychosocial Factors

Depression is common in MS, and death by suicide occurs seven times more frequently than in the general population. Combining counseling with body work therapies can be highly effective in countering this depression.

Psychological stress has been clearly identified as a trigger for relapses of MS and possibly contributes to disease progression.[23–25] Furthermore, coping styles may effect susceptibility to the harmful effects of stress in MS.[26] Given the relatively modifiable nature of life stress and coping, patients with MS should be encouraged to learn some form of stress reduction, stress management, or coping techniques (see Chapter 93, Relaxation Techniques).

Stress and coping should be addressed with each patient with multiple sclerosis and may affect both relapse frequency and disease progression.

Yoga

Yoga techniques have been shown to improve circulation, balance, the ability to relax, flexibility, and eyesight and to reduce muscle tension—all features typically affected by MS.[27] A yoga class modified specifically to the needs of patients with MS and performed similarly to a modified exercise class in improving fatigue for patients with MS.[28] In the absence of a yoga class for MS, an individualized yoga program developed closely with a qualified yoga teacher or therapist is likely to produce similar benefits.

Mindfulness

Mindfulness-based stress reduction is a mind-training approach that has been successfully applied for coping with difficult life circumstances and illness (see Chapter 98, Recommending Meditation). An 8-week mindfulness-based intervention demonstrated significant improvement in measures of nonphysical quality of life, depression, fatigue, and anxiety compared with usual care in patients with MS.[29] This benefit persisted for 6 months after the intervention.

Nutrition

The following are nutritional and dietary recommendations for patients with MS that generally target inflammation:

- Increase intake of foods rich in omega-3 essential fatty acids: cold-water fish, nuts, seeds, and dark green leafy vegetables.[30] These foods reduce inflammation by their effect on prostaglandins and leukotrienes (see Chapter 86, The Antiinflammatory Diet). If patients find it more convenient to take supplements of these essential fatty acids, suggest a docosahexanoic acid (DHA) dose of 400 to 600 mg/day and a gamma-linolenic acid (GLA) dose of 240 to 320 mg/day.
- Consume less than 5% of energy from saturated fat. This approximates to 10 g of saturated fat per day. Dietary saturated fat and cholesterol trigger the arachidonic acid cascade and increase the production of proinflammatory leukotrienes.[31]
- Consume less than 1% of energy from trans fat. This is approximately 2 g/day. This is done by avoiding processed or packaged foods. Avoiding trans fats altogether is possible because trans fat occurs infrequently in nature. Trans fat may be even more vulnerable to oxidation, and thus an inflammatory reaction, than saturated fat.
- Consider a reduced-gluten or gluten-free diet. Case reports have noted gluten sensitivity manifesting as optic neuritis,[32] and other studies have shown an increase in some proteins from the gut in patients with MS and immunoglobulin G against gliadin and gluten.[33] Considering the difficulty of instituting a gluten-free diet, a reasonable course would be to conduct simple laboratory testing for tissue transglutaminase and gliadin antibodies in the patient newly diagnosed with MS.

Supplements

Vitamin D

The role of vitamin D in decreasing the incidence of MS and in alleviating the symptoms has been thoroughly evaluated.[34] Vitamin D was shown to prevent the development of experimental allergic encephalomyelitis—an MS-like disease—completely in a mouse model.[35] The dose of vitamin D is variable, depending on the patient's exposure to sunlight. Doses up to 4000 units a day have been used without toxicity for up to 6 months. A general guideline is to recommend 2000 units/day from April through October and 4000 units/day from November through March.

Dosage

Usual dose is 800 to 4000 units/day. Titrate for a serum level near 40 ng/mL.

Precautions

Watch for symptoms of hypercalcemia such as weakness, fatigue, sleepiness, headache, and loss of appetite.

> For dark-skinned individuals and those living farthest from the Equator, be sure to monitor 25-hydroxyvitamin D levels and supplement to keep the level near 40 to 50 ng/mL.

Calcium

Calcium supplementation has been found to be synergistic with vitamin D for suppressing experimental allergic encephalomyelitis in mice.[36]

Dosage

Give calcium 800 to 1200 mg/day in divided doses. Take with vitamin D.

Alpha-Lipoic Acid

Alpha-lipoic acid is rapidly absorbed from the gut, crosses the blood-brain barrier, and has powerful antioxidant activity. It not only augments the function of vitamins C, E, and glutathione,[37] but also raises the body's level of glutathione.[38]

Dosage

The dose is 600 to 1200 mg/day.

Precautions

Nausea, vomiting, and rash are possible.

Glutathione

Endogenous glutathione provides the primary cellular defense against free radicals. Glutathione functions both as an antioxidant (in the form of glutathione peroxidase) and as a detoxifying agent for many xenobiotics.[39] The most effective way of raising intracellular levels of glutathione is by intravenous infusion.

Dosage

The dose is 600 to 800 mg intravenously diluted in 10 to 20 mL sterile water and infused over 15 to 20 minutes two or three times a week.

Precautions

Rapid infusion of glutathione can provoke respiratory distress, coughing, rhinorrhea, and vertigo.

N-*Acetylcysteine*

N-Acetylcysteine taken orally raises glutathione levels. Nausea and vomiting are common with doses higher than 2 g/day.

Dosage

Prescribe 1 g twice daily.

Precautions

It can cause nausea, vomiting, and diarrhea, and it has an unpleasant odor.

Magnesium

Magnesium is required for adequate levels of metabolized vitamin D products to be maintained in circulation. At 800 mg/day, magnesium also has a mild effect on the muscle spasticity often associated with MS.

Dosage

The dose is 600 to 1200 mg/day.

Precautions

Individual tolerances for magnesium are variable. Advise patients to decrease the dose if diarrhea develops.

B-Complex Vitamins

The B vitamins have been shown to aid in cognitive function, act as antioxidants, and decrease the production of inflammatory cytokines.

Dosage

Varies by preparation.

Vitamin B_{12}

Deficiency of vitamin B_{12} and errors in vitamin B_{12} metabolism are known to cause demyelination of the CNS.[40] High doses of vitamin B_{12} given intramuscularly have been shown to improve brainstem nerve function in chronic, progressive MS.[41] Teaching patients self-injection of vitamin B_{12} can be a cost-effective way of improving overall well-being.

Dosage

Oral doses are 1000 to 2000 mcg/day in the form of methylcobalamin. Intramuscular doses of hydroxycobalamin are 1000 mcg/day for 5 days, then twice weekly for 4 weeks, and then twice monthly.

Botanicals

Ashwagandha (Withania somnifera)

Ashwagandha is an Ayurvedic herb (see the discussion of Ayurveda later), also known as winter cherry, that is sometimes called Indian ginseng in reference to its rejuvenating and tonic effects on the nervous system. Ashwagandha's antiinflammatory, antioxidant, anxiolytic, and antidepressant activities all make this herb an important supplement for patients with MS.[42,43]

Dosage
Give 1 to 6 g of the whole herb in powdered form two or three times a day.

Precautions
Some Ayurvedic herbs have been found to have high levels of contaminants such as lead. By knowing the supplier's source of the herb, you can be sure your patient is not taking a contaminated product.

Ginkgo biloba
Ginkgo, in addition to its antioxidant effects, also enhances neurotransmission.[44]

Dosage
The dose is 120 to 240 mg/day.

Marijuana (Cannabis sativa)
Numerous case reports and randomized controlled trials support the use of smoked marijuana, cannabis extracts, and synthetic cannabinoids for MS-related symptoms, especially spasm and tremor.[45–47] Potential legal issues and unwanted side effects must be considered. This is an active area of research.

Dosage
The dose varies considerably with the potency of the whole herb. Consider products standardized to 2.5 to 30 mg delta-9 tetrahydrocannabinol or equivalent daily in divided doses.

Hormones

Estriol
Most patients with MS who become pregnant experience a significant decrease in symptoms. Research has shown that estriol causes an immune shift from T-helper 1 to T-helper 2 cells. Studies have documented a reduction in symptoms and a decrease in gadolinium-enhancing lesions on MRI in women and men with MS who are treated with estriol[47,48] (see Chapter 34, Hormone Replacement in Men, and Chapter 35, Hormone Replacement Therapy in Women).

Dosage
Prescribe 4 mg twice daily. Estriol is available only through compounding pharmacies at this time.

Precautions
Although estriol is considered a "weak" estrogen compared with estradiol, it remains a hormone with the same potential risks, albeit lower, as any hormone treatment. When prescribing estriol to nonmenstruating women with an intact uterus, adding small amounts of progesterone (25 to 50 mg/day) is prudent.

Testosterone
Much like estriol's protective role in women, testosterone has been found to ameliorate MS symptoms in male and female patients.[49] Laboratory measurement of testosterone before treatment is important to determine optimal dosing, and monitoring levels periodically is important to decrease the potential for side effects.

Dosage
Use micronized testosterone from compounding pharmacies.

- For men: 10 to 30 mg/day
- For women: 2 to 5 mg/day

Precautions
Because testosterone can influence prostate physiology, use only after a complete evaluation of prostate function, and continue to monitor men for signs and symptoms of prostatic hypertrophy or prostatic carcinoma.

Dehydroepiandrosterone
Dehydroepiandrosterone (DHEA) serves as a metabolic intermediate in the pathway for synthesis of testosterone, estrone, and estradiol. It also affects lipogenesis, substrate cycling, peroxisome proliferation, mitochondrial respiration, protein synthesis, and thyroid hormone function.[50] Although the evidence for benefit from DHEA in lupus is stronger, researchers in MS have clinically associated low DHEA levels with MS relapses.

Dosage
- Men: 10 to 30 mg/day
- Women: 5 to 15 mg/day

Precautions
DHEA is a hormone that can have potential untoward effects in an individual patient. Monitor the patient and serum levels carefully while prescribing this substance.

Pharmaceuticals

Corticosteroids
Evidence indicates that the administration of corticosteroids improves symptoms of and disability from acute MS relapses.[51] High-dose regimens have become the mainstay of the approach to relapse. Evidence indicates that oral therapy can have the same results as intravenous therapy,[52] although intravenous therapy is generally indicated for acute optic neuritis. Whether corticosteroids affect the overall degree of recovery or the long-term course of the disease is unclear.[51] Plasma exchange is indicated for patients with severe attacks refractory to high-dose corticosteroids.

Dosage
Methylprednisolone, 1 g/day intravenously or (equivalent oral regimen); prednisone, 1250 mg orally daily for 3 to 5 days. Low-dose oral dosage regimens vary; the most common regimen is prednisone 60 mg orally once a day for 5 days, then 40 mg orally for 5 days, then 20 mg for 5 days, then 10 mg for 5 days, and finally 5 mg for 5 days.

Precautions
Side effects include congestive heart failure, hypertension, psychosis, osteoporosis, peptic ulcer with possible perforation, immune suppression with increased susceptibility to infection, and decreased carbohydrate tolerance. Gastric side effects are substantially increased with the oral route of administration. High-dose corticosteroids may be associated

with defects in long-term memory,[53] possibly through affecting memory consolidation[54] and disruption of sleep architecture.[55] A further concern is that use of high-dose corticosteroids outside of a relapse may actually contribute to progression of disability in some patients.[56]

Interferon Beta

Interferon beta-1b (Betaseron) and interferon beta-1a (Avonex, Rebif) were originally thought to increase the resistance of tissues, including those of the CNS, against viral infections. Currently, no data suggest that viral inhibition underlies the effects of interferon beta on MS in any way.[57] The precise mechanism of action of these drugs is not known. Clearly, the effect of interferon beta on disease progression is only modest, and some studies showed no benefit compared with placebo.[58] Long-term benefit (beyond 2 years) is also uncertain.

Dosage

Interferon beta-1b comes as a powder that must be mixed with saline solution immediately before injection and given subcutaneously every other day. The cost is approximately $10,000 per year. Interferon beta-1a preparations are injected intramuscularly once a week (Avonex) or three times per week (Rebif).

Precautions

Injection site reaction, headache, fever, flulike symptoms, pain, diarrhea, constipation, lymphocytopenia, elevation of liver enzymes, myalgias, depression, and anxiety may occur.

Glatiramer Acetate

Glatiramer acetate (Copaxone) is a synthetic copolymer of the most prevalent amino acids in myelin basic protein. The drug is thought to work by mimicking myelin basic protein and thus redirecting inflammatory cells to the drug instead of the myelin. Again, the effects of glatiramer acetate on disease progression are only modest.

Dosage

The dose is 20 mg subcutaneously daily.

Precautions

Glatiramer is well tolerated by most patients. Local injection site reaction is the most prominent adverse reaction.

Mitoxantrone

Mitoxantrone (Novantrone) is an antineoplastic agent that is used predominantly with secondary progressive phase MS.

Dosage

Individualized.

Precautions

Cardiotoxic effects are the major limitation associated with using this agent.

Natalizumab

Natalizumab is a selective adhesion molecule inhibitor used for the treatment of relapsing forms of MS. It was withdrawn from the market shortly after U.S. Food and Drug Administration approval because of the development of progressive multifocal leukoencephalopathy in two patients. This drug is being reintroduced for MS therapy on a selective, controlled basis.

Corticosteroids and immunomodulatory drugs have proven efficacy for treating multiple sclerosis, but they also have potentially serious side effects. The high financial cost of immunomodulatory drugs should also be considered when making recommendations.

Therapies to Consider

Traditional Healing Systems

Traditional Chinese Medicine

Traditional Chinese medicine (TCM) is a codified ancient healing system with a holistic approach that employs therapies such as acupuncture, herbs, and behavioral recommendations. It generally views MS as representing a heterogeneous group of causes and disease processes. From a TCM perspective, patients with MS often exhibit the signs of spleen deficiency with dampness blocking the channels or liver or kidney deficiency. In the hands of an experienced practitioner familiar with MS, TCM can be a safe and effective modality. Additionally, separate aspects of TCM such as acupuncture are often used for MS-related symptoms. Use of acupuncture has been reported in up to 35% of patients with MS.[59] As with TCM, acupuncture is safe and possibly effective for MS when it is performed by a qualified practitioner.

Ayurveda

Ayurveda is among the oldest existing healing traditions. In explaining disease and healing processes, it relies on the interplay of the three *doshas,* or cardinal humors: *vata* (formed of ether and air), *pita* (formed of fire and water), and *kapha* (formed of earth and water). The Ayurvedic description of MS is analogous to that of biomedicine: an excess of pita (inflammation) burns up the kapha (myelin) and results in an excess of vata (weakness, fatigue).[60] Ayurvedic treatments for MS often target the reduction of pita (inflammation) and the replenishing of the kapha (myelin) with medicinal oils, diet, herbs, and lifestyle changes.

Prevention (of Relapse) Prescription

- Eliminate tobacco smoke.
- Practice some form of stress reduction technique regularly.
- Exercise moderately and consistently; do not exercise to the point of fatigue.
- Ensure adequate rest and sleep.
- Get adequate sunlight or at least 800 units of vitamin D daily.
- Consume less than 10 g of saturated fat a day.
- Eliminate trans fat.
- Increase foods rich in omega-3 fats.
- Supplement with docosahexanoic acid at 400 to 600 mg/day.
- Supplement with gamma-linolenic acid at 240 to 320 mg/day.
- Reduce or eliminate gluten from the diet.

Therapeutic Review

Lifestyle

- Smoking cessation — A 1
- Aquatic exercise — B 1
- Moderate alcohol intake — C 2
- Regular sunshine — C 1

Mind-Body Therapy/Stress Reduction Techniques

- Yoga — B 1
- Mindfulness meditation — B 1

Nutrition

- Limit saturated fat to less than 10 g/day. — B 1
- Eliminate trans fats. — C 1
- Increase foods rich in omega-3 fatty acids, or take supplements of docosahexanoic acid, 400 to 600 mg daily, and gamma-linolenic acid, 240 to 320 mg daily. — B 1
- Reduce or eliminate gluten. — C 1

Supplements

- Vitamin D: 2000 units daily if deficient (keep serum level near 40 ng/mL) — B 1
- Calcium: 800 mg daily — B 1
- Glutathione: 600 to 800 mg intravenously two or three times weekly — B 2
- *N*-Acetylcysteine: 1 g twice daily — B 2
- Alpha-lipoic acid: 600 to 1200 mg daily — B 1
- Magnesium: 600 to 1200 mg daily — B 2
- B-complex vitamins: doses vary by preparation — B 1
- Vitamin B_{12} oral dose: 1000 to 2000 mg daily OR — B 1
- Vitamin B_{12} intramuscular injection: 1000 mcg twice a month — B 1

Botanicals

- *Ginkgo biloba:* 120 to 240 mg daily — C 1
- Ashwagandha: 1 to 6 g two to three times daily — B 2
- Medical marijuana: 2.5 to 30 mg of delta-9 tetrahydrocannabinol daily in divided doses — B 2

Hormones

- Estriol: 4 mg twice daily topically — B 2
- Testosterone: men, 10 to 30 mg daily; women, 2 to 5 mg daily — B 2
- Dehydroepiandrosterone: men, 10 to 30 mg daily; women, 5 to 15 mg daily — B 2

Pharmaceuticals for Acute Attacks

- Corticosteroids: methylprednisolone (Solu-Medrol), 1000 mg daily for 3 to 5 days, or prednisone, 1250 mg orally daily for 3 to 5 days with no taper — A 3

Pharmaceuticals for Relapsing-Remitting Disease

- Interferon beta: Avenox, 30 mcg intramuscularly every week; or Rebif, 44 mcg by subcutaneous injection three times weekly — A 3
- Glatiramer acetate (Copaxone): 20 mg by subcutaneous injection once daily — A 2
- Natalizumab (Tysabri): 300 mg intravenously every 28 days — A 3

Pharmaceuticals for Secondary Progressive Multiple Sclerosis

- Mitoxantrone (Novantrone): 12 mg/m^2 intravenously once every 3 months — A 3

KEY WEB RESOURCES

Multiple Sclerosis Foundation. http://www.msfocus.org/default.aspx.	This not-for-profit organization seeks to provide "a comprehensive approach to helping people with MS maintain their health and well-being" through programming and education. The Web site provides a wide variety of information including disease basics, support group contacts, articles on complementary and alternative medicine therapies, online forums, and links for health professionals.
National Multiple Sclerosis Society. http://www.nationalmssociety.org.	The Society's mission is to "mobilize people and resources to drive research for a cure and to address the challenges of everyone affected by MS." The Web site features updates on fundraisers and research, a multimedia library, and advocacy and research-oriented resources.

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Chapter 13

Parkinson Disease

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Pathophysiology

Clinical Signs and Symptoms

Parkinson disease is a progressive neurodegenerative disorder. People with Parkinson disease often exhibit a characteristic tremor, a shuffling gait, and a masked facial expression. However, the effects of Parkinson disease are much more widespread.

Preclinical Stage

Parkinson disease likely starts many years before it is first recognized by either physicians or patients. The early symptoms are subtle and nonspecific. Usually, Parkinson disease progresses slowly, but the rate of progression is highly variable. In retrospect, many people can point to early signs that may have existed years before they first suspected they had Parkinson disease. The most common of these early symptoms are constipation and a decreased sense of both smell and taste. Sleep difficulties such as rapid eye movement (REM) sleep behavior disorder and restless legs syndrome may also predate motor symptoms by many years. Family members may have noted a decrease in the range of facial expression, a softness and flatness in the voice, and a more passive personality. Some people diagnosed with Parkinson disease are found to have suffered from late-onset depression for several years before diagnosis.

Early Symptoms

Although the cardinal features of Parkinson disease are described as resting tremor, rigidity, bradykinesia, akinesia, postural instability, flexed posture, and "freezing" episodes, these do not all manifest at once. Early motor signs may be subtle and nonspecific. Often they are recognized only in retrospect. A decrease in arm swing or stride length on one side while walking can lead to pain in the shoulder, upper back, low back, or hip. Decreased fine motor coordination can cause difficulty with buttons and clasps. Thus, getting dressed in the morning may become a slower process. Additional movements may slow and decrease in amplitude. For example, handwriting often becomes smaller and more difficult to read. When tremors first appear, they often are intermittent and most obvious during stressful situations.

As the disease progresses, physical signs become more obvious. Tremor often is more constant. However, it may be absent altogether in some people, especially older ones. Parkinsonian tremor usually is present only at rest. Some people learn to control the tremor by keeping their hands active. As walking becomes more difficult, people with Parkinson disease tend to become more sedentary. Difficulty with initiating movement, in combination with worsening balance, can make arising from soft chairs and car seats an arduous process. As the disease advances, akinesia (lack of movement) and bradykinesia (slowness of movement) continue to become more prominent. Posture may become more stooped. People with Parkinson disease may attribute these signs to weakness or stiffness of their limbs and body.

Nonmotor Symptoms

In addition to the better-known motor symptoms of Parkinson disease, people with this disorder experience a wide range of nonmotor symptoms. Sometimes these symptoms can be even more disabling than the motor symptoms. The nonmotor symptoms of Parkinson disease can be categorized broadly as psychiatric, autonomic, sleep-related, and sensory symptoms (Table 13-1).

Advanced Disease

Unfortunately, some symptoms of advanced Parkinson disease are not responsive to any of the currently available medications or surgery. Motor freezing, or episodes when people feel that their feet are "glued to the floor," can be difficult to treat with medications. However, specially modified canes and walkers, which use a laser to project a red line for patients to step over, can be useful for breaking these episodes. Other strategies include walking to a rhythm, such as a marching song. Safety modifications in the home such as grab bars in the bathroom and kitchen can help prevent falls

TABLE 13-1. Nonmotor Symptoms in Parkinson Disease

Psychiatric	Depression Anxiety Apathy Dementia Hallucinations Impulse control disorders
Autonomic	Constipation Orthostasis (lightheadedness on standing) Excessive sweating Urinary incontinence
Sleep Disorders	Insomnia REM sleep behavior disorder Restless legs syndrome Excessive daytime sleepiness Fatigue
Sensory	Impaired sense of smell and taste Blurred vision Numbness and tingling Pain

REM, rapid eye movement.

and extend a patient's independence. As fine motor skills diminish, switching to garments without buttons and shoes with Velcro or elastic laces can help with getting dressed. People who have low voice volume may be helped by the Lee Silverman Voice Therapy (LSVT) program.[1]

Prevalence

Parkinson disease is one of the most common neurodegenerative disorders. It is estimated to affect 500,000 people in the United States.[2] Parkinson's disease typically begins after the age of 50, and its prevalence increases with age. The lifetime risk of developing this disorder is 2% for men and 1.3% for women.[3]

Risk Factors

Epidemiologic studies have investigated factors that increase the risk of developing Parkinson disease. By design, such studies cannot identify definitive causes. Although Parkinson disease generally is more common in industrialized societies, it is found with greater frequency in rural areas[4] and increases with exposure to pesticides,[5] heavy metals,[6] and drinking well water.[7]

Large doses of the pesticide rotenone cause a parkinsonian syndrome in laboratory rats that is used experimentally as a model for studying Parkinson disease.[8] Ironically, rotenone is allowed in organic farming practices, although typical exposure rates have not been shown to cause Parkinson disease.

Trichloroethylene (TCE) is a degreaser used to clean metal in factories, as a dry cleaning solvent, and in some household cleaning agents. Results of a study of twins showed that occupational exposure to TCE increased the risk of Parkinson disease fivefold.[9]

Increasing exposures to cigarettes and coffee are correlated with a lower risk of developing Parkinson disease.[6] It is not clear whether these agents are protective or whether early changes in the dopamine-mediated reward systems in the brains of people destined to develop Parkinson disease make them less susceptible to the addictive qualities of nicotine and caffeine. Smoking and coffee drinking certainly are not recommended as preventive measures.

A large, prospective population-based study in Rotterdam, The Netherlands, found that a higher dietary intake of omega-3 fatty acids was associated with a decreased risk of Parkinson disease.[10] The effect was entirely the result of intake of plant-based alpha-linolenic acid, rather than fish oils. Even if it is not preventive, fish oil may still have value for patients with Parkinson disease. A separate double-blind, placebo-controlled study of patients with Parkinson disease and major depression found improved mood symptoms in patients taking fish oil, with or without antidepressants.[11] Additionally, fish oil supplements were shown to reduce the risk of sudden cardiac death in otherwise healthy men in the Physician's Health Study.[12]

Nutrition Suggestions for People With Parkinson Disease

- Eat foods high in fiber to lessen constipation.
- Foods high in omega-3 fatty acids may be beneficial.
- Eat colorful fruits and vegetables for dietary sources of antioxidants.

Pathogenesis

The underlying cause of Parkinson disease remains elusive. The variety in the constellation of symptoms and in the rate of progression suggests that Parkinson disease is a collection of similar disorders rather than a single entity. A single etiology therefore is unlikely to emerge. The variety of epidemiologic risk factors suggests multiple competing factors including genetics and toxic exposures. The balance of these factors determines whether an individual will go on to develop Parkinson disease.

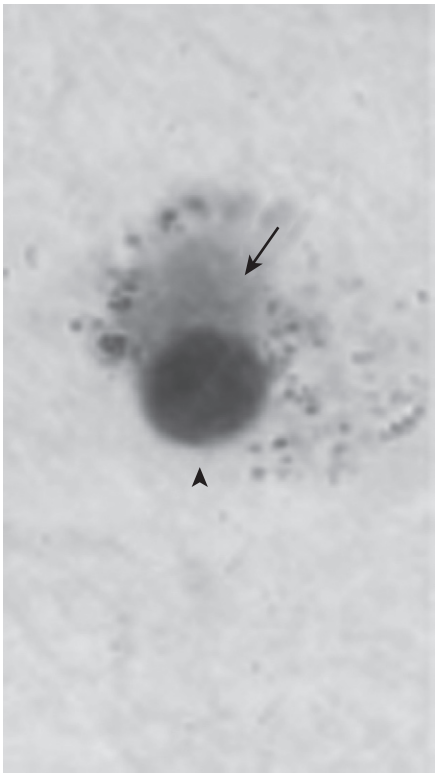
Lewy Bodies

The hallmark pathologic features of Parkinson disease are the death of dopaminergic neurons in the brainstem and the presence of intraneuronal inclusions called Lewy bodies. Lewy bodies contain multiple constituents. However, research has focused on aggregations of the protein alpha-synuclein bound to the intracellular chaperone protein ubiquitin[13] (Fig. 13-1).

Braak Hypothesis

A German pathologist, Hideo Braak, and his colleagues, conducted an extensive and detailed study of the progression of Lewy body pathology in Parkinson disease.[14,15] They demonstrated that the pathology of Parkinson disease begins not in the motor centers of the brain but in the lower brainstem. It spreads up to involve the dopaminergic neurons of the substantia nigra pars compacta only later in its course. This evolution and Braak's proposed staging system support the concept of a preclinical stage of Parkinson disease. The study also suggested that Parkinson disease is not simply a disease of dopamine deficiency. Other neurotransmitters, including the serotonergic, histaminergic, and noradrenergic systems, are affected as well. These other neurotransmitters are involved in the etiology of many of the nonmotor symptoms of Parkinson disease.

FIGURE 13-1
A combination of a pale body *(arrow)* and a small Lewy body *(arrowhead)* in melanized projection cells of the substantia nigra. (From Braak H, Del Tredici K, Rüb U, et al. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging.* 2003;24:197–211.)



Mitochondrial Hypothesis

One recurring theme in theories on the etiology of Parkinson disease is dysfunction of the mitochondria. Evidence indicates damage to mitochondrial complex I in people with Parkinson disease.[16] Impaired energy metabolism in the mitochondria of dopaminergic neurons may lead to production of reactive oxygen species.[17] The resulting oxidative damage to cell proteins, lipids, and DNA eventually can cause cell death.[18]

Alpha-Synuclein

Alpha-synuclein has been implicated in the pathogenesis of Parkinson disease, although the mechanism still is uncertain. Alpha-synuclein can be found bound to ubiquitin within Lewy bodies in areas of the brain affected by Parkinson disease.[13] However, unbound alpha-synuclein may be more harmful to neurons.[19] In conjunction with dopamine, alpha-synuclein enhances a neuron's susceptibility to death from oxidative stress.[20,21] Studies have also suggested that misfolded alpha-synuclein can spread from cell to cell, analogously to how the prion proteins spread in Creutzfeldt-Jacob ("mad cow") disease.[22,23]

Integrative Therapy

An integrative approach to treating Parkinson disease should start with optimizing general health through exercise and diet. Some people choose to take supplements for their potential neuroprotective benefits, whereas others prefer to wait for definitive studies. As Parkinson disease progresses, pharmaceuticals are eventually needed to help control motor symptoms. A thorough discussion of the integrative treatment of the nonmotor symptoms of Parkinson disease would be very lengthy and is beyond the scope of this chapter. However, addressing patients' nonmotor symptoms may be even more important to improving quality of life than treating their motor symptoms.

Exercise and Movement

Aerobic Exercise

Aerobic exercise has a multitude of benefits for people with or without Parkinson disease. A systematic review including multiple exercise modalities found significant benefit for people with Parkinson disease.[24] Improvements were found in physical functioning, health-related quality of life, strength, balance, and gait speed. Data from animal studies suggested that aerobic exercise also may be neuroprotective and slow the progression of Parkinson disease.[25,26] Furthermore, exercise is helpful in reducing depression and anxiety,[27] both very common issues in Parkinson disease. The forms of exercise that have been studied range widely from treadmill exercise,[28] to playing games on a Nintendo Wii,[29] to dancing the tango.[30] No clear evidence favors one form of exercise over another. Therefore, choosing an exercise program that is enjoyable enough to be continued is the best strategy.

Tai Chi

Tai chi is a martial art that started in ancient China as a means of self-defense. However, over time people began to use it primarily for health purposes. Tai chi emphasizes the cultivation of internal energy, *qi,* through the meditative properties of paying close attention to the details of its movements. Many different styles of tai chi are practiced, but all involve slow, relaxed, graceful movements. Each movement flows into the next. The body is in constant motion, and posture is important. Individuals practicing tai chi also must concentrate and put aside distracting thoughts. They must breathe in a deep and relaxed but focused manner. In the Chinese community, people commonly practice tai chi in nearby parks—often in early morning before going to work.[31]

Tai chi has been shown to reduce the risk of falls in an older population without Parkinson disease.[32] Although large controlled studies on Tai chi in Parkinson disease are lacking,[33] some preliminary reports on its efficacy have been published. One randomized clinical trial found tai chi to be effective in the prevention of falls.[34] Another pilot study showed promising improvements in balance and mobility, but it concluded that larger and longer studies were needed.[35] An additional study showed no objective benefit on gait or balance after 16 weeks of tai chi training, although the participants subjectively reported improvement.[36] Therefore, although overwhelming evidence of its efficacy is not yet available, tai chi certainly is safe, and it shows promise as potentially effective in helping people with Parkinson disease.

Benefits of Exercise in Parkinson Disease
Aerobic exercise has multiple benefits including:
- Increasing energy levels
- Decreasing depression and anxiety
- Potentially slowing disease progression
- Tai chi and yoga can help maintain and improve balance.

Supplements

Coenzyme Q10

Coenzyme Q10 (CoQ10), or ubiquinone, is the electron receptor in mitochondrial complexes I and II. Its level is significantly reduced in the mitochondria of people with early Parkinson disease.[37] In animal studies, oral supplementation was shown to increase CoQ10 levels in brain mitochondria.[38] Oral CoQ10 was also shown to reduce the loss of dopaminergic neurons in an animal model of Parkinson disease.[39] One randomized controlled trial in people with Parkinson disease showed a statistically significant slowing of the decline in a clinical rating scale (Unified Parkinson's Disease Rating Scale) at the highest dose of 1200 mg of CoQ10 with 1200 units of vitamin E.[40] The trend was for the 300-mg and 600-mg doses to provide some benefit; however, the 300-mg dose was slightly better than the 600-mg dose. A second trial using 1200 and 2400 mg along with 1200 units of vitamin E is now under way.[41]

Dosage

The dose is 1200 mg in three or four divided doses daily.

Precautions

CoQ10 is well tolerated with few side effects. No significant long-term safety data are available at these doses.

Glutathione

Glutathione is a potent, naturally occurring intracellular antioxidant. Its levels are significantly reduced in the substantia nigra of people with early Parkinson disease.[42] Glutathione was tried as a twice-daily intravenous infusion in one small open-label study.[43] A more recent double-blinded study using intravenous infusions three times a week showed a positive trend early, but the condition worsened after the treatments stopped.[44] Currently, not enough evidence is available to support the use of glutathione.

N-*Acetylcysteine*

Although some evidence indicates that glutathione can be transported actively across the blood-brain barrier, this agent cannot cross passively or in large volume.[45] Therefore, endogenous production is likely the primary source of brain glutathione stores. *N*-acetylcysteine is a precursor to glutathione that is able to cross the blood-brain barrier.[46] It may therefore be a more effective way of increasing intraneuronal glutathione. In animal studies, *N*-acetylcysteine was shown to increase glutathione in the brain.[47] It was also shown to protect against cell death in animal models of Parkinson disease.[48] Although it smells like rotten eggs, *N*-acetylcysteine can be well tolerated in people.[49]

Dosage

The dose is 1200 mg per day, generally divided into 600 mg twice daily.

Precautions

Frequent side effects include nausea, vomiting, and diarrhea.[50]

Vitamin D

Vitamin D is a secosteroid hormone that has modulating effects on immune and neural cells in addition to its classical actions on calcium and bone metabolism.[51] This vitamin can be consumed in the diet, as well as manufactured in the skin with exposure to sunlight. Vitamin D deficiency is markedly more common in people with Parkinson disease.[52,53] Additionally, in a dose-dependent fashion, one study linked vitamin D deficiency with a greater risk of developing Parkinson disease. People with serum 25-hydroxyvitamin D concentrations greater than 20 ng/mL had a 65% lower risk than did people with levels lower than 10 ng/mL.[54] Vitamin D was also demonstrated to be neuroprotective in animal models of Parkinson disease.[55,56] Administration of 1,25-dihydroxyvitamin D_3 was shown to increase glial cell line–derived neurotrophic factor (GDNF) mRNA and protein levels in the striatum of rats.[57] GDNF shows promise as a neuroprotective agent in animal models of Parkinson disease.[58,59]

Dosage

Consider supplementing with vitamin D_3 to keep serum levels between 30 and 80 ng/mL. A general rule of thumb is that 1000 units a day of vitamin D_3 will increase the serum level by 8 to 10 ng/mL.

Vitamin E

Vitamin E (tocopherol) has been looked at in one of the longest studies on neuroprotection. Ten-year follow-up data from the Deprenyl and Tocopherol Antioxidative Therapy for Parkinson's Disease (DATATOP) study found no evidence that 2000 units of vitamin E could slow the progression of Parkinson disease.[60] Additionally, 14-year data from the Nurses' Health Study did not find any reduction in the risk of developing Parkinson disease associated with taking vitamin E supplementation. However, eating nuts, which are high in vitamin E, did significantly reduce the risk of developing Parkinson disease. Nut consumption may have served as a marker for a healthier diet.[61]

Vitamin B_6 (Pyridoxine)

Vitamin B_6 can increase the peripheral conversion of levodopa to dopamine and should therefore be avoided in people taking carbidopa/levodopa. The decarboxylase inhibitor carbidopa should prevent this effect, but it may not at high doses of vitamin B_6.[62]

Creatine

Creatine is a supplement often used to improve athletic performance and increase muscle mass. Creatine is obtained both through diet and synthesis in the body.[63] It is found primarily in skeletal muscles. However, creatine crosses the blood-brain barrier easily and subsequently is converted into phosphocreatine. Phosphocreatine can serve as an energy buffer, decreasing the demand for mitochondrial adenosine triphosphate (ATP) production by donating its phosphate group.[18] In animal models of neurodegenerative diseases, creatine was shown to protect neurons from oxidative damage and death.[64] Because of this theoretical promise, creatine was included in a group of trials designed for rapid identification of agents that warrant further study in neuroprotective trials. In a small, 12-month trial, creatine was found to slow the progression of Parkinson disease marginally.[65] Additionally, no safety issues were identified. However, the same percentage of subjects in the creatine and placebo groups had

progressed to require pharmaceutical treatment of their Parkinson disease symptoms.[66] A much longer, 5-year-long study with 1720 subjects now is under way, although the results will not be known until at least 2015.[67]

Dosage
Prescribe 5 g orally twice per day.

Precautions
Creatine supplementation has been documented as being associated with a weight gain of approximately 1 to 2 kg from water retention. Anecdotal reports have also noted gastrointestinal distress, renal dysfunction, muscle cramps, and hepatic dysfunction.[68]

Cytidine Diphosphate–Choline
Cytidine diphosphate (CDP)–choline, or citicoline, is an intermediate in the synthesis of phospholipids, which are essential components in the assembly and repair of cell and mitochondrial membranes. Therefore, CDP-choline may have neuroprotective qualities as well as therapeutic effects in Parkinson disease.[69,70] Several studies investigated CDP-choline as a supplement to levodopa. Investigators found that CDP-choline allowed for a reduction of the levodopa dose by up to 50% without any reduction in symptom control.[69] CDP-choline may enhance dopaminergic therapy in Parkinson disease through multiple mechanisms. It decreases reuptake of dopamine and thereby increases levels at the synapse. Additionally, it activates tyrosine hydroxylase and leads to greater dopamine production.[71]

Dosage
The dose is 500 to 1200 mg orally per day.

Precautions
CDP-choline can worsen levodopa side effects and lead to increased dyskinesias. A reduction in levodopa dosing may be warranted if CDP-choline is added.

Botanicals

Green Tea (Epigallocatechin Gallate)
Epidemiologic studies suggested that drinking three cups of tea per day can decrease the risk of developing Parkinson disease by 28%. Although other caffeinated beverages such as coffee are also linked with a reduced risk of Parkinson disease,[6] evidence indicates that other constituents of green tea may account for at least some of the beneficial effects.[72] In addition to caffeine, green tea contains multiple polyphenols, catechins, and flavonols.[73] The potent antioxidant epigallocatechin gallate (EGCG) is the most thoroughly studied. Moreover, green tea may be helpful in Parkinson disease not only as an antioxidant but also as an inhibitor of both apoptosis and toxic alpha-synuclein fibrils.[74–76]

Dosage
Recommended dose is three cups per day.

Precautions
Green tea can be a strong diuretic.

Curcumin
Curcumin is a phenolic compound with antiinflammatory properties that is found in the spice turmeric. Turmeric is used commonly in Indian and Asian foods, especially in curries. Curcumin has been used also for centuries in the Ayurvedic medical tradition in India. Curcumin has been shown to be a potent antioxidant that can attenuate loss of glutathione in cultured dopaminergic cells.[77] It was also shown to reduce cell loss in an animal model of Parkinson disease.[78] Additionally, curcumin protected against apoptosis in a cultured dopaminergic cell line.[79] The aggregation of alpha-synuclein and toxic misfolded variants was reduced.[80]

Dosage
Studies in people with Parkinson disease have not yet been done. However, typical doses of curcumin for other conditions range from 450 mg of curcumin capsules to 3 g of turmeric root daily in divided doses.[81] As an alternative to taking curcumin capsules, people may incorporate more turmeric into their diet.

Precautions
Curcumin may cause mild stomach upset at high doses of several grams.

Mucuna pruriens *(Cowhage)*
Mucuna pruriens (velvet bean or cowhage) is a leguminous plant that has been used for centuries in Ayurvedic medicine for the treatment of Parkinson disease. *Mucuna pruriens* contains levodopa as well as two components of the mitochondrial electron transport chain, CoQ10 and reduced nicotinamide adenine dinucleotide (NADH).[82] In a single-dose, randomized controlled trial, a *Mucuna* seed powder formulation was as effective as levodopa in reducing Parkinsonian symptoms.[83] This formulation had a quicker onset and caused less dyskinesia than levodopa. An open-label study of another formulation in 60 patients over 12 weeks suggested that HP-200 was well tolerated and helped alleviate parkinsonian symptoms.[84] Currently, neither formulation is available commercially.

Acupuncture

Acupuncture is the insertion of fine needles into specific points along energy pathways called meridians. Acupuncture traditionally is part of the whole medical system of traditional Chinese medicine. Few studies have been conducted on the effects of acupuncture in people with Parkinson disease. Two meta-analyses of the current literature suggested that evidence is not sufficient to support or refute the use of acupuncture in Parkinson disease.[85,86] Both reviews concluded that larger randomized controlled trials were warranted, especially because some studies with design flaws did show promising results. For Parkinson disease, acupuncture may be especially useful in the treatment of some nonmotor symptoms or associated symptoms such as back and joint pains. One open-label study of acupuncture in 20 patients with Parkinson disease showed statistically significant improvements in sleep.[87] Additionally, 85% of patients reported subjective improvement in at least one individual symptom. Another pilot study showed positive trends toward decreased nausea, improved sleep, greater ease of activities of daily living, and improved quality of life.[88]

Pharmaceuticals

Levodopa

Levodopa remains the gold-standard therapeutic agent in Parkinson disease. It is an amino acid that easily crosses the blood-brain barrier, where it is converted into dopamine to increase the neuronal supply. Levodopa is combined with a DOPA decarboxylase inhibitor (carbidopa in the United States or benserazide in Europe) to prevent conversion in the peripheral bloodstream. Levodopa remains the most effective treatment for most of the motor symptoms of Parkinson disease, with the possible exception of tremor. The use of this agent often is delayed to reduce the risk of developing fidgety movements, known as dyskinesias, as a side effect. Levodopa is delayed frequently in the mistaken belief that early treatment will shorten the number of years that it will be effective.

Dosage

Carbidopa/levodopa 25/100 three times a day in early disease. As Parkinson disease progresses, people may take up to 2 g of levodopa per day in doses divided as frequently as every 2 hours.

Precautions

Levodopa can cause lightheadedness, fatigue, nausea, confusion, hallucinations, dyskinesias, and lower extremity edema. However, in comparison with the dopamine agonists, levodopa tends to cause less severe side effects for proportionately greater benefit.

Dopamine Agonists

Ropinirole and pramipexole are the two primary dopamine agonists used in the United States. They have very similar efficacy and are extremely effective for treating primarily the motor symptoms of Parkinson disease. These medications act as a replacement for the brain's decreased dopamine levels by directly stimulating dopamine receptors. They often are used in early Parkinson disease to delay the introduction of levodopa and reduce the risk of developing dyskinesias.[89] Extended-release formulations of both ropinirole and pramipexole are available.

Dosage

Ropinirole: Start at 0.25 mg three times a day (maximum, 24 mg per day). Pramipexole: start at 0.125 mg three times a day (maximum, 4.5 mg per day).

Precautions

Both dopamine agonists have a similar range of side effects. The most common side effects are sleepiness, fatigue, nausea, and lower extremity swelling. Some people have fallen asleep while driving without first feeling sleepy.[90] Dopamine agonists also can increase obsessive and compulsive behaviors.[91] Rarely, serious problems (i.e., gambling, sexual obsessions) can occur. Milder impulse control problems are common.

Rasagiline

Rasagiline is a highly selective monoamine oxidase type B (MAO-B) inhibitor. It slows the endogenous breakdown of dopamine and its precursor, levodopa. Unlike rasagiline's older cousin, selegiline, no amphetamines are produced during its degradation in the body. This difference is significant because amphetamines are thought to be neurotoxic. Rasagiline can be used as a stand-alone treatment in early Parkinson disease although its symptomatic effect is rather mild. In later disease, rasagiline can extend the length of action of levodopa and reduce "off" time.

Studies have suggested that rasagiline may be neuroprotective through antiapoptotic effects. In one study using a delayed start design, rasagiline slowed the progression of clinical symptoms of Parkinson disease.[92,93]

Dosage

Prescribe 1 mg orally, once per day.

Precautions

Rasagiline usually is very well tolerated with few side effects. However, it rarely can cause a dangerous excess of serotonin when it is taken in conjunction with antidepressant medications. Symptoms of serotonin syndrome include flushing, sweating, tremors, diarrhea, and elevated blood pressure. In addition, rasagiline also should not be taken with medications containing dextromethorphan.

Catechol-O-Methyltransferase Inhibitors

Entacapone and tolcapone both inhibit the degradation of dopamine and levodopa by blocking the enzyme catechol-O-methyltransferase (COMT). Entacapone is used much more frequently because tolcapone has been associated with rare cases of liver failure. In patients taking tolcapone, hepatic enzymes must be monitored carefully. Entacapone can increase the length of action of levodopa when the two agents are taken concurrently. However, entacapone has no effect on its own. It is also available as a combination pill with carbidopa/levodopa.

Dosage

The dose is 200 mg taken with each dose of carbidopa/levodopa (maximum, 1600 mg per day [eight doses]).

Precautions

Entacapone can potentiate the side effects of levodopa including dyskinesia, lightheadedness, confusion, and hallucinations. People should be warned that entacapone can turn the urine dark orange or dark yellow.

Amantadine

Amantadine is an antiviral medication used to treat and prevent influenza infections. It was serendipitously found to reduce Parkinson disease motor symptoms when it was given prophylactically in a nursing home. This drug can be used as a stand-alone treatment or in conjunction with rasagiline for early symptoms, including tremor.[94,95] Later in the course of the disease, it can be used to reduce dyskinesias, fidgety movements that are a side effect of levodopa.

Dosage

Give 100 mg two to three times a day.

Precautions

Amantadine can cause confusion and hallucinations, especially in older patients. Fatigue, lower extremity edema, a lacy rash (livido reticularis), and lightheadedness are other common side effects.

Zonisamide

Zonisamide is an antiepileptic medication that has been found to be effective in Parkinson disease as well. It has specific efficacy for reducing tremor. Zonisamide may work by several mechanisms. It has been found to stimulate dopamine synthesis and also may directly inhibit the basal ganglia's indirect pathway through delta opioid receptors.[96] Zonisamide was shown to reduce neuronal and astroglial cell loss in animal models of Parkinson disease.[97,98]

Dosage

The dose is 25 to 100 mg per day as one dose or divided into two doses.

Precautions

Because kidney stones can occur in up to 1% to 2% of people taking zonisamide,[99] people taking this drug should be advised to keep well hydrated. Other side effects include weight loss, dry mouth, fatigue, and nausea.

Anticholinergic Medications

Anticholinergic medications rarely are used as a primary treatment for Parkinson disease given the high incidence of side effects such as hallucinations, confusion, drowsiness, dry mouth, urinary retention, and blurry vision. However, trihexyphenidyl can be very effective for treating tremor that is refractory to other medications.

Dosage

Trihexyphenidyl dose may be titrated up from 1 mg once or twice daily to three times daily and then up to a maximum of 15 mg total per day as clinically indicated.

Surgery

Deep Brain Stimulation Surgery

Deep brain stimulation surgery for Parkinson disease involves the placement of a permanent electrode into the basal ganglia for continuous high-frequency electrical stimulation. Deep brain stimulation is considered when patients still are responsive to levodopa yet the effects of the drug wear off too quickly. Some surgical candidates may seem to cycle rapidly from feeling "frozen" to being wildly dyskinetic without spending much time in a comfortable state. Other people may be considered for surgery if they cannot tolerate a high enough dose of levodopa because of side effects. In a study of 255 patients who fit these criteria, deep brain stimulation surgery was shown to be more effective than optimal medical management.[100] This study found that people who received deep brain stimulation were more likely to experience clinically significant improvement in motor function (71% versus 32%). On average, they gained 4.6 hours of time with good motor function per day. However, serious adverse events were more common with deep brain stimulation. In another study, significant improvements in motor function were seen 4 years after surgery.[101]

Mind-Body Therapy

Depression and anxiety are extremely common in Parkinson disease. Approximately 20% to 40% of surveyed patients report these conditions.[102,103] Depression in Parkinson disease frequently can go unrecognized, in part because of the significant overlap of outward manifestations.[104] In Parkinson disease, depression may decrease quality of life even more than motor symptoms.[105] It is important to screen for these disorders and then to initiate counseling and other treatments as needed.

Increased stress levels have been observed to exacerbate the symptoms of Parkinson disease temporarily. Although no significant evidence exists for or against their use, mindfulness-based stress reduction programs may be considered. Other mind-body exercises such as yoga and qi gong should be considered as well.

Prevention Prescription

For Parkinson disease, risk reduction rather than prevention is the goal.

- Engage in regular aerobic exercise.
- Drink three cups of tea per day, preferably green tea.
- Maintain a diet high in antioxidants and omega-3 fatty acids.
- Eat a handful (not a canful) of nuts daily (rich in vitamin E and in B vitamins).
- Reduce exposure to pesticides. Wash all fruits and vegetables carefully, including those that are grown organically.
- Reduce exposure to heavy metals. Test and filter well water as appropriate.
- Reduce exposure to industrial solvents and dry cleaning.

Therapeutic Review

Given here is a summary of the therapeutic options for Parkinson disease. Because Parkinson disease can have such a variety of manifestations and symptoms, the ladder approach will not always work. However, for mild motor symptoms, it may be useful to consider. Because this disease is chronic and progressive, most patients eventually will need to use strategies from multiple rungs of the ladder.

Removal of Exacerbating Factors

- If other medical conditions allow, stop all medications that can induce parkinsonism. These medications include neuroleptics such as haloperidol, risperidone (Risperdal), and perphenazine, as well as metoclopramide and prochlorperazine. More rarely, lithium, valproate, amlodipine, and amiodarone lead to parkinsonism. Reduce exposures to pesticides. Have well water tested annually for heavy metals and pesticides. Remedy any abnormalities.

Mind-Body Therapy

- Facilitate optimism. The placebo effect is very strong in Parkinson disease. B1

Exercise

- Encourage regular aerobic exercise. A2
- Consider tai chi for stress management and improving balance. B1

Nutrition

- A high-fiber diet can help with constipation. B1
- Encourage foods rich in omega-3 fatty acids such as salmon, walnuts, pumpkin seeds, and flax seeds. C1
- Use turmeric when cooking. C1
- Drink three cups of tea per day, preferably green tea. B1

Neuroprotection

- Coenzyme Q10: 400 mg three times daily B2
- Creatine: 5 g twice daily B2
- *N*-acetylcysteine: 600 mg twice daily C2
- Rasagiline: 1 mg daily B2

Therapeutic Supplements

- CDP-choline: 500 to 1200 mg daily B2
- If the patient is taking carbidopa/levodopa, reduce its dose by 30% to 50% when CDP-choline is prescribed.

Acupuncture

- Acupuncture may help with the nonmotor and pain symptoms of Parkinson disease. B2

Pharmaceuticals

The general strategy is to start with a monoamine oxidase B inhibitor (as long as it is not contraindicated) and then try either amantadine or a dopamine agonist. In patients with mild cognitive impairment, consider starting with carbidopa/levodopa.

- Rasagiline: 1 mg daily A2
- Amantadine: 100 mg two to three times daily A2
- Dopamine agonists A2
  - Ropinirole: Start with 0.25 mg three times daily and titrate up to a maximum of 24 mg per day.
  - Pramipexole: Start with 0.125 mg three times daily and titrate up to a maximum of 4.5 mg per day.
  - Carbidopa/levodopa IR: Slowly titrate up from 25/100 mg ½ tablet three times daily. Stop at lowest effective dose. May increase up to 1 g of levodopa (i.e., one 25/250 mg tablet four times daily) as necessary. May divide into more frequent but smaller doses. A2
- For tremor-predominant Parkinson disease, start with
  - Zonisamide: 25 to 100 mg daily A2
  - Trihexyphenidyl: Titrate up from 1 mg once or twice daily and then three times daily (maximum of 15 mg per day). B2
- If carbidopa/levodopa wears off early, consider adding
  - Rasagiline: 1 mg daily (if not already being used) A2
  - Entacapone: 200 mg with each dose of carbidopa/levodopa up to eight doses per day A2
- If dyskinesias develop and are causing the patient problems, try decreasing the dose of carbidopa/levodopa or divide it into smaller but more frequent doses. If these modifications are not possible, consider adding
- Amantadine: 100 mg two to three times daily B2

Surgery

- Consider deep brain stimulation surgery targeting either the subthalamic nucleus or the globus pallidus internus for patients who respond to levodopa yet have severe motor fluctuations with rapid wearing off or dyskinesias. A3

KEY WEB RESOURCES

Worldwide Education and Awareness for Movement Disorders. http://wemove.org.	Information on Parkinson disease for patients
American Parkinson Disease Association. http://www.apdaparkinson.org.	Local and national Parkinson disease events
Michael J. Fox Foundation for Parkinson's Research. http://www.michaeljfox.org.	News about current Parkinson disease research
Environmental Working Group's 2011 Shopper's Guide to Pesticides in Produce. http://www.foodnews.org/walletguide.php.	List of the most and least contaminated crops
U.S. Environmental Protection Agency Ground Water and Drinking Water. http://www.epa.gov/safewater.	Information on water testing, filtering, and safety
ActiveForever laser light. http://www.activeforever.com/p-630-u-step-walker-laser-light-for-parkinsons-freezing.aspx.	Laser light to attach to a walker to help with freezing episodes (provides a red line for patients to step over)
LSVT Global. http://www.lsvtglobal.com.	Lee Silverman's voice training program for improving speech in Parkinson disease

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References are available online at expertconsult.com.

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Chapter 14

Otitis Media

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Pathophysiology

Otitis media (OM) literally means "inflammation of the middle ear" and is commonly known as an "ear infection." Fluid, either sterile or containing infective pathogens, develops behind the tympanic membrane (TM), with drainage impeded by a congested eustachian tube (Fig. 14–1). In children, the eustachian tube is small and at times tortuous, leading to increased susceptibility to OM. The National Institutes of Health[1] delineates OM into three categories: acute OM (AOM), OM with effusion (OME) and chronic OM with effusion (chronic serous OM, or CSOM). AOM is the most frequently diagnosed subtype, typically following upper respiratory congestion and causing acute inflammatory symptoms such as pain and fever. Earache may be caused by inflammation of the TM and by distention of the TM by pressure from fluid trapped behind the TM. OME may persist asymptomatically for some time following AOM, but it may also be associated with recurrent AOM episodes, as well as chronic inflammatory changes. This state of persistent fluid presence behind the TM, known as CSOM, may be associated with auditory and speech impairment.[2] Most cases of AOM are preceded by upper respiratory tract inflammation and congestion. Common triggers include viral (influenza, adenovirus) and bacterial pathogens (nontypeable *Haemophilus influenzae, Streptococcus pneumoniae, Moraxella catarrhalis*),[3] atopy (allergic rhinitis and cow's milk allergy),[4,5] exposure to prenatal and postnatal tobacco smoke,[6] and exposure to air pollution.[7]

Conventional Therapy

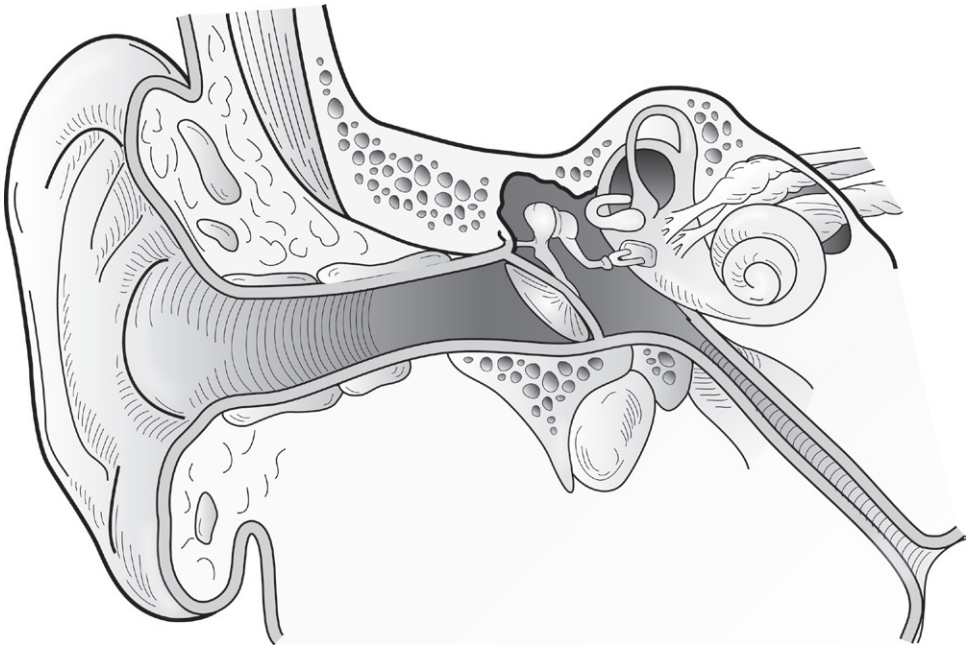
Although widely debated, the use of antibiotics for AOM is currently the standard of care for children younger than 2 years old and for many older children and adults as well, even though up to 80% of cases resolve spontaneously.[3] Great concern exists about the appropriate use of antibiotics for the condition in an age when we are witnessing increasing rates of microbial resistance to antiinfectives.[8] Furthermore, antibiotic use is associated with an increased rate of adverse effects, including diarrhea and allergic reactions. AOM is most frequently diagnosed in young children (ages 6 to 15 months), and more frequent use of antibiotics in early childhood is now linked to increased incidence of atopic disease such as asthma.[9] A "wait-and-see" approach is now increasingly prescribed, using symptomatic relief measures instead of initial antibiotic treatment; the documented decrease in antibiotic usage has not been associated with a corresponding increase in adverse sequelae.[10]

A "wait-and-see" approach is now increasingly prescribed, using symptomatic relief measures instead of initial antibiotic treatment.

Conventional prevention recommendations include advocating for universal childhood administration of influenza and pneumococcal vaccines. Evidence supporting this policy is inconclusive. Some studies have demonstrated a decrease in episodes of AOM and OME in vaccinated versus unvaccinated groups,[11] whereas others have not.[12] In the case of pneumococcal immunization, concerns have been raised regarding the emergence of new, nonvaccine strains and antibiotic-resistant pneumococcal subtypes despite the reduction in vaccine strains associated with OM.[13,14] The conventional management of CSOM includes a wait-and-see approach, and if fluid persists for some length of time (more than 3 months), myringotomy and pressure-equalizing tube placement is advised.[2] CSOM is the most common reason for elective surgery in children (other than circumcision) in the United States.[15] Even this approach, however, is under scrutiny with regard to when and whether the benefits outweigh the risks.[16]

Concern about the safety and efficacy of conventional approaches has led more practitioners to develop an interest in integrating complementary and alternative medicine (CAM) therapies for the prevention and treatment

FIGURE 14-1
The ear. The Eustachian tube in children is small.



of OM. Additionally, many patients use over-the-counter remedies for management of symptoms—pain, fever, and congestion—associated with OM. The use of these products in infants and young children is strongly discouraged by the U.S. Food and Drug Administration because of concerns about lack of efficacy and potential for harm.[17] Therefore, safe and effective alternatives for symptom management are desirable.

Integrative Therapy

In integrative care, the primary goal is prevention of OM, and the secondary goal is the use of natural methods for symptom management to optimize children's inherent healing mechanisms. Effective preventive measures include breast-feeding[18,19] and avoiding environmental triggers such as second-hand smoke and air pollution.[20,21]

> Effective preventive measures include breast-feeding and avoiding environmental triggers such as second-hand smoke and air pollution.

Regarding symptom management, patients can be educated to view OM-associated symptoms such as fever and congestion as the body's way of fighting infection. Natural viral infections theoretically allow for natural immune system development. Of course, one must consider the degree of symptoms and the possibility of overwhelming bacterial infection requiring the use of pharmaceutical agents, including antibiotics. Commonly used CAM therapies for OM management include biologically based therapies (botanical and nutritional), homeopathy, and manipulative and body-based methods.

Botanicals

Combination Herbal Extract Ear Drops

Botanically based naturopathic topical ear drops were shown to be effective and safe in prospective randomized and controlled trials.[22,23] The specific product tested included the following extracts: garlic oil *(Allium sativum),* mullein flower *(Verbascum thapsus),* calendula flower, St. John's wort *(Hypericum perfoliatum),* lavender, and vitamin E, in an olive oil base. These components have antiviral, antibacterial, antifungal, and anti-inflammatory properties. This topical botanical combination was as effective for AOM pain relief as prescription anesthetic ear drops with or without concurrent antibiotic use. No significant adverse effects were reported in these two trials.

Dosage

The product used in this study is from Israel and may be difficult to find in the United States. A similar product, *Ear Drops Children's Formula* by Gaia Herbs (Brevard, NC) is available. It also contains goldenseal and lobelia but does not include calendula.

Larch Arabinogalactan

Larch arabinogalactans, polysaccharides made from the bark of the larch tree and consisting of galactan backbones with side-chains of galactose and arabinose sugars, were linked in one report to decreased frequency and severity of pediatric AOM.[24] Larch arabinogalactan is a source of dietary fiber and also serves as a prebiotic, or substrate for growth of probiotic organisms. Whether its immune stimulating effects result from this mechanism or from others is unclear.

Dosage

One teaspoon of larch arabinogalactan powder in juice or water two to three times a day until symptoms have resolved.

Precautions
It can cause gas or bloating similar to fiber.

Nutrition

Cod Liver Oil
Cod liver oil, which contains omega-3 essentially fatty acids as well as vitamins A and D, was studied in combination with selenium (an antioxidant mineral) in a small pilot trial for prevention of AOM.[25] Eight children, serving as their own historical controls, received this combination of nutritional supplements for one "OM season" and were noted to receive antibiotics for significantly fewer days than during the previous OM season. Larger, controlled trials are needed before general recommendations can be made.

Xylitol
Based on success in reducing mouth bacteria associated with dental cavities, xylitol, a sugar alcohol, was studied for AOM prevention in four blind randomized controlled trials. The two earliest published trials[26,27] demonstrated 41% and 40% reductions in risk of developing AOM, whereas the more recent two trials[28,29] did not show any significant difference in AOM prevention versus placebo. More study is warranted to determine whether dosing amount and frequency are related to the success of xylitol in preventing AOM episodes. Xylitol has few noted adverse effects, mainly diarrhea and mild abdominal pain in a minority of children studied. It can be found commercially in chewing gum preparations.

Probiotics
Probiotics have been studied for both prevention and treatment of OM and OM-associated upper respiratory infections. A Finnish trial in 571 children 1 to 6 years old who were in child care centers compared prevention with *Lactobacillus* GG–containing milk versus milk that did not contain probiotic, three times per day, 5 days per week for 7 months.[30] Children who drank the probiotic milk were absent 1 less day from child care over the study period. This finding was statistically although not clinically significant. A follow-up study by the same research group compared a daily probiotic blend with placebo for 24 weeks in 306 AOM-prone children 10 months to 6 years old.[31] Probiotic treatment did not reduce the occurrence of AOM episodes. Finally, a Swedish study examined the efficacy of a probiotic nasal spray for prevention of AOM in 108 children 6 months to 6 years old.[32] This complex study design also included treatment with prophylactic antibiotics at various intervals and compared the study group with a placebo control group. During the study period, significantly more children in the probiotic study group had no AOM recurrences and normal middle ear examinations than did the placebo group. Reported adverse effects did not differ significantly between groups (see Chapter 102, Prescribing Probiotics).

Dosage
The foregoing study included two strains of *Streptococcus sanguis,* two strains of *Streptococcus mitis,* and one strain of *Streptococcus oralis* in equal proportions. The mixture corresponded to a suspension of 5×10^8 colony-forming units per milliliter. Dosing was three puffs into each nostril twice a day for 10 days.

Homeopathy
Table 111–6 in Chapter 111 suggests homeopathic remedies for OM. Five published studies evaluated the efficacy of homeopathic remedies for treatment of AOM in children.[3] Overall, despite limitations in study design, findings suggested a reduction in AOM-associated symptoms such as pain, as well as a decrease in antibiotic use and AOM recurrences. In the one double-blind randomized controlled trial, children receiving individualized homeopathic remedies had more significant reductions in symptoms (pain) at 24 and 64 hours than did controls.[33] Of course, extrapolating the importance of these positive findings of individualized treatments to a larger, generalized pediatric population is difficult. However, this study design did take into account the actual practice of homeopathy, which is based on individualizing remedies. *N*-of-1 study designs may be useful in evaluating efficacy of highly individualized therapies such as homeopathy[34] (see Chapter 111, Therapeutic Homeopathy).

Biomechanical Therapy

Osteopathy
Osteopathic manipulative treatment was studied in two published trials for preventing recurrent OM, with the goal of decreasing the need for surgical intervention for CSOM and recurrent AOM. Degenhardt and Kuchera[35] treated eight children with recurrent AOM in an uncontrolled pilot study. Patients received weekly osteopathic manipulative treatment for 3 weeks; intervention was performed in a complementary manner, concurrently with traditional medical management. Five children had no recurrence of symptoms, and only one child required myringotomy and tube placement surgery at 1-year follow-up.

Mills et al[36] performed a prospective, controlled trial of osteopathic manipulative treatment in 57 children with recurrent AOM. The control group received routine pediatric care, and the intervention group received osteopathic manipulative treatment plus routine care for 9 visits over the 6-month study period. Children receiving osteopathic manipulative treatment had significantly fewer episodes of AOM, surgical procedures, and "surgery-free months." No adverse reactions were reported.

> Children receiving osteopathic manipulative treatment have significantly fewer episodes of acute otitis media, surgical procedures, and "surgery-free months."

Chiropractic
Chiropractic treatments have been anecdotally reported to reduce recurrence of AOM and the need for surgical tympanostomies and pressure-equalizing tube placements for CSOM. Published trials to date were uncontrolled nonrandomized cohort studies.[37–39] All trials reported improvement during the treatment course. Given the typical course of AOM to resolve spontaneously, however, studying the efficacy and safety of chiropractic in a randomized controlled trial would be instructive.

Pharmaceuticals

Conventional pharmaceutical treatment for AOM historically has relied on antibiotics that target the most common bacterial pathogens such as *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis.* First-line treatment is typically amoxicillin, at a dose of 50 mg/kg divided twice daily, with second-line therapy including amoxicillin-clavulanic acid (Augmentin or generic), second-generation cephalosporins (cefdinir compliance is typically excellent given good palatability and ease of administration with a 5-day dosing option), or azithromycin (also convenient, given once daily for 5 days).

Surgery (Myringotomy With Tympanostomy Tube Placement)

Myringotomy with placement of tympanostomy tubes is the preferred surgical procedure for CSOM under certain conditions. Guidelines for circumstances when the procedure is warranted have changed over time. The most recent, relevant American Academy of Pediatrics policy was published in 2004.[2] This policy notes that the need for surgery depends on "hearing status, associated symptoms, the child's developmental risk, and the anticipated chance of timely spontaneous resolution of the effusion." Specifically, "candidates for surgery include children with OME lasting 4 months or longer with persistent hearing loss or other signs and symptoms, recurrent or persistent OME in children at risk regardless of hearing status, and OME and structural damage to the tympanic membrane or middle ear." Most important, the authors of the policy wisely counsel that "ultimately, the recommendation for surgery must be individualized based on consensus between the primary care physician, otolaryngologist, and parent or caregiver that a particular child would benefit from intervention."

Prevention Prescription

- Limit exposure of children to environmental tobacco smoke and air pollution.
- Encourage exclusive breast-feeding for the first 4 to 6 months of life.
- Recommend a diet high in nutritious foods such as fresh fruits and vegetables, whole grains, and hormone- and antibiotic-free proteins.
- Advise those with clinical signs and symptoms of allergy and inflammation to avoid cow's milk, and identify all food allergies and eliminate consumption of offending foods.
- Avoid unnecessary antibiotic exposures.
- Consider preventive use of cod liver oil given once daily with dosing based on omega-3 fatty acids as appropriate for age and weight, xylitol at 10 g/day divided five times per day, and prebiotics or probiotics given once daily at a dose typically exceeding 5 billion colony-forming units of live probiotics.

Therapeutic Review

Environmental

- Remove potential allergens and triggers of upper respiratory inflammation (tobacco smoke, cow's milk protein). B1

Botanicals

- Naturopathic/botanical ear drops: Instill 2 drops in affected ear(s) every 4 hours as needed for pain. B2

Homeopathy

- Use individualized homeopathic remedies for symptoms associated with acute otitis media (see Table 111-6 in Chapter 111, Therapeutic Homeopathy). C2

Manipulative and Body-Based Methods

- Consider a trial of osteopathic or chiropractic treatment, especially for patients with otitis media with chronic effusion who are at high risk for surgical intervention. C2

Pharmaceuticals

- Use antibiotics judiciously in children less than 6 months of age and in all patients with significant systemic symptoms (fever, irritability) affecting daily functioning. A2
- Use ibuprofen or acetaminophen judiciously for pain relief. B2

Surgery

- Myringotomy tubes. B2

KEY WEB RESOURCES

American Academy of Pediatrics (AAP) Section on Complementary and Integrative Medicine. http://www.aap.org/sections/CHIM

National Center for Complementary and Alternative Medicine (NCCAM). *Complementary and Alternative Medicine Use and Children.* http://nccam.nih.gov/health/children

Pediatric Complementary and Alternative Medicine Research and Education (PedCAM) Network. http://www.pedcam.ca

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References are available at expertconsult.com.

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Chapter 15

Chronic Sinusitis

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Pathophysiology

Prevalence

Since 1981, chronic sinusitis has been the most common chronic disease in the United States. It is currently the most common respiratory condition in the world. According to the National Center for Health Statistics (a division of the Centers for Disease Control and Prevention [CDC]), approximately 40 million residents of the United States of all age groups suffer from this ailment.[1] Chronic sinusitis affects nearly 15% of the population or 1 out of every 7 people. Twenty-two percent of all women between the ages of 45 and 64 years have chronic sinusitis (15% of men in this age group have it), an incidence approximately equal to that of hypertension. Sinusitis is second only to arthritis among the most common chronic diseases for women in this age group. In men in this age group, sinusitis ranks fourth, behind hypertension, hearing impairment, and arthritis. It was the primary reason for nearly 12 million physician office visits in 1995,[2,3] and more than 200,000 sinus surgical procedures were performed in 1994,[4] (the current estimate is approximately 300,000). Medical costs for diagnosing and treating this condition are estimated to be greater than $10 billion annually.

When sinusitis is considered together with allergic rhinitis (the fourth most common chronic condition), asthma, and chronic bronchitis (the eighth and ninth most common conditions, respectively), respiratory disease resulting from these ailments affects more than 90 million people—nearly 1 out of every 3 U.S. residents—and thus constitutes our first environmental epidemic. In the 1960s, not 1 of these 4 conditions was among the top 10 chronic health problems.

Etiology

The modern-day plague of *air pollution* is insidiously destroying the respiratory tract of those breathing polluted air. According to the Environmental Protection Agency (EPA), 60% of U.S. residents currently live in areas where the air quality makes breathing a risk to their health. A 1993 study performed by the EPA and Boston's Harvard School of Public Health reported that 50,000 to 60,000 deaths a year are caused by particulate air pollution.[5] A subsequent study in 1995 bolstered the earlier findings while concluding that people who live in highly polluted cities die earlier (approximately 10 years sooner, a 15% decrease in life expectancy) than if they had been breathing healthier air. In addition to particulates, other components of toxic air include carbon monoxide, ozone, sulfur dioxide, nitrogen dioxide, hydrocarbons, and lead.

The nose and sinuses are lined by the respiratory epithelium. By virtue of the histologic and physiologic characteristics of its outermost lining, the *ciliated mucous membrane* or *mucosa,* the nose and sinuses serve as the body's *air filter*, *humidifier*, and *temperature regulator*, as well as *protector of the lungs*. This continuous mucous membrane that extends from just inside the nostrils to the alveolar sacs in the lungs is a connected porous protective shield for the body's air portal. The respiratory epithelial mucosa serves as a vital component of the immune system and acts as the first line of defense against bacteria, viruses, pollen, animal dander, cigarette smoke, dust, chemicals, automobile exhaust, and other potentially harmful air pollutants. The bulk of its job of filtration, humidification, and temperature regulation occurs in the nose and in the four pairs of paranasal sinuses (maxillary, ethmoid, frontal, and sphenoid) comprising the entrance and vestibule of the respiratory tract.

Although the human body is a self-healing organism, this self-rejuvenating process typically requires a period of rest and recovery. The primary challenge preventing healing of the respiratory mucosa is that we breathe continuously approximately 20,000 times per day. When the air that we breathe is polluted and dry, as indoor air tends to be, especially during the winter months, the mucous membrane can easily become mildly inflamed from the chronic irritation, in addition to one or more of the etiologic factors listed later. Without the opportunity for rest and recovery, this situation often leads to *chronic inflammation*, the underlying pathophysiologic process of chronic sinusitis. A chronically

inflamed mucosa is weak and therefore more vulnerable to cold viruses, the most common trigger for sinus infections. It can also become hyperreactive and more sensitive to a wide variety of allergens, foods, and chemicals.

Nothing is more important to optimal physical well-being than the quality of the air breathed and the ability to breathe it. Pollutant-laden air often has far less than the optimal 20% oxygen or negative ion content (3000 to 6000 ions/cm^3), thus adding to its effect as a chronic irritant in creating inflamed and hypersensitive mucous membranes. Chronically inflamed mucosa often results in increased mucus secretion (rhinorrhea and postnasal drip), head and nasal congestion with some degree of obstruction of the ostia, headaches, and nasal allergy.

Risk Factors for Acute and Chronic Sinusitis

- Infections: The common cold causes inflammation and ciliostasis. Candidiasis, yeast overgrowth, or fungal sinusitis can cause severe respiratory and systemic inflammation.
- Environment (air pollution, both indoor and outdoor, and pollen)
- Lifestyle (diet, cigarettes, and other sources of smoke)
- Allergies: Half of chronic sinusitis sufferers have allergies to pollen or food.
- Food sensitivities
- Emotional stress, especially repressed anger and grief (unshed tears)
- Dry air: Air with less than 30% relative humidity occurs in an arid or semiarid climate and is also the result of forced-air heating systems, air conditioning (especially in cars), oxygen therapy, and wind.
- Cold air: The ideal temperature is higher than 65°F.
- Occupational hazards: Those at highest risk include automobile mechanics, construction workers (especially carpenters), painters, beauticians, firemen, and airport and airline personnel.
- Gastroesophageal reflux disease
- Dental infection: Infection in the upper teeth can spread to the maxillary sinuses.
- Malformations (polyps, cysts, deviated septum)

Fungal Sinusitis

Since the early 1990s, I have treated the patients who have presented with the most severe and challenging cases of chronic sinusitis by using an antifungal regimen. A landmark Mayo Clinic (Rochester, Minn) study,[6] published in September 1999, reported that an immune system response to fungus rather than to bacterial infection is the cause of most cases of chronic sinusitis. The investigators reached this conclusion after studying 210 patients with chronic sinusitis and finding 40 different kinds of fungus, including *Candida*, in the mucus of 96%. In a control group of normal, healthy volunteers, very similar organisms were found. The investigators concluded that the immune system response to these fungi in patients with chronic sinusitis is markedly different from that in healthy people and that this unusual immune reaction is responsible for the chronic inflammation, pain, and swelling of the mucous membranes associated with sinusitis. These investigators called the condition "allergic fungal sinusitis." However, the investigators failed to speculate on the possible impact of previous multiple courses of broad-spectrum antibiotics on the immune response to the fungal organisms in these patients. The resultant profound disruption of the normal bacterial flora of the mucosa likely contributed to the immune response observed. This issue was not addressed, however, and this study concluded simply by stating that "We must begin looking at chronic sinusitis as more than simply a bacteriological and/or anatomical problem, but as a dysfunction of the immune system mediated by a fungus."

Between October 1999 and February 2000, my colleagues and I[7] conducted a study with 10 patients of an allergist-immunologist who were symptomatic despite aggressive conventional treatment for their chronic sinusitis. (Four of the patients also had asthma.) The study consisted of 5 group sessions with follow-up evaluations at 1-year and again at 7.5 years. Dr. William Crook's *Candida* Questionnaire and Score Sheet (Fig. 15-1) was used as part of the baseline measurement, and all 10 patients scored in the "probably yeast-connected" category or higher. They were treated with the Sinus Survival Program (currently called the Respiratory Healing Program; discussed later), in addition to fluconazole. Statistically significant improvement was measured 1 month following the introduction of fluconazole and again at the end of the 5-month study. Although asthma outcomes were not measured, 3 of the 4 asthmatic patients also reported a marked improvement in their asthma, and they were able to reduce the dose or stop using their inhalers. In both the 1-year and 7.5-year follow-up assessments, improvements in sinusitis symptoms and quality of life were either maintained or enhanced in all participants. This is the only published long-term study of a nonsurgical treatment for chronic sinusitis and the only long-term study of the treatment of fungal sinusitis.

An allergic inflammatory response to fungal organisms is an important etiologic factor in chronic sinusitis.

The Common Cold and Sinitus

Information on this topic can be found online at expertconsult .com

Symptoms and Diagnosis

Chronic sinusitis is defined as persistent or recurrent episodes of infection or inflammation of one or more sinus cavities, episodes that produce most or all of the following symptoms and signs: headache, facial pain, head congestion, purulent postnasal drainage or rhinorrhea, and fatigue.[9] I now recognize that purulent mucus does not always mean infection, but it does always indicate some degree of inflammation. Although most otolaryngologists rely on the computed tomography scan for a definitive diagnosis of sinusitis, in a primary care setting I have found that a good history and physical examination to detect the presence of most or all of the defining signs and symptoms can provide a reliable diagnosis of acute sinusitis. In my experience, the patients who are most debilitated by chronic sinusitis have some degree of fungal sinusitis. Unfortunately, even in 2010, no consistently

Most sinus infections or cases of acute sinusitis are caused by cold viruses. However, anything that causes obstruction of the flow of mucus through the ostia can also trigger a sinus infection. A lifetime of chronic sinusitis typically begins with the common cold. The cold that persists beyond 7 to 10 days is most likely symptomatic of acute sinusitis. In a 1993 study at the University of Virginia, college students and university employees who thought they had the common cold underwent computed tomography scanning of the sinus. Eighty-seven percent of the study subjects were found to have sinus infections.[8]

FIGURE 15-1
Candida Questionnaire and Score Sheet. (From Crook W. *The Yeast Connection: A Medical Breakthrough*, 3rd ed. Jackson, TN: Professional Books; 1986.)

Candida Questionnaire and Score Sheet

This questionnaire is designed for adults and the scoring system isn't appropriate for children. It lists factors in your medical history that promote the growth of *Candida albicans* (Section A), and symptoms commonly found in individuals with yeast-connected illness (sections B and C).

For each "Yes" answer in Section A, circle the point score in the box at the end of the section. Then move on to sections B and C and score as directed. Filling out and scoring the questionnaire should help you and your doctor evaluate the possible role of candida in contributing to your health problems. Yet, it will not provide an automatic "Yes" or "No" answer.

SECTION A: HISTORY POINT SCORE:

(1) Have you taken tetracyclines (Sumycin, Panmycin, Vibramycin, Minocin, etc.) or other antibiotics for acne for one month or longer? 25
(2) Have you, at any time in your life, taken other "broad spectrum" antibiotics* for respiratory, urinary, or other infections for 2 months or longer or in shorter courses 4 or more times in a 1-year period? 20
(3) Have you taken a broad spectrum antibiotic* — even in a single course? 6
(4) Have you, at any time in your life, been bothered by persistent prostatitis, vaginitis, or other problems affecting your reproductive organs? 25
(5) Have you been pregnant
2 or more times? 5
1 time? 3
(6) Have you taken birth control pills
For more than 2 years? 15
For 6 months to 2 years? 8
(7) Have you taken prednisone, Decadron or other cortisone-type drugs, by injection or inhalation:
For more than 2 weeks? 15
For 2 weeks or less? 6
(8) Does exposure to perfumes, insecticides, fabric shop odors and other chemicals provoke:
Moderate to severe symptoms? 20
Mild symptoms? 5
(9) Are your symptoms worse on damp, muggy days or in moldy places? 20
(10) Have you had athlete's foot, ringworm, jock itch or other chronic fungus infections of the skin or nails? Have such infections been:
Severe or persistent? 20
Mild to moderate? 10
(11) Do you crave sugar? 10
(12) Do you crave breads? 10
(13) Do you crave alcoholic beverages? 10
(14) Does tobacco smoke really bother you? 10

TOTAL SCORE, SECTION A:

* Including ampicillin, amoxicillin, Augmentin, Keflex, Ceclor, Bactrim, Septra, Levaquin, Zithromax, and many others. Such antibiotics kill off "good germs" while they are killing off those which cause infection.

SECTION B: MAJOR SYMPTOMS

For each of your symptoms, enter the appropriate figure in the point score column:
Not at all 0 points
Occasional or mild 3 points
Frequent and/or moderately severe 6 points
Severe and/or disabling 9 points
Add total score and record it in the box at the end of this section.

POINT SCORE:

(1) Fatique or lethargy
(2) Feeling of being "drained"
(3) Poor memory or concentration
(4) Feeling "spacey" or "unreal"
(5) Depression
(6) Numbness, burning, or tingling
(7) Muscle aches
(8) Muscle weakness or paralysis
(9) Pain and/or swelling in joints
(10) Abnominal pain
(11) Constipation
(12) Diarrhea
(13) Bloating
(14) Troublesome vaginal discharge
(15) Persistent vaginal burning or itching
(16) Prostatitis
(17) Impotence

(18) Loss of sexual desire
(19) Endometriosis or infertility
(20) Cramps and/or other menstrual irregularities
(21) Premenstrual tension
(22) Spots in front of the eyes
(23) Erratic vision

TOTAL SCORE, SECTION B:

SECTION C: OTHER SYMPTOMS
For each of your symptoms, enter the appropriate figure in the point score column:
Not at all 0 points
Occasional or mild 1 point
Frequent and/or moderately severe 2 points
Severe and/or disabling 3 points
Add total score and record it in the box at the end of this section.

POINT SCORE:

(1) Drowsiness
(2) Irritability or jitteriness
(3) Incoordination
(4) Inability to concentrate
(5) Frequent mood swings
(6) Headache
(7) Dizziness/loss of balance
(8) Pressure above ears, feeling of head swelling and tingling
(9) Itching
(10) Other rashes
(11) Heartburn
(12) Indigestion
(13) Belching and intestinal gas
(14) Mucus in stools
(15) Hemorrhoids
(16) Dry mouth
(17) Rash or blisters in mouth
(18) Bad breath
(19) Joint swelling or arthritis
(20) Nasal congestion or discharge
(21) Postnasal drip
(22) Nasal itching
(23) Sore or dry throat
(24) Cough
(25) Pain or tightness in chest
(26) Wheezing or shortness of breath
(27) Urinary urgency or frequency
(28) Burning on urination
(29) Failing vision
(30) Burning or tearing of eyes
(31) Recurrent infections or fluid in ears
(32) Ear pain or deafness

TOTAL SCORE, SECTION C:

TOTAL SCORE, SECTION A:

TOTAL SCORE, SECTION B:

GRAND SCORE:
The Grand Total Score will help you and your doctor decide if your health problems are yeast-connected. Scores in women will run higher as 7 items in the questionnaire apply exclusively to women, while only 2 apply exclusively to men.

IF YOUR SCORE IS:	SYMPTOMS ARE:
180 (women) 140 (men)	almost certainly yeast-connected
120 (women) 80 (men)	probably yeast-connected
60 (women) 40 (men)	possibly yeast-connected
Less than 60 (women) 40 (men)	probably not yeast-connected

reliable laboratory tests are available to make this diagnosis definitively. I have relied on the patient's history, Dr. William Crook's *Candida* Questionnaire and Score Sheet (see Fig. 15-1), and the therapeutic response to antifungal treatment to confirm the diagnosis of fungal sinusitis.

Integrative Therapy: Respiratory Healing Program

Although antibiotics have been the mainstay of conventional medical treatment for chronic sinusitis, often followed by sinus surgery if the problem has not resolved, these therapeutic modalities increasingly offer only temporary relief and fail to resolve or cure the problem of chronic sinusitis. In a study of 161 children with acute sinusitis, researchers concluded that "antimicrobial treatment offered *no benefit* in overall symptom resolution, duration of symptoms, recovery to usual functional status, days missed from school or child care, or relapse and recurrence of sinus symptoms."[10] For the growing numbers of patients who have failed to respond to repeated courses of broad-spectrum antibiotics and surgery, for postoperative patients, and for the growing numbers of people who elect not to have (or are not candidates for) surgery or to take antibiotics, the Respiratory Healing Program has consistently produced successful outcomes.

The *goal* of this integrative holistic treatment program for chronic sinusitis is to address the primary cause (inflammation) by healing the chronically inflamed mucous membrane. Although this is a relatively complex problem with multiple risk factors contributing to chronic inflammation, what makes this approach so effective is that each of these factors is either mitigated or eliminated.

Components of the Respiratory Healing Program for Chronic Sinusitis

1. Treating and preventing sinus infections and colds
2. Practicing nasal hygiene: spraying, steaming, and irrigating
3. Eating a healthy, antiinflammatory, and hypoallergenic diet in combination with antiinflammatory and antioxidant vitamins and supplements
4. Improving indoor air quality
5. Treating yeast overgrowth or fungal sinusitis
6. Detoxification
7. Strengthening and restoring balance to the immune system
8. Healing the issues in the tissues: mental, emotional, spiritual, and social health factors

If the patient closely adheres to the first seven components listed here, he or she will usually experience significant improvement in 1 to 2 months, regardless of how many years the patient has suffered with chronic sinusitis. Depending on the patient—the severity of the condition, the level of commitment, and my sense of the patient's capability—I'll typically introduce all but the last two components at the first session, followed a month later by measures to strengthen immunity. The third and fourth sessions, 2 and 3 months into the program, are focused on mental and emotional health and on spiritual and social health, respectively.

The keys to curing chronic and fungal sinusitis are becoming a highly skilled practitioner in the *art of preventive medicine* (specifically preventing sinus infections) and making a commitment to *healing one's life.* My more than 3 decades of experience in treating extremely challenging cases of chronic sinusitis have made it apparent that mental, emotional, social, and spiritual factors have a profound impact on the degree of inflammation and immune dysfunction. Specifically, repressed anger may be the single most significant cause (see Chapter 100 Emotional Awareness for Pain). To have the greatest therapeutic benefit, the recommendations that follow should be practiced on a daily basis and incorporated into one's lifestyle. From the foregoing published study and from statistics I have derived from patient questionnaires since 1990, more than 90% of patients who make at least a 3-month commitment (and three to four office visits) to the Respiratory Healing Program experience, at a minimum, a significant improvement, and in most cases, chronic sinusitis is cured.

Integrative Therapy: Treating and Preventing Sinus Infections and Colds*

Natural "Antibiotics"

Garlic

Allimed or Allimax (both are 100% pure allicin, the active ingredient in garlic) is my first choice because studies have shown it to be highly effective as an *antibacterial,*[11,12] *antiviral* (kills cold viruses),[13] and *antifungal.*[14] In my practice, it has been consistently effective in treating and preventing sinus infections and colds. However, it needs to be taken in therapeutic doses. Allimed (450 mg/capsule) and Allimax (180 mg/capsule) are both available in liquid form for children.

Dosage

For treating a sinus infection: Allimed, two capsules three times daily for 10 days; Allimax, five capsules three times daily for 10 days. For treating colds and preventing sinus infections: at the first sign of a cold, Allimed, two capsules (or Allimax, five capsules) three times daily for 2 to 3 days; then if symptoms have subsided, one capsule (or Allimax, two capsules) twice daily for 2 to 3 days.

Echinacea and Elderberry

The commercial formulation EchinOsha with Elderberry contains two antiviral herbs, *Echinacea*[15] and elderberry[16] (also effective for the influenza virus), as well as osha root, which helps to strengthen the immune system. This preparation is contraindicated during pregnancy and in patients with autoimmune disease.

Dosage

EchinOsha, for treating colds and flu: 1 to 2 teaspoons every 2 to 4 hours for as long as symptoms are present. Or *Echinacea* extract, 2 dropperfuls four to five times a day.

*Editor's Note: Dr. Ivker has financial ties to some of these products, which are sold through his Web site.

Yin Chiao
This antiviral Chinese herb is available in health food stores.

Dosage
For treating colds: three to five tablets or capsules (300 to 500 mg each) four or five times a day in the first 48 hours.

Grapefruit Seed Extract
In capsule or liquid form, grapefruit seed extract, which is antifungal and antiviral, is available in health food stores.

Dosage
The dose is 250 mg three times daily or 10 drops in water three times daily (the liquid has an unpleasant taste).

Nasal Sprays

Sinus Survival Spray
This saline nasal spray contains aloe, calendula, and yarrow leaf (antiinflammatory herbs), in addition to grapefruit seed extract (Table 15-1).

Dosage
One to two sprays in each nostril every 1 to 2 hours during infection; apply a dab of peppermint oil to the *outside* of the nostrils following each application. Use for both treatment and prevention on a daily basis.

Nasal Rescue (Ionic Silver Spray)
This is highly effective in killing bacteria, viruses, and fungi. It contains ionic silver.

Dosage
One spray in each nostril every 15 to 20 minutes for maximum effectiveness; apply a dab of peppermint oil to the outside of the nostrils following each application. Use only for treating infection.

Nasal Hygiene (see Table 15-1)

Steam Inhaler
This acts as a decongestant[17,18] and mucolytic. Add a highly medicinal eucalyptus oil, peppermint oil, and tea tree oil to the steam. Use three to four times a day for at least 15 to 20 minutes if treating an infection and once or twice daily preventively and for treating chronic inflammation.

Irrigation
Perform three to four times a day for treating a sinus infection, immediately following use of the steam inhaler.[19,20] A pulsatile irrigator is the most effective irrigating device and the only one that has been shown to remove the biofilm. Irrigation is one of the best methods for quickly eliminating (and preventing, once or twice daily) sinus infections, as well as for treating chronic and fungal sinusitis (see Chapter 109, Sinus Irrigation).

Antiinflammatory and Antioxidant Vitamins and Supplements

Vitamin C
A regimen of 3000 to 5000 mg three times a day with meals is followed, for the antiinflammatory and antioxidant effects. Use this high dosage until symptoms subside, and then reduce the dose to 2000 mg three times a day. Vitamin C is

TABLE 15-1. Physical and Environmental Health Components of Sinus Survival Program

MEASURE	PREVENTIVE MAINTENANCE	TREATMENT
Sleep	7–9 hr; no alarm clock	8–10+ hr/day
Negative ions or air cleaner	Continuous operation; use ions especially with air conditioning	Continuous operation
Room humidifier, warm mist	Use during dry conditions, especially in winter if heat is on and in summer if air conditioner is on	Continuous operation
Saline nasal spray	Use daily, especially with dirty or dry air	Use daily every 2–3 hr
Steam inhaler	Use as needed with dirty or dry air	Use two to four times/day; add eucalyptus oil
Nasal irrigation	Use as needed with dirty or dry air	Use daily, two to four times/day, after steam
Water, filtered	Drink ½ oz/lb body weight; with exercise, drink 2–3 oz/lb	½–⅓ oz/lb of body weight
Diet	Emphasize fresh fruit and vegetables, whole grains, fiber; limit sugar, dairy, caffeine, and alcohol	No sugar, dairy, alcohol
Exercise, preferably aerobic	Minimum of 20–30 min three to five times/wk; avoid outdoors with high pollution or pollen levels and extremely cold temperatures	No aerobic; moderate walking allowed; avoid outdoors with high pollution or pollen levels and cold temperatures

Modified from Ivker RS. *Sinus Survival: The Holistic Medical Treatment for Sinusitis, Allergies, and Cold.* 4th ed. New York: Tarcher/Putnam; 2000.

most effective if it is taken in the form of Ester C or a mineral ascorbate (for better absorption and gastrointestinal tolerance), rather than as ascorbic acid. If diarrhea occurs, then the dose should be reduced.[21–26]

Vitamin D_3

The dose is 100,000 units daily for the first 3 days of a sinus infection. Vitamin D_3 is a potent immune strengthener and can safely be taken at 5000 to 10,000 units daily on an ongoing basis. Studies have revealed that most illnesses are accompanied by a deficiency in vitamin D.[27–31]

Grape Seed Extract

Patients should take 300 mg in the morning on an empty stomach. Grape seed is a powerful antioxidant, antiinflammatory, and antihistamine.[32–34]

Fish Oil

Eicosapentaenoic acid 1000 to 3000 mg/docosahexaenoic acid 500 to 900 mg per day. This is an omega 3/omega-6 combination. Fish oil is a potent natural antiinflammatory.[35–37]

Sinupret Plus

One tablet three times daily. This herbal combination serves as a highly effective natural antiinflammatory for the mucous membrane of the upper respiratory tract.

Sleep

Nine to 10 or more hours for treating sinus infections; 7 to 9 hours for prevention. Adequate sleep is perhaps the most effective and convenient and least expensive way to strengthen the immune system.

Diet

Patients should eat mostly organic vegetables and fruits, nongluten grains (brown rice, quinoa, millet, buckwheat, amaranth), fiber, and protein; they should *avoid* sugar, dairy, wheat, other carbohydrates (especially gluten grains), caffeine, and alcohol. Sugar weakens immunity; wheat, dairy, and gluten grains are most common causes of food allergy (often a trigger of sinus infections).

Patients should also drink filtered water, at least ½ oz/lb of body weight (e.g., 160 lb = 80 oz/day). For colds, patients should drink lots of warm or hot liquids; ginger root or peppermint tea is recommended, possibly including ginger, honey, lemon, cayenne, cinnamon, and a teaspoon of brandy.

Emotional Factors

Treat the emotional cause. Most sinus infections are triggered by repressed anger or unshed tears. I recommend the safe release of anger, as well as reflecting on whether the patient is feeling grief or some sense of loss. The feeling of grief or loss is typically not as obvious as the anger, but it is probably there, just a bit deeper. Journaling is another excellent method for releasing either or both of these painful emotions (see Chapter 96, Journaling for Health).

Improving Indoor Air Quality

Ideal air quality is rated by clarity (freedom from pollutants), humidity (between 35% and 55%), temperature (between 65°F and 85°F), oxygen content (21% of total volume and 100% saturation), and negative ion content (3000 to 6000 .001 micron ions/cm^3). Air that is clean, moist, warm, oxygen rich, and high in negative ions is healing to the mucous membrane (see Table 15-1). To create optimal indoor air I recommend the following:

- A negative ion generator[38–40]: used as an air cleaner and placed in the rooms in which patients spend the bulk of their time, especially the bedroom and office
- Furnace filter: an electrostatic or a pleated filter (e.g., Filtrete by 3M)
- Air duct and furnace cleaning
- Carpet cleaning
- Use of a humidifier: a warm mist room unit, especially during the winter months
- Plants, especially those that can remove formaldehyde (Boston fern, chrysanthemums, striped *Dracaena*, dwarf date palm) and carbon monoxide (spider plant)

Treating Yeast Overgrowth and Fungal Sinusitis

Most severe and unresponsive (to conventional treatment) cases of chronic sinusitis require anti-*Candida* antifungal treatment. Although very similar in its holistic scope, the comprehensive treatment program for fungal sinusitis or yeast overgrowth and candidiasis is more challenging than the regimen for simple chronic sinusitis (i.e., without a significant degree of *Candida* overgrowth), chiefly because of the restrictive *Candida*-control diet. The treatment program depends on how sick the patient is, which can be reliably determined through the patient's medical history and Dr. Crook's *Candida* Questionnaire and Score Sheet (see Fig. 15-1). If yeast symptoms are confined to the gastrointestinal tract or vagina, the program is shorter and simpler than if the yeast toxins have spread throughout the body and are causing recurrent sinus infections along with inflammation in other parts of the body (e.g., myalgia, arthralgia, mental "fog," or severe fatigue). In the case of systemic inflammation, which is most often the situation in patients with severe chronic sinusitis, curing the condition can take from 6 months to 1 year.

The treatment program for fungal sinusitis consists of four components. I recommend integrating all four of the following components simultaneously for the best possible outcomes:

1. Reduce the overgrowth of *Candida*.
2. Eliminate the fuel for the growth of *Candida* organisms through diet. Starve them!
3. Restore normal bacterial flora in the bowel.
4. Strengthen the immune system.

Reducing the Yeast Overgrowth

Until recently, I relied heavily on the prescription antifungal fluconazole (Diflucan) to kill *Candida*. The dosage I prescribe is 200 mg daily for 6 weeks, followed by 200 mg

every other day for 3 weeks. Although this drug works well, it often results in a *die-off*, or Herxheimer reaction, which usually occurs during the first 2 weeks of treatment and typically lasts for 2 days to 1 week. The medication is so effective in killing yeast that as the organisms die, they release a "flood" of toxins into the bloodstream that can cause fatigue, headaches, congestion, increased mucus drainage, nausea, loose stools, flulike aches and pains, and any other symptom (usually resulting from inflammation) that yeast toxins are known to produce. Distilled water, both drunk and used as an enema, vitamin C, and ibuprofen can all help to relieve these die-off symptoms.

Although for a short time patients may possibly feel worse than they did before they started taking the drug, they may also choose to look at the "regression" resulting from die-off as a confirmation of the diagnosis of *Candida* overgrowth, as well as a hopeful sign that they are eliminating yeast and will be feeling much better very soon. Following die-off, most patients experience a level of health significantly greater than they had before treating the *Candida* overgrowth.

Prescription drugs, however, rarely provide the entire solution. In addition to antifungal supplements and probiotics, patients must also be prepared to adhere strictly to the dietary recommendations.

In 2004, I discovered antifungal supplements, Allimax and Allimed, that are nearly as effective as fluconazole, although not as fast acting as the drug. These supplements have no harmful side effects (antifungal drugs have a minimal risk of liver toxicity), and the die-off reaction is usually less severe. Allimed contains the same 100% pure allicin, called allipure, as Allimax, but each capsule is 450 mg, rather than the 180-mg capsules of Allimax. Allimed is available only through practitioners and is slightly less costly than Allimax, although it is still expensive. Allimed has become my first choice for mild to moderate candidiasis; in patients with severe cases, I use it in conjunction with fluconazole. These supplements also work well in treating sinus infections, as noted earlier, because they are highly effective antibacterial agents.

Other antifungal supplements that I have had success with include the following:

- Candex or Candisol: This supplement contains an enzyme that destroys the cell wall of *Candida* organisms and reduces die-off symptoms. It is especially helpful in patients who have both sinusitis and asthma. Not infrequently, the die-off symptoms worsen asthma and make breathing more difficult. This supplement is well tolerated and is a consistent component of the *Candida* treatment program. Candex is readily available in most health food stores; Candisol, which has a higher strength of the active ingredient, is available only through practitioners.
- Flora-Balance or Latero-Flora: This unique strain of bacteria, *Bacillus laterosporus B.O.D.,* is available in some health food stores as Flora-Balance or through physicians as Latero-Flora. It has been tested extensively and found to be highly effective for gastrointestinal dysfunction, food sensitivities, and candidiasis.
- Grapefruit seed extract: In liquid or capsule form, this supplement is also available in nearly all health food stores.
- CandiBactin-AR (Metagenics, San Clemente, Calif): This supplement is a combination of essential oils from the mint family, especially red thyme oil and oregano oil. Although I have not had much experience with it personally, I do know several practitioners who have had success using it. I am also aware of successful treatment of candidiasis with just oregano oil.

I take an aggressive approach to treating fungal sinusitis and usually use several of the foregoing products in combination (but not all of them together), along with either fluconazole or Allimed.

Numerous products available in health food stores can help to eliminate *Candida.* Most contain caprylic acid, garlic, pau d'arco, plant tannins, grapefruit seed extract, oregano oil, and other herbs that act directly on *Candida* or indirectly by strengthening the immune system. Although most of these products do not work as quickly as the regimen I have recommended here, I have observed that patients find it helpful to *rotate* antifungal supplements and not continue using the same one longer than approximately 2 months.

Eliminating the Fuel for Candida Through Diet

While at the same time strengthening the immune system, diet is the foundation of any antifungal treatment program. Because every individual has a unique body chemistry, no two *Candida*-control diets will be exactly the same. Moreover, every physician who treats candidiasis and fungal sinusitis has somewhat different dietary recommendations. However, most people with yeast overgrowth are far more susceptible to food allergies, and the following basic principles apply to almost anyone who opts for a *Candida*-control, hypoallergenic, and antiinflammatory diet:

- The diet consists primarily of protein and fresh organic vegetables and a limited amount of complex carbohydrates and fat-containing foods, along with a small amount of fresh fruit.
- Sugar and concentrated sweets are always avoided.
- The minimum time frame for maintaining the diet is 3 to 6 months, although the diet can be less restrictive the longer it is followed.
- The best practice is to rotate the acceptable foods and not eat a particular food more than once every 3 or 4 days. This is especially true for grains.
- Changing one's diet can be a challenge. The more involved the patient is in the process—planning, shopping, and cooking—the easier and more rewarding it will be.

For the first 21 days, avoid starch and high-sugar foods, including fruit. Also avoid yeast and mold foods (see later).

Foods to Include at the Onset of the Diet

- Vegetables: should be eaten freely; 50% to 60% of total diet; raw or lightly steamed; organic and clean (wash well); vegetables with high water content and low starch preferable

  - Green leafy: all lettuce, spinach, parsley, cabbage, kale, collard greens, watercress, beet greens, mustard greens, bok choy, sprouts
  - Other low-starch vegetables: celery, zucchini, summer squash, crookneck squash, green beans, broccoli, cauliflower, brussels sprouts, radish, bell pepper (green, red, yellow), asparagus, cucumber, tomato, onion, leek, garlic, kohlrabi
  - Moderately low starch: carrot, beet, rutabaga, turnip, parsnip, eggplant, artichoke, avocado, water chestnuts, peas (green, snow peas), okra
- Protein: emphasis at breakfast and lunch with no less than 60 g per day; antibiotic-free and hormone-free meats; fresh deep-water ocean fish; raw organic seeds and nuts; acceptable proteins: fish, canned fish (salmon and tuna, no more than twice per week), turkey, ground turkey, chicken, lamb, wild game, Cornish hens, eggs (two to four per week), and seeds and nuts (almonds, cashews, pecans, filberts, pine nuts, Brazil nuts, walnuts, pistachios, sunflower seeds, sesame seeds [raw or dry roasted], pumpkin seeds)
- Complex carbohydrates: starchy vegetables, legumes (introduced after the first 21 days), and whole grains; only enough consumed to maintain energy (ideally, one serving a day or less); restriction varied according to food allergy, which can be determined with food rotation
  - Starchy vegetables: new and red potatoes, sweet potatoes, yams, winter squash (acorn, butternut), pumpkin
  - Legumes: lentils, split peas, black-eyed peas, beans (kidney, garbanzo, black, navy, pinto, lima, adzuki)
  - Nongluten grains: brown rice, millet, quinoa, buckwheat, and amaranth, sprouted or cooked, organic and clean; available in bulk at health food stores; grains rotated every 4 days; tasty as breakfast cereals, in salads and soups, and in casseroles and stir-fry; stored away from light and heat in airtight containers; other whole grains (with gluten) that should be eaten in only limited amounts: barley, spelt, wild rice, corn, oats, cornmeal, bulgur, couscous
- Flaxseed oil: 1 to 2 tablespoons daily; used on grains or vegetables or as a salad dressing, *not* heated or used for cooking; kept refrigerated and away from light; other acceptable oils (cold-pressed): extra virgin olive oil, canola, walnut, macadamia nut, used within 6 weeks of opening

Foods to Include After 21 Days

- Fruits: Fruits are introduced into the diet slowly, one serving per day until the patient is sure they do not make symptoms worse. One starts with melons, berries (blueberries, raspberries, huckleberries, blackberries), lemon, and grapefruit (only after the first 21 days of the diet) and then chooses from among most other fresh fruits, all of which are generally sweeter than the first group. These include apple, pear, peach, orange, nectarine, apricot, cherry, and pineapple. Fruit juices should be very diluted, at least 1:1 with water. Freshly squeezed is best. Full-strength fruit juices, canned fruit juices, and all dried fruits are avoided.
- Yeast- and mold-containing foods: These are allowable only if the patient is not allergic. However, I would introduce them very gradually (no more than one particular food every 3 to 4 days) and not before at least 3 weeks into the diet. These foods include the following: fermented dairy products such as yogurt, kefir, buttermilk, low-fat cottage cheese, and sour cream; fermented foods such as tofu, tempeh, miso, and soy sauce; and raw almond butter and raw sesame tahini.

Foods to Avoid

- *Refined sugar and sugar-containing foods:* cakes, cookies, candy, doughnuts, pastries, ice cream, pudding, soft drinks, pies; anything containing sucrose (table sugar), fructose, maltose, lactose, glucose, dextrose, corn sweetener, corn syrup, sorbitol, or mannitol; honey; molasses; maple syrup; date sugar; barley malt; rice syrup; NutraSweet; and saccharine; table salt (often contains sugar; sea salt preferred)
- *To diminish sugar cravings:* chromium picolinate, 200 mcg twice daily; biotin, 500 to 1000 mcg twice daily; and a yeast-free B-vitamin complex, 50 mg twice daily, only if the patient is not already taking a comprehensive multivitamin; craving also eliminated by 4 days without any sugar
- *Milk and dairy products:* all cheeses (unsweetened soy milk and butter allowed, but not in excess)
- Bread and other yeast-raised baked items, including cakes, cookies, and crackers; whole grain cereals; pastas; tortillas; waffles; and muffins
- Beef and pork
- *Mushrooms:* all types
- Rye and wheat (avoided for first 3 weeks)
- Grapes, plums, bananas, dried fruit, canned fruit, and canned vegetables
- Alcoholic beverages
- *Caffeine:* both tea and coffee (herbal tea and green tea allowed)
- White or refined flour products, packaged or processed and refined foods
- Fried foods, fast foods, sausage, and hot dogs
- Vinegar, mustard, ketchup, sauerkraut, olives, and pickles (raw apple cider vinegar allowed)
- Margarine, preservatives (e.g., in frozen vegetables)
- Refined and hydrogenated oils
- Leftovers (can be frozen for later)
- Rice milk (high carbohydrate content)

This diet is meant to be a guide. The responses to it will vary greatly depending on the severity of the candidiasis, food allergies, and the type of medication (if any) the patient is taking to eliminate *Candida.* Most people who closely adhere to it will experience a significant improvement within 1 month. If the diet is followed for 3 to 4 weeks in addition to taking medication or antifungal supplements and the patient

reports no improvement, however, then I would recommend going back to the basic vegetable (low-starch) and protein diet and being highly suspicious of food allergy or leaky gut syndrome. The offending food is often something that is eaten every day and for which the patient has developed a craving. If new foods are reintroduced very gradually, every 3 to 4 days, then the offending food should be easily detected from the symptoms that arise after eating it.

Initially many patients complain, "There's nothing to eat on this diet." Losing 8 to 10 lb during the first month is not unusual. Many different nutritious and tasty choices are available, however, and the weight loss will subside after the first month unless your patient is significantly overweight. A key factor in successfully maintaining the diet lies in finding desirable recipes. *Candida*-control diet cookbooks are relatively easy to locate in most health food stores.

This *Candida*-control, hypoallergenic, and antiinflammatory diet is essentially the same diet I recommend to all my patients with chronic sinusitis, although it need not be quite as restrictive if fungal sinusitis is not a significant factor.

My basic dietary recommendations are to avoid milk and dairy products, sugar, wheat, caffeine, and alcohol,[41–46] as well as to increase intake of fresh organic vegetables and fruits, whole grains, fiber, and protein.

Restoring Normal Bowel Bacterial Flora

The best way to restore normal bacterial flora in the bowel is through the administration of probiotics, specifically containing *Lactobacillus acidophilus* and *Bifidobacterium bifidum* (see Chapter 102, Prescribing Probiotics). Patients should start taking a probiotic supplement at the very beginning of the treatment program for fungal sinusitis. The beneficial bacteria cannot grow back fully until the yeast overgrowth in the bowel has been greatly diminished. The intestinal bacteria can be restored through a multitude of *Lactobacillus acidophilus* and *Bifidobacterium bifidum* products available in health food stores.

Many yogurt products do not contain a high amount of viable organisms by the time they reach the consumer. This is especially true of highly processed yogurt products and those with many additional ingredients. People who are sensitive to dairy products, as well as those with chronic respiratory disease, should not use yogurt as a consistent source of beneficial bacteria because the milk protein may contribute to inflammation of the mucous membrane. Brands of yogurt that have added sweeteners should be avoided.

Strengthening the Immune System

Immune strengthening is a vital aspect of treating *Candida* overgrowth and fungal sinusitis. The three steps described previously can all contribute in varying degrees to a stronger immune system.

Both regular aerobic exercise[47] and, especially, adequate sleep, in addition to the recommendations for strengthening mental, emotional, social, and spiritual health (see later), can have a profound impact on creating a strong immune system. The combined effect of these aspects of the Respiratory Healing Program can potentially have a far greater effect on immune function than can any single supplement or food.

The improvement in chronic sinusitis can become evident within 2 to 3 weeks of beginning the *Candida* treatment program, but a period lasting 3 months to 1 year (the most severe cases can take this long) is usually required to complete the healing process. Practitioners should strongly recommend that patients maintain a healthy diet without reverting back to excess sugar and alcohol or an excess of any food.

Detoxification

In conjunction with treating *Candida* overgrowth (especially because these organisms are releasing massive amounts of toxins as they die), a detoxification process should be initiated (see Chapter 104, Detoxification). Options for detoxification include the following:

Water

Patients are advised to drink lots of water (filtered or distilled), at least half an ounce per pound of body weight.

UltraInflamX-360

The core medical food drink UltraInflamX-360 (Metagenics, San Clemente, Calif) *reduces inflammation and promotes accelerated detoxification.* This highly researched nutraceutical contains patented, proprietary ingredients. Published research is available in the literature,[48–50] and clinical trials originated from the Functional Medicine Research Center in Gig Harbor, Washington. I recommend a 3-month course of UltraInflamX-360, with the following regimen:

- First week: one scoop twice daily
- Second and third weeks: two scoops twice daily
- Following the third week, for 3 days only, no food eaten, and two scoops taken four to five times per day
- Fourth, fifth, and sixth weeks: two scoops twice daily
- Seventh, eighth, and ninth weeks: two scoops once daily
- Tenth, eleventh, and twelfth weeks: one scoop daily

Natural Cellular Defense

Natural Cellular Defense (NCD, Waiora, Boca Raton, Fla) is a detoxifier, alkalinizer, and immune strengthener. It is composed of a mineral (clinoptilolite zeolite), micronized and purified by a patented process, and suspended in sterile water. The supplement is approved by the Food and Drug Administration as generally recognized as safe (GRAS). NCD removes heavy metals, dioxins, and petrochemical and other environmental toxins. As an alkalinizer (raises digestive pH), NCD assists immune function by eliminating many bacteria and viruses in the gastrointestinal tract, as well as *Candida* (they thrive in a more acidic environment).

Colon Hydrotherapy

I recommend *colonic treatments* as a rapid method of removing excess *Candida* from the bowel and mitigating die-off effects. Much more effective than an enema, colon

hydrotherapy is best done on a weekly basis (twice during the first week) for 6 weeks, in conjunction with taking an antifungal drug. The hydrotherapy can help cleanse the bowel of *Candida,* toxins, and dead yeast organisms while assisting the inflamed lining of the bowel to begin the healing process. Colonic treatments can also significantly enhance the detoxification process by stimulating the liver to release toxins (the liver is the primary detoxification organ in the body) while also helping to flush the small bowel with all the water that the body is absorbing through the colon (large bowel). These treatments need to be performed by trained colon hydrotherapists, who are usually found in most cities by calling the office of a naturopath or chiropractor.

Far-Infrared Sauna

Although I have had no experience either personally or with patients who have used a far-infrared (FIR) sauna, numerous reports and references[51–53] on its efficacy for detoxification have been published. Several FIR sauna devices are portable, convenient, and economical and can be used in the privacy of the patient's home.

The primary advantage of the FIR sauna is that a conventional sauna heats the air in the chamber to a very high temperature, which, in turn, heats the body. The FIR sauna works differently. Neither oxygen nor nitrogen molecules in the air can block the FIR wave, thus allowing the FIR wave to penetrate the body to a depth of approximately 2 inches, without hurting the skin by the hot air.

Mind-Body Therapy

Mental and Emotional Health Recommendations

Most sufferers of chronic sinusitis have repeatedly heard the message "You're going to have to live with it" from their physicians, or they have come to this conclusion themselves. This belief often adds to already existing feelings of anger, sadness, fear, and possibly hopelessness. Essential mental and emotional components of the Respiratory Healing Program include the following: modifying beliefs and attitudes through *affirmations* and *visualizations*; creating a *goal list* and an *ideal life vision* (developing clarity about personal and professional objectives); learning to express painful emotions, especially through the *safe release of anger*, *journaling*, and finding more *humor*, *optimism,* and *play* in life.

Physical problems with the nose and sinuses bioenergetically correspond to mental and emotional issues associated with self-evaluation, truth, intellectual abilities, openness to the ideas of others, the ability to learn from experience, emotional intelligence (the ability to identify, experience, and express feelings), and feelings of adequacy. These issues are all associated with the sixth ("third eye") chakra in Ayurvedic medicine. I have found most patients with chronic sinusitis to be high achievers, perfectionists who set very high standards of performance for themselves and who tend to be unforgiving of themselves and others for making mistakes. The repressed anger felt by most sinus sufferers is often self-directed. Assisting the patient to a heightened sense of awareness of these possible contributing factors can help to begin the process of healing.

Mental and Emotional Health Practices

- Affirmations
- Visualizations[54]
- Goal or ideal vision list

These first three items should be practiced daily for 10 to 20 minutes. Affirmations are most effective when written, recited, and visualized.

- Anger release (safely): punching (a punching bag, sofa, or pillow), screaming, or stamping while simultaneously exhaling the "shhhh" sound; highly therapeutic for chronic sinusitis
- Journaling[55]
- Optimism
- Humor
- Biofeedback
- Psychotherapy: cognitive therapy and family therapy
- Play
- Energy medicine modalities: healing touch, Reiki, qi gong, or craniosacral therapy

Spirituality

Spiritual and Social Health Recommendations

Integrative holistic medicine is based on the belief that *unconditional love is life's most powerful healer*. Its corollary, *the perceived loss of love is our greatest health risk*, is also the spiritual cause of chronic sinusitis and all disease. Healing the spirit is by far the most powerfully therapeutic component of the Respiratory Healing Program. Spiritual health is simply learning to love ourselves in body, mind, and spirit. The first step in the Respiratory Healing Program is to love and nurture the sinuses (i.e., to heal the chronically inflamed mucous membrane). To heal the self spiritually involves connecting to a higher power (God, Spirit, or whatever term one is comfortable with) in a personal way and becoming attuned to this energy. By engaging in this spiritual healing process, individuals experience a profound reduction in feelings of fear and a greater capacity for unconditional love of self and of others. They also heighten their sense of soul awareness and are better able to identify special talents and gifts. This awareness helps them to fulfill their life's purpose while fully experiencing the power of the present moment. The spiritual practices I recommend most are *prayer*, *meditation,*[56] *gratitude*, and *spending time in nature*.

Relationship with others is the crucible that most strongly determines the spiritual health of each person. Optimal *social health* consists of a strong positive connection to others in community and family and intimacy with one or more people. It is often much easier to feel a connection with Spirit during moments of solitude than it is to express that connection through interactions with others. At the same time, relationships offer the greatest opportunities for spiritual growth and for learning how to receive and impart unconditional love. *True spiritual health is a balance between the autonomy of the self and intimacy with others.*

On the basis of a growing number of relationship studies, researchers have concluded that social isolation is statistically just as dangerous as smoking, high blood pressure, high cholesterol, obesity, or lack of exercise. Another study has shown that marital conflict can weaken immunity. [57]

The primary opportunities available to each person for improving social health include *forgiveness*, *friendships*, *selfless acts and altruism*, *support groups*,[58] and especially *marriage*, *committed relationships*, and *parenting*. Practicing forgiveness is particularly challenging for and most helpful to the typical patient with chronic sinusitis. Much of the patient's anger, which often precipitates a sinus infection, is ultimately self-directed for making mistakes. In learning to forgive themselves, such patients are able to expand their capacity to forgive others and thereby heighten intimacy in their relationships (see Chapter 97, Forgiveness).

The three primary components of the Respiratory Healing Program for treating, preventing, and curing chronic sinusitis are as follows: stop infection, reduce or eliminate inflammation of the mucous membrane, and strengthen immunity.

Preventive Prescription

- Become more *aware* of the quality and quantity of the air you are breathing, water you are drinking, the food you are eating, the exercise and sleep you are getting, and, most importantly, the stress you are experiencing, especially *anger* with yourself or others.
- Pay more *attention* to how each of the foregoing factors affects the condition of your sinuses.
- Once you have learned what factors contribute most to the way your sinuses feel, then determine which of the recommendations in the earlier Integrative Therapy section are consistently effective in improving the way you feel. The *daily practices* that are most helpful to nearly every sinus sufferer are adequate sleep and water intake, elimination of dairy products and a significant reduction in sugar intake, use of a saline or aloe nasal spray, inhalation of medicinal eucalyptus oil, nasal irrigation (any method), journaling, anger processing, and a spiritual or meditative practice.
- *Repeat* to yourself several times a day:
  - I am always doing the best I can. There are no mistakes, only lessons.
  - Everything is happening at just the right time.
  - I love and approve of myself.
- Remember that you are a unique individual with a different set of needs, desires, beliefs, and gifts than anyone else. As you heighten your level of *self-awareness,* you will be much better able to care for yourself, heal your life, and potentially cure your chronic sinusitis.

Therapeutic Review

Lifestyle

- Sleep: Adequate good-quality sleep can help improve immune function. C1
- Use a negative ion generator as an air cleaner in the bedroom and office. B1
- Saline nasal spray: Use daily every 2 to 3 hours. Saline sprays containing aloe vera and grapefruit seed extract are most helpful. C1
- Steam inhaler: Use this device for 15 to 20 minutes two or three times daily. B1
- Medicinal eucalyptus oil: This can be added to the steam for optimal benefit or inhaled from a tissue. C1
- Nasal irrigation: Use one of several methods for nasal irrigation, although a pulsatile irrigator is most effective. Perform two to three times daily. This modality is best performed following steam inhalation therapy. B1
- Exercise: Engage in regular aerobic exercise three to five times per week for at least 20 to 30 minutes. A1

Nutrition

- Avoid milk and dairy products, sugar, wheat, caffeine, and alcohol. C1
- Increase intake of fresh organic vegetables and fruits, whole grains, fiber, and protein. C1
- Increase water intake (filtered or distilled) to at least ½ oz/lb of body weight. C1
- If candidiasis is suspected (e.g., history of multiple antibiotics), strict adherence to a *Candida*-control diet is recommended. This diet avoids yeast-containing foods such as breads and foods that promote yeast growth such as refined sugars, processed foods, cheeses, peanuts, vinegar, and alcoholic beverages. C1

Supplements

- Vitamin C: 1000 to 2000 mg three times daily A2
- Vitamin D_3: 5000 to 10,000 units daily A2

Continued

- Grape seed extract: 100 to 300 mg daily in the morning on an empty stomach 
- Selenium: 100 to 200 mcg daily 
- Essential fatty acids: 2 tablespoons/day of flaxseed oil and 3 to 4 g docosahexaenoic acid/eicosapentaenoic acid daily 

Botanicals

- Garlic as 100% pure allicin (Allimed or Allimax): 450 mg daily preventively or 900 mg three times per day for treating a sinus infection or fungal sinusitis 
- Echinacea: 2 dropperfuls four to five times per day daily for treating a sinus infection 
- Grapefruit seed extract: 250 mg twice daily for treating a sinus infection or fungal sinusitis 

Pharmaceuticals, Surgery, and *Candida* or Fungal Sinusitis Treatment

- Fluconazole or other antifungal drugs, if the history and symptoms indicate *Candida* or yeast overgrowth and fungal sinusitis 
- *Candida*-control diet 
- Antifungal supplements 
- Probiotics containing *Lactobacillus acidophilus* and *Bifidobacterium bifidus* 
- Surgery (polypectomy), usually indicated for nasal polyps 

Mind-Body Therapy

- Affirmations, visualizations, goals or ideal life vision list, practiced daily for 10 to 20 minutes 
- Anger release (safely) 
- Journaling 
- Biofeedback 
- Psychotherapy 
- Energy medicine modalities: healing touch, Reiki, qi gong, or craniosacral therapy 

Spirituality

- Prayer, meditation 
- Gratitude, intuition, spiritual practices: observing a weekly Sabbath; fasting; practices around earth, air, fire, and water 
- Forgiveness, communication exercises: shared vision, attentive listening 
- Support groups 

KEY WEB RESOURCES

Respiratory Healer Network. www.respiratoryhealer.com.
This Web site, with which I am affiliated, offers on-line respiratory healing training for practitioners.

Sinus Survival. www.sinussurvival.com.
This Web site, with which I am affiliated, provides products and educational resources for patients engaged in implementing the Respiratory Healing Program.

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References are available at expertconsult.com.

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Chapter 16

Viral Upper Respiratory Infection

Bruce Barrett, MD, PhD

Viral infection of the upper respiratory tract causes the common cold, humanity's most frequent illness.[1–4] Acute viral respiratory infections are often categorized as being caused by influenza, the most serious of the viruses, or all others.[5–7] Noninfluenza upper respiratory infection (URI), or common cold, accounts for more than 25 million doctor visits and 40 million lost days of school and work each year in the United States alone.[8] Total annual economic costs are estimated at approximately $40 billion in the United States, thus making noninfluenza URI the seventh most expensive illness.[9] Although colds are often considered a nuisance rather than a major public health threat, even rhinovirus, the least pathogenic of the common cold viruses, causes death among older and immunocompromised patients.[10–12] On average, children experience four to six symptomatic colds per year, along with several asymptomatic infections. Day care attendance is a reported risk factor.[13,14] For adults, the average is two to three symptomatic colds per year and perhaps one or two asymptomatic infections.[15–17] Some people are especially prone to colds; others get them infrequently.[18] We do not really know why. Despite numerous investigations, both biologic and psychosocial determinants of susceptibility are poorly understood.[19–27]

Pathophysiology

As an experienced *illness*, the common cold is characterized by nasal congestion and drainage, sneezing, sore or scratchy throat, cough, and general malaise.[28–30] Cough may or may not be present and tends to occur later in the disease. The cough sometimes lasts for weeks after other symptoms have resolved. The severity of symptoms varies markedly, from barely noticeable to truly debilitating.[31] Although true fever is not typical, feelings of feverishness and chilliness are common.[32]

As an infectious *disease*, viral URI is characterized by replication of viruses in oral, nasal, and upper respiratory epithelium,[33] as well as by activation of local and systemic immune responses.[34–36] Viral replication within epithelial cells triggers cytokine-mediated local inflammatory reactions and recruitment of white blood cells. Parasympathetic neural pathways activate and coordinate local responses. Blood vessels dilate and capillaries leak, causing edematous tissue swelling in the nasal passages.[37] Mucous glands are activated, leading to copious discharge in some people. Inflammatory changes in the respiratory epithelium persist for days or weeks after viral shedding subsides. Nevertheless, viruses are sometimes cultured from occasional hosts weeks after the initial infection. Activation of inflammatory mechanisms leading to bronchial constriction makes viral URI the most frequent cause of asthma exacerbation.[38]

Rhinovirus is the single most common etiologic agent, but it accounts for less than half of all URIs.[39–41] Other viruses include adenovirus, coronavirus, enterovirus, influenza virus, parainfluenza virus, and respiratory syncytial virus.[4,42] Metapneumovirus,[43,44] and then bocavirus,[45–47] were more recently discovered. Others as yet undiscovered may exist, given that even the best research laboratories fail to identify an etiologic agent in up to one fourth of people with obvious colds. A few bacteria, such as *Streptococcus* and *Haemophilus influenzae,* may cause illnesses with symptoms similar to those of the common cold.

Respiratory viruses follow seasonal patterns. Influenza and respiratory syncytial virus infection occur only during the winter months. Rhinovirus URIs tend to occur in the fall and spring. Adenovirus appears year round. Parainfluenza miniepidemics are episodic. Outbreaks of atypical agents, such as the pertussis bacteria *(Bordetella pertussis),* may further complicate the picture.

Integrative Therapy

No effective cure exists for the common cold. Even the best positive trials report only modest symptomatic benefit and little or no duration benefit.

Exercise

Although moderate regular exercise protects against infection, excess activity such as running a marathon increases the risk of infection temporarily.[48–50]

Nutrition

Chicken Soup

Hot chicken soup is the epitome of traditional cold remedies and could no doubt be supported by many personal testimonies. Chicken soup as a cold remedy is also somewhat supported by at least two human studies, one reporting inhibited neutrophil chemotaxis[51] and the other suggesting increased nasal mucus velocity and decreased nasal airflow resistance.[52] No randomized controlled trials (RCTs) using patient-oriented outcomes are available. Use of soup made from free-range chickens and substantial quantities of wholesome organic vegetables can be cautiously supported.

Hot Toddy

I have been impressed by the number of people, including several physicians, who have come up after a lecture to tell me that their favorite cold remedy was some form of hot alcoholic beverage, such as a "hot toddy" or hot buttered rum. Although to my knowledge no trials have tested any of these remedies, testimonies of symptomatic benefit should not be totally disregarded. At a societal level, the inverse relationship between moderate regular consumption of alcoholic beverages and the number and severity of colds is well known.[22] Those who consume one or two drinks daily have fewer and less severe colds than both those who drink heavily and those who drink not at all. One study found this relationship to be most pronounced for red wine.[53] Personally, I like to add a bit of rum to a cup of hot orange juice as a nighttime cold remedy. However, this would be contraindicated in patients with alcohol use disorders, in children, in pregnant women, and in anyone needing to use a motor vehicle or operate hazardous machinery.

Healthful exercise, nutritious diet, positive attitude, and healthy relationships are important.

Botanicals

Plants have long been used for medicinal purposes.[54–57] Those used for upper respiratory tract infections are discussed here.

Andrographis: Andrographis paniculata *(also Known as* Justicia paniculata*)*

Andrographis is indigenous to Asia, with traditional use most prominent in India. Of 28 *Andrographis* species, *Andrographis paniculata* is most commonly used. According to Ayurvedic tradition, andrographis is attributed many important medicinal properties, including use for constipation, digestion, fever, pain, sore throat, and snake bite, as well as to clean the blood. In the West, andrographis is most commonly used as common cold treatment or preventive.

Various laboratories have reported antimicrobial,[58] antihyperglyemic,[59,60] antiinflammatory,[61] immunomodulatory,[62,63] and psychopharmacologic[64] effects attributable to andrographolide, flavonoids,[65] and other phytochemical constituents. At least 8 RCTs have been conducted, with more than 1000 subjects, to test various andrographis derivatives in URIs, including pharyngitis.[66–73] Systematic reviews by Coon and Ernst[74] and Poolsup et al[75] concluded the following:

> Collectively, the data suggest that *A. paniculata* is superior to placebo in alleviating the subjective symptoms of uncomplicated upper respiratory tract infection. There is also preliminary evidence of a preventative effect. *A. paniculata* may be a safe and efficacious treatment for the relief of symptoms of uncomplicated upper respiratory tract infection; more research is warranted.[74]

> Current evidence suggests that *A. paniculata* extract alone or in combination with *A. senticosus* extract may be more effective than placebo and may be an appropriate alternative treatment of uncomplicated acute upper respiratory tract infection.[75]

The most recent trial was not included in those reviews, but it also reported positive results.[76] Based on published evidence, and with no indications of serious safety concerns, for adults seeking relief from URI symptoms to try andrographis-based cold remedies seems reasonable. Evidence is not sufficient to favor one product over another, any specific dosing regimen, or any particular standardization procedure for phytochemical content. For pregnant women and children, it seems prudent to recommend against use because of the paucity of data from these populations and because of the possible risk of harm.

Dosage and Standardization

Most clinical trials used products standardized to 4% andrographolide. One reasonable dose regimen would be a 300-mg tablet, four times daily, for the first few days of a cold.

Precautions

This herb is generally well tolerated. It can, however, cause gastrointestinal distress, urticaria, fatigue, and headache. In high doses, it may cause transient elevation of liver enzymes.

Several trials support the use of *Andrographis*. This is one to watch.

Astragalus: Astragalus membranaceus; Astragalus mongholicus

Astragalus is an important medicinal plant in traditional Chinese medicine.[77] Although dozens, if not hundreds, of reported uses are recognized, astragalus extracts are commonly used for both treatment and prevention of the

common cold.[78] Even though some antiviral activity has been reported, immunomodulation is the purported mechanism of action. Indeed, several studies have reported immunoactivity from astragalus, from enhanced immunoglobulin production to restoration of lost T-cell activity.[79–83] Astragalus root contains astragaloside, flavonoids, and saponins, which are thought to be involved in various hypothesized mechanisms of action. Unfortunately, because no human URI trials have been conducted, no clear recommendations can be made for or against use for treatment or prevention of common cold.

Dosage

The dose is 4 to 7 g (up to a maximum of 28 g) daily.

Precautions

Astragalus is generally well tolerated. Immune suppression can occur with doses greater than 28 g daily.

Chamomile: Matricaria chamomilla; Matricaria recutita *(German chamomile);* Chamaemelum nobile *(Roman chamomile)*

Chamomile has been used widely as botanical remedy for centuries for a variety of purposes, including dysmenorrhea, gingivitis, hemorrhoids, infantile colic, indigestion, insomnia, nausea, and vaginitis, as well as topically for numerous skin conditions.[84] In the United States, chamomile is most often used as calmative or sedative and for irritable bowel syndrome. However, chamomile is also used for acute respiratory infection, hence it merits inclusion in this discussion. As a remedy for the common cold, chamomile can be taken as herbal tea (i.e., chamomile tea), or the flowering tops can be boiled and the vapors inhaled. One trial testing inhaled vapors from boiling chamomile reported benefit, but the study was of insufficient quality to make firm conclusions.[85]

Dosage

Although this practice has no good supporting evidence, a cup or two of chamomile tea as supportive treatment for the common cold is certainly safe, and it may be beneficial.

Precautions

Even though no dose-dependent adverse reactions to chamomile are known, allergic sensitivities, including several cases of anaphylaxis, have been reported.[86]

Echinacea: Echinacea angustifolia; Echinacea purpurea; Echinacea pallida

All dozen species from the genus *Echinacea* are indigenous to North America. Native peoples discovered dozens of medicinal uses for this plant and later transferred their knowledge to European settlers.[87] In the 1920s, echinacea was introduced into Germany, where it has been popular ever since. Today, in North America, Europe, and elsewhere, echinacea extracts are widely used, especially for prevention and treatment of the common cold.[88] A considerable body of research exists regarding these uses, including 20 randomized trials with more than 3000 participants, as well as dozens of in vitro and animal studies.[89–91] Although some consensus exists that echinacea extracts display immunologic activities such as macrophage activation and cytokine expression,[92–99] investigators disagree about which of many echinacea-derived phytochemicals are involved. Various alkylamides, glycoproteins, polysaccharides and caffeic, cichoric, and caftaric acids are all implicated. Differing extracts from all three species and from various plant parts have shown immunoactivity in laboratory models. No head-to-head, dose-finding, or viral load outcome studies have been reported.

Double-blind RCTs testing echinacea extracts for prevention and treatment of the common cold were initially positive, and several European trials reported positive results.[100–107] More recent trials, including several in North America, reported mixed results, with the higher-quality trials finding no benefit.[108–112] I myself have directed two trials. Results of the first were flatly negative,[113] but results of the second trended in positive directions.[114] A trial using *Echinacea angustifolia* extracts in an induced cold rhinovirus inoculation study found little or no effect.[115] However, when all three rhinovirus inoculation studies are considered together, the results look more favorable.[116] In general, systematic reviews tend to be positive.[117–123] One negative review argued that the positive trial results could have reflected inadvertent unblinding with either placebo effect or participant reporting bias that contributed to false-positive results.[124] The possibility also exists that studies with negative results went unreported. A comprehensive safety review noted some reported allergic reactions but suggested no dose-dependent adverse effects or major drug interaction concerns.[125]

Given that echinacea extracts appear safe and that most published trial results remain positive, cautious support of echinacea use for adults, especially those with favorable personal experiences and positive expectations, seems reasonable. My opinion is that echinacea use in children should be discouraged because the only pediatric RCT found no positive effects but did report a slight increase in rash among patients randomized to echinacea.[126] Although a modest case control study found no adverse effects in pregnancy,[127] I caution against this use because the theoretical risks are substantive.

Dosage and Standardization

Trials with positive results have used differing formulations, with preparations made from leaf and flower of *Echinacea purpurea* used most widely. However, preliminary evidence suggests that alkylamides from roots of *E. purpurea* and *E. angustifolia* may have the best bioavailability and immunoactivity.[128–130] Although no consensus on standardization criteria exists, most experts do agree that echinacea extracts should be used as early as possible in the course of a cold, with multiple doses per day for the first few days of symptoms.

> Actually, more evidence is available on echinacea and vitamin C than on any single conventional therapy. Unfortunately, for every positive trial result, a negative one has been reported.

Elderberry: Sambucus nigra

Preliminary research suggested that elderberry extracts may have antiinflammatory and antiviral antiinfluenza properties.[131,132] One Norwegian RCT of 60 volunteers suggested a potential symptom reduction benefit in influenza-like

illness.[133] With only one small limited trial and no good safety data, elderberry extract is probably not ready for widespread use.

Dosage
Elderberry fluid extract, 15 mL (1 tablespoon) four times daily, or elderberry extract lozenges (175 mg four times daily), should be taken within the first 48 hours of symptoms.

Garlic: Allium sativum
Garlic is very widely used as a food and flavoring. Medicinally, garlic has dozens, if not hundreds, of reported uses. The most prominent of these is moderation of cholesterol and other lipids, for which modest beneficial activity has been reasonably established.[134–136] Use for prevention or treatment of the common cold is fairly widespread but less well researched.

Although in vitro studies have reported antibacterial and antiviral effects, only one relevant human trial has been conducted. Josling[137] reported a trial in which 146 participants were randomized to daily garlic or placebo capsule for 12 weeks. Dramatic between-group differences were observed, with 65 colds in the placebo group and 24 in the garlic group ($P < .001$). The average cold duration was 5.0 days among those taking placebo compared with 1.5 days among those taking garlic ($P < .05$). Although the study was reported as a double-blind trial, proof of blinding was not provided. The active treatment was "an allicin-containing garlic supplement" dosed at "one capsule daily." No further information on extraction methods, phytochemical composition, or amount of garlic was provided. Nevertheless, tentative support of garlic use may be reasonable because the risk of side effects is low, cardiovascular benefits are likely, and garlic is tasty.

Dosage
Fresh garlic should be used in cooking as much and as often as palatable while keeping in mind positive expectations about cardiovascular and cold prevention benefits.

Ginseng: Panax ginseng, Panax quinquefolium
Asian (*Panax ginseng*) and American (*Panax quinquefolium*) ginseng are used for many different purposes. The genus name *Panax* chosen by Linnaeus, in fact, derives from the same root word as Panacea, the Greek goddess of healing. The most widespread medical theory supporting the use of ginseng derives from traditional Chinese medicine.[138] Ginseng is thought to have "adaptogenic" attributes, which bring balance, homeostasis, and healing.[139–141] Evidence for effectiveness of a *P. ginseng* extract in preventing the common cold comes from an Italian trial of 227 people followed for 12 weeks.[142] A series of Canadian studies of a polysaccharide-rich *P. quinquefolium* extract reported immunomodulatory changes.[143,144] An RCT of 198 older nursing home residents reported reductions in both cold and flu episodes.[145] A second preventive trial using the same formulation among 323 subjects reported a statistically significant 13% difference in incidence in cold and flu episodes during 4 months of observation.[146] The proprietary formula used in this series of research has been approved for use in Canada. In the United States, for prevention-minded people to use small doses of ginseng extracts regularly during cold and flu season seems reasonable, but because evidence is preliminary and safety has not been established, use of ginseng in pregnancy and in children is not advised.

Dosage
For prevention during times of high risk, take 100 mg daily. For acute infection, consider 100 mg twice daily for 9 days.

Precautions
Ginseng is generally well tolerated. The most common side effect is insomnia. It can also cause tachycardia, palpitations, and hypertension.

Goldenseal: Hydrastis canadensis
Goldenseal is among the top-selling botanicals in the United States. In addition to cold remedies, *Hydrastis* extracts are found in treatments for allergy and in digestive aids, feminine cleansing products, mouthwash, shampoo, skin lotion, and laxatives.[84] Goldenseal accompanies echinacea in many cold therapies. However, currently no RCTs have evaluated goldenseal either alone or in combination with echinacea. The phytochemical constituent berberine is pharmacologically active and in overdose can cause significant toxicity, including cardiac arrhythmia and death.[147] Goldenseal is contraindicated in pregnancy and lactation. Berberine-rich extracts are included in many traditional Chinese medications. The demand for goldenseal has led to overharvesting and to the substitution of other plants containing berberine or similar compounds. Given these considerations, I do not recommend goldenseal to prevent or treat the common cold.

Peppermint: Mentha piperita
Peppermint and other members of the mint family are widely used for various medicinal purposes, including coughs and colds, as well as for several gastrointestinal purposes. For treating colds, mint teas and infusions are taken internally; mint oils are applied topically. Peppermint oil is composed primarily of menthol, menthone, and menthyl acetate. Menthol especially has been extracted and included in various topical cold remedies classified as "menthol rubs." Although neither mint teas nor menthol rubs have been subjected to rigorous RCTs for the common cold, both applications seem reasonable from the perspectives of cost, risk, and potential benefit, at least for adults. More concentrated preparations such as peppermint oil should not be applied to the mucosa of infants or young children because direct inflammatory toxicity can result. Bronchospasm, tongue swelling, and even respiratory arrest have been rarely reported.[147,148]

Umckaloabo: Pelargonium sidoides
Various preparations of the South African umckaloabo plant have been used for centuries, following ethnobotanical tradition.[149–151] Three RCTs in adults ($N = 746$) and three RCTs in children ($N = 819$) yielded inconsistent yet generally positive findings.[152–154] Although no dose-dependent adverse effects are known, one published report suggested that allergic reactions may be a relatively frequent problem.[155] Scientific interest in *Pelargonium* is relatively recent, and conclusions to date are tentative, yet this seems a reasonable choice for adults looking for a natural treatment for cough, cold, or bronchitis.

Dosage
EPs 7630 is an 11% aqueous ethanolic extract in which 100 g of finished product corresponds to 8 g of extracted plant material. This was the formulation used in the clinical trials,

but it may be difficult to find in the United States. The following dosage was used in clinical trials (although I do not support the use of this product in children):

Children younger than 6 years old: 10 drops three times daily
Children 6 to 12 years old: 20 drops three times daily
Those older than 12 years: 30 drops three times daily

A 1× homeopathic formulation is produced by Nature's Way (Lehi, Utah) called *Umcka ColdCare*. The dose is 1 mL of the tincture three to five times a day for those older than 12 years.

Precautions

Umckaloabo appears to be safe.

Nutritional Supplements

Vitamin C: Ascorbic acid

The use of vitamin C for prevention and treatment of the common cold became widespread after twice Nobel laureate Linus Pauling promoted his belief in this therapy in the 1950s and 1960s.[156] By the early 1970s, three major trials conducted in Toronto by T.W. Anderson et al[157–159] supported some preventive effectiveness. Over the next few decades, more than 30 trials including more than 12,000 participants were reported.[160] Approximately half of these trials reported positive results, far more than would be expected by chance, but not enough to convince the more skeptical scientists. Although no clear consensus exists to explain why some trials found benefit and others did not, tentatively concluding some preventive effectiveness seems reasonable, as noted by a Cochrane Systematic Review: "The consistent and statistically significant small benefits on duration and severity for those using regular vitamin C prophylaxis indicates that vitamin C plays some role in respiratory defense mechanisms."[161]

Dosage

The evidence supports modest preventive effectiveness for doses of 200 to 500 mg daily. Benefits of larger doses for prevention—or for treatment of new-onset colds—are supported by some trials and systematic reviews,[162] but not by others.[163] Given the generally accepted safety of ascorbic acid at doses up to several grams per day over short periods, cautious support of its use seems reasonable, especially among those with positive experiences and expectations. (Very high doses, such as the 10 g per day that Linus Pauling was reportedly taking up to his death at age 93 in 1994, have not been tested in trials and hence cannot be supported.) Regular intake of vitamin C–rich foods and juices can be enthusiastically supported because greater intake of fresh fruits and vegetables has no known risks and has been associated with many health benefits in dozens of large observational studies.

Precautions

Large doses of vitamin C can cause diarrhea, gastrointestinal distress, nausea, and heartburn.

Zinc

In some ways, the story of zinc for colds is similar to that of vitamin C. Reportedly, the physician George Eby noticed the rapid recovery from URI in a child hospitalized and given zinc for unrelated reasons. This observation was followed by an RCT in 1984 that reported positive results (but had several methodologic flaws).[164] Since then, at least 10 trials with more than 1000 participants have been conducted using various zinc preparations.[165–169] As with vitamin C, only approximately half the studies had positive results, without clear indications of the reason for this disparity. Because most zinc preparations have a distinctive taste, adequate blinding may be an issue, as more skeptical experts have argued.[168,170]

Some concerns also exist over adverse effects, such as unpleasant taste and nausea. Although zinc is an essential mineral, with many known protective effects when it is ingested in foods in appropriate doses,[171,172] the use of relatively high doses during acute illness may or may not carry some risks. Advocates recommend frequent dosing (every 2 to 3 hours) for the first 2 or 3 days of a cold, a dosing regimen that some patients will not find convenient. More recently, nasal zinc preparations have been devised, and three out of four RCTs reported benefits.[170,173–175] Issues of specific preparation, dosing, and blinding complicate interpretation of study results. Nasal irritation is common, and loss of sense of smell has been reported.[176] Large, well-designed trials are needed before the benefits of oral or intranasal zinc for the common cold can be said to be proven. My personal recommendation is to support the use of oral or zinc preparations tentatively among those who have experienced benefit or express positive feelings about the treatment, but not to recommend the use of these preparations in children, in women, or in men who have not yet tried it.[177] The U.S. Food and Drug Administration (FDA) has collected more than 100 reports of loss of sense of smell for people using nasal zinc. Zicam has been withdrawn from the market. I recommend that nasal zinc not be used.

Dosage

Zinc gluconate, 9 to 24 mg of elemental zinc, is taken every 2 hours while symptomatic.

Precautions

Zinc can inhibit the absorption of other minerals (copper), and nasal formulations have been associated with loss of smell.

> Of a dozen trials of zinc, half the results are positive and half are negative.

Probiotics

Probiotics are live bacteria that are thought to support healthy gastrointestinal function. Several trials demonstrated benefit for antibiotic-associated diarrhea,[178] and others suggested benefit for irritable bowel syndrome and a few other conditions.[179–183] Reasonably strong preliminary evidence indicates that probiotics may also prevent or ameliorate URI illness. This evidence comes from several trials testing efficacy for preventing cold and flu illness episodes.[184–190] One RCT was of older persons,[187] and two involved children.[186,189] One of these studies was aimed at preventing diarrhea illness, but instead it provided some evidence of cold and flu prevention.[189]

Dosage

In children, prevention of URI was found with a milk product containing *Lactobacillus rhamnosus* and *Lactobacillus* GG (in one study) and *Lactobacillus acidophilus* and *Bifidobacterium animalis* (in another). The dose is 5 to 10 billion colony-forming units (CFUs) twice daily.

Precautions

Probiotics should be avoided in persons who have compromised immunity.

Nasal Irrigation and Humidification

Nasal Saline

What could be more healthful and therapeutic than a mild saltwater rinse of the nasal cavities? Although saline nasal lavage is a long-standing tradition in many cultures, only fairly recently has Western biomedicine begun to integrate this practice. Several trials with positive results were conducted in people with allergic rhinitis and chronic sinus symptoms, including one trial at the University of Wisconsin Department of Family Medicine in Madison, Wisconsin.[191]

To my knowledge only two RCTs of nasal saline in people with the common cold have been conducted. Adam et al[192] randomized 140 people to 1 of 3 groups: hypertonic saline, normal tonic saline, or no treatment (two squirts per nostril, three times per day.) No significant differences among the groups were found in terms of duration or severity of symptoms. Diamond et al[193] reported a trial in which 955 participants were randomized to 1 of 3 doses of nasal ipratropium, to the "placebo" saline vehicle, or to no treatment at all. The nasal saline vehicle yielded greater benefit compared with no treatment than did any of the ipratropium doses when compared with each other or with saline.

Dosage

I suggest a mild salt water solution made with warm tap water and just enough salt to make it taste like tears (a half teaspoon of salt in 6 oz of warm water). To instill the solution, the head and neck should be nearly horizontal, with one ear down, and the nose should be positioned over a sink or basin. Using a neti pot (small tea pot) or a bulb syringe, gently pour the saline into the higher nostril. The soothing, cleaning fluids will run through the nasal cavity, coming to the other nostril and to the throat. Spit out any fluids from the mouth, and gently blow the nose with a handkerchief or tissue. Repeat the process with the other ear down. I suggest treatment twice daily for the first few days of a cold (see Chapter 109, Sinus Irrigation).

Hot Moist Air

One widespread traditional cold remedy involves the inhalation of hot moist air, often with a botanical or other additive. As noted earlier, the benefits of inhalation of vapors from chamomile tea were reported in one clinical trial.[85] At least two RCTs suggested significant benefit of nasal inhalation of unadulterated hot moist air.[194,195] However, two subsequent trials found no benefit.[196,197] Although recommending humidification when the air is dry and perhaps advocating the inhalation of hot moist air for those who find it comforting seem reasonable, water boils at 100 °C, and inhalation of vapors near this temperature may cause significant thermal damage. Be careful.

Dosage

Some patients find it beneficial to add a handful of chamomile flowers or 5 to 10 drops of eucalyptus essential oil to the water. Place the head under a towel, and inhale the steaming vapors for 10 to 15 minutes. Repeat as needed.

Mind-Body Therapy

Placebo, Meaning, and Mind-Body Effects

Since 2000, I have read the reports of hundreds of trials and dozens of systematic reviews of common cold research and have become increasingly convinced of the importance of mind-body effects, otherwise described as placebo or meaning effects.[198–202] Positive thinking, suggestion, expectancy, and belief in the therapeutic value of a given remedy can be powerful healing forces. Although regular exercise, balanced nutrition, and tobacco cessation are clearly associated with fewer and less severe illness episodes, so too are positive mental health attributes such as a favorable psychological profile and healthful social relationships. Psychological predispositions, especially sociability and a positive emotional style, are predictive of both symptomatic and physiologic outcomes. For the integrative clinician, this means that understanding an individual's belief system may be a crucial part of the therapeutic encounter. If a patient already believes in a safe therapy, reinforcing that belief may enhance the therapeutic response. If a patient is wary of a remedy mentioned, do not press the issue. Remember that reassurance, empathy, empowerment, and positive prognosis can all be usefully employed in the clinical encounter.

> Belief in a therapy—positive expectation—should usually be supported rather than discounted.

Psychosocial Influences

As in virtually all illness, the common cold involves both psychological and physiologic elements and is influenced by social factors. Stress, both acute and chronic, increases risk. In a series of groundbreaking studies, Cohen et al showed that certain psychosocial variables predicted whether volunteers would become infected when they were exposed to rhinovirus. Childhood socioeconomic status,[203] number and quality of social relationships,[204] acute and chronic stress,[205–207] and negative emotion[208,209] measured before rhinovirus inoculation all predicted subsequent infection and viral shedding, as well as severity and duration of cold symptoms. Work by other investigators confirmed these findings.[210–215] Together, these observations suggest that maintenance of psychological and social health (positive attitude, healthy relationships) may be as important as maintenance of physical health (exercise, nutrition, hand washing, smoke avoidance) for preventing colds and moderating symptoms.

Conventional Therapies

Antihistamines

Drugs blocking the effects of histamine have been sold as cold remedies for more than a century, but they have been subjected to less in terms of rigorous RCT research than alternatives such as vitamin C, zinc, and echinacea. Nevertheless, some reasonable evidence indicates modest benefit, in terms of reduction of nasal drainage, for first-generation antihistamines such as diphenhydramine, clemastine fumarate, or chlorpheniramine.[216–219] These effects appear to result more from anticholinergic mechanisms than from antihistamine effects, however, and second-generation "nonsedating"

antihistamines do not seem to provide benefit.[220] For adults who do not mind the potential sedating or membrane-drying effects, or for patients with an allergic response, a first-generation antihistamine may be a reasonable choice. For children, in whom no positive evidence of benefit in colds exists whatsoever, antihistamines should be reserved for allergic rather than infectious rhinitis.

Decongestants

The oral decongestant pseudoephedrine was tested in several clinical trials and appears to have minor benefit in terms of reduction of nasal congestion and drainage.[221–224] Side effects including anxiety, dizziness, insomnia, and palpitations are fairly common. More worrisome is the potential for elevated blood pressure and cardiac arrhythmia. Phenylpropanolamine, for decades a popular over-the-counter decongestant, was taken off the market after studies suggested increased mortality, especially in older persons.[225]

The topical intranasal decongestant oxymetazoline was shown to decrease nasal airway resistance, as well as mucus production and drainage.[226–229] Intranasal phenylephrine has been less extensively studied but likely has similar effects. Unfortunately, these proven benefits come at the risk of nasal membrane dryness, discomfort, or nosebleed. These drugs should be used for no more than 4 days because rebound nasal congestion can occur.

Conventional treatments such as antihistamines, decongestants, and cough remedies may help slightly with some symptoms, but they do tend to have side effects.

Cough Suppressants

Dextromethorphan, the active ingredient in cough remedies designated with "DM," is widely used as an over-the-counter cough suppressant. Codeine and, to a lesser extent, hydrocodone are prescribed for cough. Presumably, these drugs work through similar opioid-mediated mechanisms and as such have side effects including sedation, constipation, and, potentially, respiratory suppression. Although most patients and clinicians agree that these remedies work, considerable debate exists over effect size and mechanism of action, given that little appropriate evidence is available.[230–232] The best systematic review of cough remedies for children and adults concludes: "There is no good evidence for or against the effectiveness of OTC medicines in acute cough."[233] Benzonatate (Tessalon Perles) is licensed as a prescription antitussive, but it appears to have been given this indication without any good evidence.

Analgesics and Antipyretics

There is little doubt that acetaminophen and nonsteroidal antiinflammatory drugs (NSAIDs) such as aspirin, ibuprofen, and naproxen are effective for pain and fever, which may accompany common cold. However, some suggestion also exists that viral shedding may be prolonged.[234,235] Although the limited use of NSAIDs for pain reduction is eminently reasonable, the widespread use of NSAIDs for general common cold symptoms is not justified. Evidence of benefit is marginal, and many thousands of people die each year from NSAID-attributable gastrointestinal hemorrhage and congestive heart failure.[236–238]

Anticholinergics

Ipratropium nasal spray was tested in several high-quality RCTs for amelioration of symptoms of infectious and allergic rhinitis.[239,240] These trials, including a dose-response trial of 955 patients with community-acquired common cold,[193] suggested a definite benefit in terms of reduced nasal congestion and drainage. Common side effects of these drugs include headache, uncomfortable nasal dryness, and nosebleed.

Combination Formulas

The multibillion dollar market in cold remedies is dominated by numerous products containing combination formulas. Loopholes in FDA regulations have allowed pharmaceutical companies to mix various decongestants, antihistamines, analgesics, and antitussives and then market them under a variety of brand names with exaggerated or false claims. Although some evidence of effectiveness from early trials exists for combining a decongestant with an antihistamine,[216] few, if any, of the currently marketed products have been tested in large, well-controlled RCTs. Personally, I recommend against using any combination cold formula, with a possible exception for patients who are convinced that a specific formula works for them. Perhaps most importantly, clinicians and parents should be made aware that no cold formula has ever been proved to work in children. For pain, acetaminophen (paracetamol) may be justified, but in my opinion, virtually nothing else is.

Prevention Prescription

- Eat a nutritious diet with foods rich in vitamin C (fruits and vegetables) and zinc (meat, nuts, cereals, seafood, and pumpkin seeds).
- Do not smoke.
- Maintain regular exercise and movement, and be careful not to overstrain.
- Maintain supportive social relationships.
- Reduce exposure to people with colds.
- Reduce stressors, and foster positive emotions.
- Wash your hands frequently.
- Obtain an annual influenza vaccine.
- Vitamin C (200 to 500 mg daily), *Panax ginseng* (100 mg daily), and probiotics have some effectiveness for the prevention of colds and flu.

Therapeutic Review

The therapeutic options for the common cold are summarized here. None of these options are proved beyond reasonable doubt to be safe and effective. Nevertheless, they are all reasonable given the best current evidence of benefit and harm.

Botanicals

- Andrographis: 300 mg four times daily as soon as symptoms appear and continued for 3 to 4 days B1
- Echinacea: No one formulation appears to work better than another. Consider one of the following three to four times daily for the first 3 to 4 days of a cold:
  - 1 to 2 mL of extract in juice or water sublingually
  - 150 to 300 mg powdered extract
  - 1 to 5 mL of tincture (1:5 in ethanol) B1
- *Pelargonium*/umckaloabo: EPs 7630 is an 11% aqueous ethanolic extract in which 100 g of finished product corresponds to 8 g of extracted plant material. This was the formulation used in the clinical trials but may be difficult to find in the United States. Dosage used in clinical trials:
  - Those older than 12 years old: 30 drops three times daily
  - A 1 × homeopathic formulation is produced by Nature's Way called *Umcka ColdCare*. The dose is 1 mL of the tincture three to five times a day for those older than 12 years. B1

Nutritional Supplements

- Vitamin C: 500 to 1000 mg three times daily for the first 3 to 4 days of symptoms B1
- Zinc gluconate or acetate: 23-mg tablets every 2 hours while awake B2

Pharmaceuticals

- First-generation (sedating) antihistamines may decrease nasal congestion, but they may cause drowsiness.
  - Diphenhydramine: 25 to 50 mg every 6 hours
  - Clemastine: 1 to 2 mg two to three times daily as needed
  - Chlorpheniramine: 4 mg every 6 hours B2
- Intranasal decongestants appear to be effective in decreasing nasal congestion and drainage, but quite often they cause nasal dryness, irritation, or nosebleed, and, rarely, insomnia, palpitations, or elevated blood pressure. B2
  - Intranasal ipratropium appears to be effective in decreasing nasal congestion and drainage, but it may cause headache, nasal irritation, or nosebleed.
  - Nasal ipratropium 0.03%: two sprays in each nostril two to three times daily. It is also effective for nasal congestion. B2

Biomechanical Therapy

- Hot moist air: Consider adding 5 to 10 drops of eucalyptus oil or chamomile tea to the water, and inhale deeply for 10 to 15 minutes. C1

Nasal Irrigation

- Consider twice daily nasal irrigation with normal or hypertonic saline with a bulb syringe, nasal spray, or neti pot (see Chapter 109, Sinus Irrigation). C1
- Astragalus, chamomile, garlic, ginseng, peppermint, and chicken soup are all unproven but probably safe, supportive therapies. C1

KEY WEB RESOURCES	
Department of Family Medicine, University of Wisconsin School of Medicine and Public Health. http://www.fammed.wisc.edu/research/past-projects/nasal-irrigation	Instructions on nasal irrigation available in English and Spanish
Integrative Medicine, Department of Family Medicine, University of Wisconsin School of Medicine and Public Health. http://www.fammed.wisc.edu/sites/default/files//webfm-uploads/documents/outreach/im/ss_andrographis.pdf	Monograph on *Andrographis*
Integrative Medicine, Department of Family Medicine, University of Wisconsin School of Medicine and Public Health. http://www.fammed.wisc.edu/sites/default/files//webfm-uploads/documents/outreach/im/ss_pelargonium.pdf	Monograph on *Pelargonium*
National Center for Complementary and Alternative Medicine, National Institutes of Health: http://nccam.nih.gov/news/newsletter/2010_february/coldnflu1.htm	Clinical information on the common cold

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References are available at expertconsult.com.

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Chapter 17

HIV Disease and AIDS

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Pathophysiology

Acquired immunodeficiency syndrome (AIDS) is a potentially life-threatening disease caused by the human immunodeficiency virus (HIV). HIV infection in humans, considered pandemic by the World Health Organization (WHO), affects approximately 0.6% of the world's population. The virus, which is transmitted by sexual contact and contact with blood and certain other body fluids, attacks a class of T lymphocytes called $CD4^+$ cells, macrophages, and dendritic cells and results in severe declines in both number and effective function of this arm of the immune system. The result is a dramatically weakened immune system with a host at risk for life-threatening opportunistic infections, including *Pneumocystis carinii* pneumonia (PCP), *Mycobacterium avium-intracellulare* sepsis, and cerebral toxoplasmosis, and Kaposi's sarcoma. Before the advent of effective antiretroviral medications, AIDS was a fairly progressive and almost universally fatal condition.

Currently, no vaccine or cure for HIV is publicly available. Since 1996, AIDS has been transformed into a serious but manageable chronic illness by the widespread use of antiretroviral medications (highly active antiretroviral therapy [HAART]). Many of the current challenges in the management of the HIV-positive patient in developed nations pertain to minimizing the possibility of developing viral resistance while maximizing quality of life by preventing or controlling the adverse effects associated with long-term use of antiretrovirals. In the developing world, where the HIV epidemic continues to spread, the cost of antiretroviral medications is prohibitive, and the number of deaths from AIDS continues to mount.

Integrative Therapy

People with HIV disease typically use alternative approaches for several reasons. First is to promote healthier functioning of the immune system; this approach can apply both to patients very early in the course of HIV infection who are not yet taking antiretroviral medications and to those with more advanced disease who are receiving conventional medications. Second is for a claimed antiviral effect of the therapy, as in the use of intravenous vitamin C infusions. Third is to treat an HIV-associated symptom or condition. Fourth is to mitigate one or more of the side effects of conventional antiretroviral medications, as in the use of glutamine supplements for protease inhibitor–associated diarrhea. Fifth is simply to improve their quality of life.

A 2008 review concluded that complementary and alternative medicine (CAM) use is more common among HIV-positive individuals who are men who have sex with men (MSM), nonminority, better educated, and less impoverished, and that the use of CAM is also associated with greater HIV-symptom severity and longer disease duration.[1] A study from New England confirmed that although the advent of effective pharmaceutical treatment for HIV has led to a decrease in the use of CAM, rates of use nevertheless remain high. In a cohort of HIV-positive adults ($N = 642$) followed semiannually in the Nutrition for Healthy Living (NFHL) study, between 1995 and 1999, HAART use increased from 0% to 70%, but ingested CAM use decreased only from 71% to 52%.[2] The investigators concluded that most people with HIV at this point apparently feel that "CAM therapies complement, rather than replace, HAART [and that] physicians should routinely ask about ingested CAM therapy use in HIV-positive patients."[2]

Pharmaceuticals

Thirty medications have been approved by the U.S. government to fight HIV and AIDS, and many more are in development. These medications fall into several groups, or classes. The first category is the antiretrovirals, used for their specific activity against HIV. These agents are currently divided into three groups: (1) the nucleoside reverse transcriptase inhibitors, which include zidovudine (Retrovir), emtricitabine

(Emtriva), abacavir (Ziagen), didanosine (Hivid), stavudine (Zerit), and lamivudine (Epivir); (2) the protease inhibitors, which include indinavir (Crixivan), nelfinavir (Viracept), amprenavir (Agenerase), and numerous others; and (3) the nonnucleoside reverse transcriptase inhibitors, which include efavirenz (Sustiva) and nevirapine (Viramune), among others. Newer classes include entry inhibitors (including fusion inhibitors) such as enfuvirtide (Fuzeon), integrase inhibitors such as raltegravir (Isentress), and multiple-class combination drugs such as efavirenz + tenofovir + emtricitabine (Atripla). Currently, the most common approach is to use these agents in combinations of at least three drugs—usually two nucleoside reverse transcriptase inhibitors and either one protease inhibitor or one nonnucleoside reverse transcriptase inhibitor—to reduce the possibility of viral resistance. Research is looking at the possibility that antiviral medications should be withheld during the early stages of HIV infection to minimize the problems with long-term toxicity of these agents. Other investigators are examining the risk-to-benefit analysis of "drug holidays" (i.e., planned periods off medication to minimize toxicity).

The second category of pharmaceuticals, used less widely since the advent of effective antiretroviral medications, comprises the prophylactic agents used for prevention of specific HIV-related opportunistic infections. These drugs include trimethoprim-sulfamethoxazole (Septra, Bactrim) for PCP and toxoplasmosis prophylaxis and azithromycin and rifabutin for prophylaxis of *Mycobacterium avium* infection.

Studies have shown that if $CD4^+$ counts rise and remain higher than 250, prophylaxis for HIV-related opportunistic infections may be safely discontinued.

Nutrition

Early research in the 1980s showed that decreases in body weight, body mass index, and body fat percentage may be the first signs of declining nutritional status resulting from HIV disease and may begin even during the early asymptomatic phase of HIV infection. Many patients with HIV infection or AIDS experience HIV-associated wasting and lose body mass despite nutritional intake that should be adequate for their height and weight. In a study of nutritional status in 108 HIV-positive patients, some with and some without AIDS, body weight, serum cholesterol level, and $CD4^+$ level progressively decreased over a 6-month period, and HIV-associated wasting persisted.[3] This study also found a significant relationship between low serum cholesterol—a marker for poor nutrition—and adverse patient outcome.

Nutrition counseling and intervention in the early stages of HIV disease constitute important components of a prevention-oriented treatment plan because these measures may help forestall adverse nutritional changes in HIV-positive patients. Although definitive data supporting specific nutritional recommendations are scarce, reasonable suggestions include the following: a diet high in omega-3 essential fatty acids such as flaxseed and fish oils; small, frequent meals to ensure intake of adequate calories and to reduce the likelihood of malabsorption; avoidance of simple sugars, which some studies show may inhibit immune function on a short-term basis; and avoidance of large amounts of alcohol and caffeine. In 227 HIV-infected patients, adherence to a Mediterranean dietary pattern was favorably related to cardiovascular risk factors in patients with fat redistribution.[4]

Another purpose for which nutritional interventions are widely used is to address the problems with malabsorption experienced by many HIV-positive patients. Common recommendations include the use of *Lactobacillus, Bifidobacterium,* and other "friendly bacteria" to maintain proper balance of intestinal flora (see Chapter 102, Prescribing Probiotics); the use of a multivitamin supplement to prevent the development of subclinical vitamin deficiencies even in patients eating a well-balanced diet; and the use of glutamine supplements to promote the health of colonic mucosa. Although these recommendations have not yet been shown to affect the course of HIV disease progression, all are safe and reasonable to include in an integrative treatment plan.

Supplements

Multivitamins

Many clinicians have routinely recommended multivitamin supplementation for HIV-positive patients. A double-blind placebo-controlled study of multivitamin (vitamins B, C, and E) supplementation in 1078 HIV-positive pregnant women in Tanzania demonstrated that over a 6-year follow-up period, women taking multivitamins had significantly less progression to WHO stage 4 disease or died as compared with women given placebo (relative risk = 0.71).[5] Subjects in the multivitamin group also had significantly higher $CD4^+$ and $CD8^+$ cell counts and significantly lower viral loads. Adding vitamin A to this multivitamin regimen did not improve the outcomes and, in fact, reduced the benefit of multivitamin therapy on some of the outcome measures.

Vitamin A

Vitamin A supplementation has been extensively studied for ameliorating infection with HIV in adults and for possibly reducing the likelihood of vertical HIV transmission. An association between lower vitamin A levels, lower $CD4^+$ counts, and higher risk of progression to AIDS was reported.[6] A study in African women demonstrated a connection between vitamin A deficiency and increased maternal-to-fetal transmission of HIV.[7] Other prospective trials, however, including one with 341 HIV-positive patients followed over 9 years, demonstrated no significant difference in risk of AIDS progression with vitamin A levels.[8] Trials of high-dose vitamin A supplementation also failed to show an effect on $CD4^+$ or $CD8^+$ counts, viral loads, lymphocyte responsiveness to mitogens, or progression of disease.[9] The association between vitamin A deficiency and increased vertical transmission of HIV initially reported in Kenya was not borne out in subsequent U.S. studies. The Women and Infants Transmission Study (WITS), a large prospective ongoing cohort study, found that vitamin A level does not correlate with increased risk of HIV vertical transmission in North America.[10] The investigators suggested that vitamin A supplementation in addition to prenatal vitamins is not necessary.

Vitamin B_{12}

Supplementation with a B-complex vitamin may be beneficial in HIV-infected patients. Lack of vitamin B_{12} has been associated with peripheral neuropathy and myelopathy; a

9-year prospective cohort study in 310 patients found vitamin B_{12} levels to be an early and independent marker of HIV disease progression, and time to development of AIDS was found to be 4 years less on average in persons observed to have lower vitamin B_{12} levels.[11] Results of intervention trials using B_{12} supplementation have been equivocal. Nevertheless, vitamin B_{12} supplementation continues to be widely used in HIV disease.

Antioxidants: Vitamins C and E, Selenium, and Alpha-Lipoic Acid

Vitamins C and E both have been explored for a role in treatment of HIV disease, owing to their antioxidant properties. Other substances, including selenium and alpha-lipoic acid, are commonly used for the same purpose. In addition, vitamin C has been shown in vitro to inhibit viral replication at high doses.[12] On the basis of this finding, intravenous vitamin C has been widely used to achieve the high serum levels necessary for antiviral activity. No evidence supports this aggressive approach, although anecdotally it has not been proved to be as dangerous as was initially feared. The role of antioxidant supplements in general in HIV disease requires further study. A 2009 review of 19 studies showed that evidence to support standard selenium supplementation in patients with HIV is both limited and insufficient, yet although the available evidence for selenium supplementation is weak, its low toxicity and side effect profile seem to pose minimal risks, especially at low doses.[13] Vitamins E and C at more standard doses are safe and may decrease lipid peroxidation and enhance the immune system; however, conclusive evidence on the effects of these vitamins in HIV disease is still lacking.

Dosage

Vitamin E 400 units daily; vitamin C 500 to 2000 mg three times daily

N-*Acetylcysteine*

Because of the strong evidence that depletion of glutathione levels correlates with progression of HIV infection,[14] much interest has focused on use of the nutritional supplement *N*-acetylcysteine (NAC) as a means to replete intracellular glutathione levels. Despite its early promise, however, NAC has not been proved beneficial in the treatment of HIV disease. One randomized controlled trial[15] failed to show any influence of NAC on T-cell counts or disease progression. Despite the lack of evidence supporting its use, this supplement is commonly used.

Dosage

The dose is 600 to 1200 mg daily.

Precautions

No adverse effects of NAC supplementation have been reported.

L-*Carnitine*

L-Carnitine may be helpful in mitigating some of the adverse effects of antiretroviral medications, including peripheral neuropathy and dyslipidemia. Acetylcarnitine acts to facilitate transport of essential fatty acids across cell membranes and thus may have a role in normalizing intracellular lipid metabolism and regulating peripheral nerve function and regeneration. Decreased levels of carnitine have been found in HIV-positive people; in addition, patients with AIDS experiencing neuropathy with zidovudine or didanosine therapy had significantly lower levels of acetylcarnitine than did patients with AIDS but without neuropathy.[16] One open trial of oral acetyl-L-carnitine supplementation (1500 mg twice daily) for up to 33 months in 21 HIV-positive patients with established antiretroviral-induced neuropathy found an improvement in neuropathic grade in 76% of patients.[17] HIV RNA load and $CD4^+$ and $CD8^+$ cell counts were not altered.

An increased proliferation of peripheral blood mononuclear cells in vitro was noted after oral supplementation with L-carnitine; a significant decrease in triglyceride levels was also noted.[18]

Dosage

Give 2000 to 3000 mg orally daily for HIV-positive patients with peripheral neuropathy or high triglyceride levels.

Precautions

No significant adverse effects of or interactions with L-carnitine have been demonstrated to date; further study of this supplement is needed to substantiate the possible benefits.

L-*Glutamine*

L-Glutamine supplementation has been shown in animal models to speed proliferation of colonocytes. Glutamine deficiency is also hypothesized to play a role in the process of HIV-associated wasting.[19] Many patients taking protease inhibitors experience chronic diarrhea as a medication side effect. A randomized trial involving 35 HIV-positive men with protease inhibitor–induced diarrhea found that when added to a regimen of fiber and probiotic supplementation, L-glutamine (30 g/day) significantly decreased the frequency of diarrhea and the need for antidiarrheal medications.[20] Anecdotally, many patients find glutamine to be helpful in mitigating this side effect even at lower and more easily administered doses.

Dosage

Give 2000 mg daily in two or three divided doses, with the dose titrated upward as needed to 40 g daily.[21]

Calcium Carbonate

Several studies to date have shown that calcium carbonate supplementation can help reduce the frequency of protease inhibitor–associated diarrhea.[22,23] The dose typically used is 500 mg twice daily, although some clinicians report that a higher dose may be more effective. This treatment has no reported interactions or adverse effects.

Dosage

Usual dose is 500 mg twice daily.

Omega-3 Polyunsaturated Fatty Acids

Patients taking antiretroviral therapy are reported to have an increased risk of cardiovascular disease. One study randomized 51 patients in a placebo-controlled double-blind trial to receive either 2 capsules of Lovaza fish oil twice daily or 2 capsules of placebo. After 12 weeks, the omega-3 group noted slightly decreased plasma triglycerides and induced

antiinflammatory effects by increasing formation of antiinflammatory leukotriene B_5.[24] Fifty-four persons with HIV and elevated serum triglycerides (higher than 150 mg/dL) were randomly assigned to a control group or an intervention group and given supplemental omega-3 fatty acids for 13 weeks. The investigators documented dramatically reduced serum triglycerides, decreased arachidonic acid in the phospholipid fraction, and reduced de novo lipogenesis associated with the metabolic syndrome in the intervention group.[25]

Dosage
Dose is 4 g/day of docosahexaenoic acid and eicosapentaenoic acid, the main essential fatty acids found in fish oil.

Precautions
High doses (more than 6 g) can increase free radical production and can have an antiplatelet effect.

Zinc
Adequate zinc is necessary for immune function, and zinc deficiency is estimated to occur in more than 50% of HIV-infected adults. A prospective randomized controlled clinical trial involving 231 HIV-infected adults with low plasma zinc levels revealed that zinc supplementation for 18 months reduced 4-fold the likelihood of immunologic failure while controlling for age, sex, food insecurity, baseline $CD4^+$ cell count, viral load, and antiretroviral therapy (relative rate, 0.24; 95% confidence interval, 0.10 to 0.56).[26]

Dosage
The dose is 15 mg for men; 12 mg for women.

Precautions
High doses can inhibit the absorption of other minerals, most significantly copper.

Chromium
Chromium is an essential micronutrient, and deficiency has been reported to cause insulin resistance, hyperglycemia, and hyperlipidemia. A randomized double-blind placebo-controlled trial enrolled 52 HIV-positive subjects with elevated glucose, lipids, or evidence of body fat redistribution who also had insulin resistance. Chromium was tolerated without side effects and resulted in a significant decrease in the following: Homeostatic Model Assessment-Insulin Resistance (HOMA-IR, an insulin resistance indicator) (median [IQR]; pre, 4.09 [3.02 to 8.79]; post, 3.66 [2.40 to 5.46]; $P = .004$); insulin (pre, 102 [85 to 226]; post, 99 [59 to 131] pmol/L; $P = .003$); triglycerides, total body fat mass (mean ± SEM; pre, 17.3 ± 1.7; post, 16.3 ± 1.7 kg; $P = .002$), and trunk fat mass (pre, 23.8 ± 1.9; post, 22.7 ± 2.0%; $P = .008$).[27]

Dosage
The dose is 400 mcg/day chromium-nicotinate.

K-PAX Immune Support Formula
In 2006, a double-blind placebo-controlled randomized clinical trial of 40 HIV-infected patients showed that a broad-spectrum micronutrient supplement could produce a statistically significant 24% increase in the mean $CD4^+$ cell count of individuals taking stable HAART ($P = .01$).[28] The micronutrient supplement tested (K-PAX Immune Support Formula, Mill Valley, Calif) included 33 ingredients and was consumed twice daily with food. The supplement is currently paid for by the New York AIDS Drug Assistance Program. For ingredients of the immune support formula used in the research, see Table 17-1.

Dosage
Four capsules twice per day (for less than 120 lb) or eight capsules twice per day (for more than 120 lb).

Botanicals

Chinese Herbal Approaches
In the traditional practice of Chinese medicine, herbal formulas are typically individualized to suit a given patient's condition, rather than standardized as a treatment for a given "disease." In the United States, however, the use of standardized formulas for certain conditions has become quite popular. Early small randomized controlled trials of two such Chinese herbal formulas (Enhance and Clear Heat, formulated by Health Concerns in California) showed a trend (statistically nonsignificant) toward fewer symptoms in the treatment group than in the placebo group.[29] However, a more recent prospective placebo-controlled double-blind study of a different Chinese formula in 68 HIV-infected adults with $CD4^+$ cell counts lower than 0.5×10^9/L found no significant differences between the intervention and placebo groups regarding viral loads, $CD4^+$ counts, symptoms, or quality of life scores. No significant therapy-related toxicities were reported, although patients taking Chinese herbs reported significantly more gastrointestinal disturbances (79% versus 38%; $P = .003$) than those receiving placebo. The investigators concluded that this particular Chinese herbal formula was not effective when administered in a Western medicine setting.[30]

A study of 18 volunteers evaluated the safety and efficacy of CKBM-A01, a Chinese herbal medicine, and patient quality of life. Although CKBM-A01 appeared to be safe, it gave no significant improvement in quality of life in asymptomatic HIV-infected patients and no significant improvement in the treatment of HIV infection based on $CD4^+$ cell counts and viral loads.[31] Well-controlled long-term follow-up studies of use of these Chinese herbal preparations are needed before Western practitioners can recommend them with confidence. Significant concerns remain regarding possible herb-drug interactions, given the large number of herbs in most Chinese formulas, especially in those patients concurrently taking conventional antiretroviral medications.

Milk Thistle
Milk thistle extract (silymarin) may help normalize liver function tests in patients taking antiretroviral therapies, especially if these patients are coinfected with hepatitis C. Numerous in vitro studies found that silymarin speeds regeneration of hepatocytes after chemical injury.[32] A significant improvement in liver function in patients with alcoholic hepatitis was noted after treatment with milk thistle extract.[33] At present, no firm evidence specifically links the hepatoprotective function of silymarin with liver damage from antiretrovirals. However, clinical experience suggests that milk thistle may be useful in this situation. Silymarin has no reported contraindications or adverse effects. Contrary to a widely held

TABLE 17-1. Immune Support Formula for HIV Infection Found in K-PAX Formulation

MICRONUTRIENT	TOTAL DAILY DOSAGE	MICRONUTRIENT	TOTAL DAILY DOSAGE
N-Acetyl cysteine (NAC)	1200 mg	Calcium	800 mg
Acetyl L-carnitine	1000 mg	Magnesium	400 mg
Alpha-lipoic acid	400 mg	Selenium	200 mcg
Beta-carotene	20,000 units	Iodine	150 mcg
Vitamin A	8,000 units	Zinc	30 mg
Vitamin C	1800 mg	Copper	2.0 mg
Vitamin B_1	60 mg	Boron	2.0 mg
Vitamin B_2	60 mg	Potassium	99 mg
Pantothenic acid	60 mg	Iron	18 mg
Niacinamide	60 mg	Manganese	10 mg
Inositol	60 mg	Biotin	50 mcg
Vitamin B_6	260 mg	Chromium	100 mcg
Vitamin B_{12}	2.5 mg	Molybdenum	300 mcg
Vitamin D	400 units	Choline	60 mg
Vitamin E	800 units	Bioflavonoid complex	300 mg
Folic acid	800 mcg	L-Glutamine Betaine HCL	100 mg 150 mg

From Kaiser J, Campa A, Ondercin JP, Leoung GS, Pless RF, Baum MK. Micronutrient supplementation increases CD4 count in HIV-infected individuals on highly active antiretroviral therapy: a prospective, double-blinded, placebo-controlled trial. *J Acquir Immune Defic Syndr.* 2006;42:523–528.

popular belief among patients with HIV disease and many practitioners, milk thistle has no documented antiviral effect either in HIV disease or in hepatitis C.

Dosage

The dose is 240 mg twice daily of standardized milk thistle (silymarin) extract.

Red Rice Yeast Extract

Hyperlipidemia is a common side effect of treatment with protease inhibitors. A standardized extract of Chinese red rice yeast can reduce cholesterol levels by up to 20% in certain patients. One randomized controlled trial showed a significant decrease in lipids with use of this supplement, with no significant toxicity.[34] Red rice yeast has not been tested specifically in protease inhibitor–related hyperlipidemia. No significant adverse effects have been reported to date in patients using this supplement (see Chapter 39, Dyslipidemias).

Dosage

The dose is 1200 mg orally twice daily.[35]

Precaution

Because this supplement can contain statin-like compounds, it is probably prudent to monitor liver function periodically in patients taking red rice yeast extract over the long term.

Herb-Supplement-Medication Interactions

An extremely active and important area of current research covers the questions of possible interactions among herbal medicines, supplements, and anti-HIV medications. In particular, herbs and supplements that induce elements of the cytochrome P-450 system have been found potentially to lead to lowered serum levels of protease inhibitors. St. John's wort, for example—an herb commonly recommended for depression—induces cytochrome P-450 activity and can lead to a decrease in indinavir levels of up to 57%; nevirapine levels can also be affected.[36] Garlic, commonly used for elevated cholesterol levels, can have similar effects through increased cytochrome P-450 activity.

Databases are now available that provide frequently updated information regarding known herb-drug and supplement-drug interactions, and practitioners caring for patients taking antiretrovirals should regularly consult these sites to provide informed counseling to patients regarding their concomitant use of herbs and supplements.

St. John's wort increases cytochrome P-450 activity and can reduce serum levels of medications metabolized by this system. It can decrease indinavir levels up to 57%.[28]

Mind-Body Therapy

Research in psychoneuroimmunology has clearly linked psychological stress to impaired immune function. Although a specific link between T-cell count or function and stress reduction in HIV disease has not been clearly established, one study did find a trend toward increased T-cell count in persons practicing a mind-body approach, and other studies found improvement in natural killer cell function and other immune parameters. Stress reduction approaches studied to date in HIV-positive patients include biofeedback, meditation, systematic relaxation, hypnosis, and cognitive-behavioral stress management training. A review of several mind-body applications from the literature follows.

Progressive Muscle Relaxation and Biofeedback

Ten HIV-positive men who were asymptomatic but had T-cell counts lower than 400 were enrolled in a randomized 10-week study in which the experimental group received a 1-hour training session twice weekly in progressive muscle relaxation and biofeedback-assisted relaxation.[35] The subjects were expected to practice the techniques daily. Follow-up at 1 month after the intervention was completed showed decreased anxiety and improved mood and self-esteem and increased T cell counts, as shown by the State Anxiety Inventory, the Profile of Mood States, the Self-Esteem Inventory, and a basic T-cell count. The extremely small sample size limits the generalizability of these findings, however.

The differing effects of guided imagery, progressive muscle relaxation, and no intervention were tested on 69 participants in an uncontrolled study over a span of 6 weeks.[38] Subjects were instructed in their particular intervention and then expected to continue daily practice for the duration of the study. The outcome showed improved quality of life scores for the guided imagery group but no change in the group practicing progressive muscle relaxation.

Mindfulness and Stress Reduction

Forty-eight HIV-1–infected adults were randomized to either an 8-week mindfulness-based stress reduction (MBSR) program or a 1-day control stress reduction education seminar. Findings provided an initial indication that mindfulness meditation training can buffer $CD4^+$ T-lymphocyte declines in HIV-1–infected adults independent of antiretroviral medication use.[39]

A small nonrandomized study examined the effects of a structured, 8-week, MBSR program on perceived stress, mood, endocrine function, immunity, and functional health outcomes in HIV-positive adults. Although functional and quality of life outcomes were not significantly affected, natural killer cell activity and number increased significantly in the MBSR group compared with the comparison group.[40]

Another study of stress management training[41] focused on both $CD4^+$ counts and quality of life measurements in 45 HIV-infected and AIDS patients (30 in the intervention group and 15 in the control group). This study found a lower mean stress level and a trend toward higher $CD4^+$ counts in the intervention group. The intervention led to immediate increases in emotional well-being and perceived quality of life, but these outcomes were not sustained at a 6-month follow-up. The presence of illness-related intrusive thinking was higher in the control group at follow-up, whereas that of the intervention group actually decreased.

Further studies are needed to distinguish whether any one of the mind-body approaches is more effective than others in patients with HIV disease. Generally, these strategies are considered extremely safe. The one exception to this general rule is that patients with a history of psychosis or unstable behavior should avoid hypnosis and should undertake other deep relaxation approaches with caution because these practices may increase the risk of relapse in certain patients (see Chapter 93, Relaxation Techniques, and Chapter 98, Recommending Meditation).

Therapies to Consider

Acupuncture

Acupuncture has been widely used both to enhance immune function and general well-being in HIV-positive patients and to treat specific HIV- or medication-related symptoms. One randomized controlled trial that examined amitriptyline plus acupuncture found no benefit of standardized acupuncture over sham (placebo) acupuncture[42] in the treatment of HIV disease–related peripheral neuropathy. Methodologic challenges in studying acupuncture make it difficult to demonstrate a small positive effect of an acupuncture intervention. Specifically, to construct a valid placebo intervention (i.e., sham acupuncture) that does not in itself carry a therapeutic benefit beyond that of placebo is difficult. In addition, individualized strategies both for specific symptoms and for overall health may have higher efficacy than that of standardized treatment protocols more amenable to study in such trials; however, these individualized strategies are extremely difficult to study in blinded trials. Thus, a trial such as this one examining standardized acupuncture treatment versus individualized choice of points may fail to show efficacy because of the lesser efficacy of the standardized approach.

Many acupuncturists believe that for this modality to be effective in peripheral neuropathy, treatment must be initiated as soon as possible after the onset of symptoms. Perhaps future acupuncture trials in HIV disease should focus on efficacy in treating new-onset neuropathies.

Massage Therapy

Massage therapy has been shown to reduce anxiety levels. Massage therapy is proposed to have a positive impact on quality of life and immune function through stress mediation. The ability of massage to produce significant effects in the treatment of patients with HIV disease or AIDS in particular requires further study. A randomized trial of massage therapy in HIV-exposed neonates showed a significant benefit[43]; other evidence is all anecdotal. Although massage therapy has not been proved to affect $CD4^+$ levels per se, evidence showed that daily massage in HIV-positive men improved natural killer cell function and increased $CD8^+$ cell counts.[44] A Cochrane Systematic Review examined the safety and effectiveness of massage therapy on quality of life, pain, and immune system parameters. The investigators concluded that some evidence supports the use of massage therapy to improve quality of life for people living with HIV infection or AIDS, particularly in combination with other stress management modalities, and that massage therapy may have a positive effect on immunologic function.[45] The benefits in terms of mood and decreased anxiety and the lack of adverse effects make massage therapy a reasonable choice for the HIV-positive patient.

Prevention Prescription

- Encourage a commitment to safe sex practices.
- Educate on the dangers of intravenous drugs.
- Provide for prompt prophylaxis of needlestick injuries in health care workers. For high-risk individuals, this involves lamivudine/zidovudine (Combivir), a 150/300-mg tablet orally twice daily for 4 weeks.

Therapeutic Review

If viral load exceeds 30,000, if $CD4^+$ counts fall to less than 500, or if patients are in any way symptomatic of HIV disease, good practice requires that they be offered combination antiretroviral medication as the mainstay of treatment. This approach does not preclude the use of integrative strategies as supportive adjuncts and to alleviate certain disease-related or medication-related symptoms.

Pharmaceuticals

- Consultation with a physician familiar with the rapidly changing range of medication options is recommended for proper choice of pharmaceutical approaches. A2

Nutrition

- Nutritional consultation early in the course of HIV infection should be recommended. C1
- Adequate calorie consumption and an emphasis on high intake of omega-3 essential fatty acids are important elements. C1
- Absorption issues should be considered as well.

Supplements

- Multivitamin daily, emphasizing vitamins B, C, and E and avoiding additional vitamin A A1
- L-Carnitine: 2000–3000 mg daily, especially in peripheral neuropathy or lipid disturbance B1
- L-Glutamine: 2000 mg daily, especially in chronic diarrhea or malabsorption syndromes B1
- Calcium carbonate supplementation: 500 mg twice daily for protease inhibitor–induced diarrhea B1

Botanicals

- Milk thistle extract: 240 mg twice daily, in patients with elevated values on liver function tests or coinfection with hepatitis C C1
- Red rice yeast: 1200 mg twice daily for hyperlipidemia B2
- Use of Chinese herbal formulas in patients not meeting criteria for pharmaceutical treatment B2
- High level of awareness among practitioners regarding possible interactions between herbal medicine, especially cytochrome P-450 inducers, and antiretroviral medications

Mind-Body Approaches

- Biofeedback, deep relaxation therapy, visualization, cognitive-behavioral stress reduction training, or another mind-body strategy B1

KEY WEB RESOURCES

• National HIV/AIDS Clinicians' Consultation Center. http://www.nccc.ucsf.edu/	This University of California San Francisco/San Francisco General Hospital–based AIDS Education & Training Centers clinical resource for health care professionals includes toll-free numbers linking physicians to expert clinical advice on HIV/AIDS management and managing health care worker exposures to HIV and hepatitis B and C, as well as consultation on antiretroviral use in pregnancy, labor and delivery, and the postpartum period.
• The Body, a subsidiary of HealthCentral Network. http: //www.thebody.com/index.html	This community-oriented commercial Web site in English and Spanish has information on prevention and treatment, coverage of major HIV/AIDS conferences, online community discussion threads, and an extensive ask-the-experts feature.
• Johns Hopkins Medicine. http://hopkins-aids.edu/.	A comprehensive HIV guide for clinicians is available from Johns Hopkins and requires signing up for an account (free).
http://locator.aids.gov/	This Web site links people to HIV testing, treatment, mental health and substance abuse services, housing, and other resources.
• National Institutes of Health HIV/AIDS Prevention & Service Provider Locator. www.aidsinfo.nih.gov	This U.S. Department of Health and Human Services project offers the latest federally approved information on HIV/AIDS clinical research, treatment and prevention, and medical practice guidelines for people living with HIV/AIDS, their families and friends, health care providers, scientists, and researchers.

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Chapter 18

Herpes Simplex Virus

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Pathophysiology

Herpes simplex is a viral disease caused by both herpes simplex virus type 1 (HSV-1) and herpes simplex virus type 2 (HSV-2). The infection is common in the United States and abroad and is usually categorized based on the site of infection, although both HSV-1 and HSV-2 can cause infections anywhere on the body. Oral herpes, generally caused by HSV-1, is the most common type and typically occurs on the lips. These lesions are frequently referred to as cold sores or fever blisters. HSV-1 primarily causes infections in the mouth, throat, face, eye, and central nervous system. Genital herpes, usually referred to simply as herpes, is the second most common form and is generally caused by HSV-2. HSV-2 primarily causes anogenital infections.

HSV is contracted only by direct contact with an active lesion or body fluid of an infected person.[1] To infect an individual, HSV travels through very small (even microscopic) breaks in the skin or mucous membranes in the mouth and genital area. The virus prefers areas where the skin is thin or moist. The clinical manifestations of primary (first episode) genital herpes are quite variable. The initial presentation tends to be more severe than recurrences, with painful genital ulcers, fevers, myalgias, tender inguinal lymphadenopathy, and headache.[2] The average incubation period is 4 days (range, 2 to 21 days). After initial infection, the virus moves to the sensory nerves, where it becomes latent until reactivated. Potential triggers for reactivation are discussed later in the chapter and are summarized in Table 18-1.

Herpes has no known cure. Once a person is infected, the immune system never removes HSV from the body. As a result of the primary infection, the body produces antibodies to the particular type of HSV and prevents another infection of that type at a different site of the body.[3] Therefore, people with immature or suppressed immune systems (e.g., newborns, transplant recipients, patients with human immunodeficiency virus infection) are more prone to recurrences and more severe complications of HSV infections. Many people infected with HSV-1 and HSV-2 show no physical symptoms, a condition known as subclinical herpes.

Asymptomatic HSV shedding occurs at some point in most people infected with herpes, and this may represent the most common form of HSV-1 and HSV-2 transmission.[3]

Many HSV-infected people experience recurrences, often within the first year of infection. A prodrome of symptoms including tingling, itching, and pain can occur and last from hours to days before lesions develop. Fewer lesions usually develop during recurrences, and these lesions are usually less painful and heal faster. Outbreaks tend to be episodic and occur an average of four to five times per year when patients are not using antiviral therapy.[3]

Integrative Therapy

Lifestyle

Condoms offer some protection against HSV-2 in both men and women; consistent condom users have a 30% lower risk of HSV-2 acquisition compared with those who never use condoms.[4]

The virus cannot pass through a latex condom, but condoms do not completely prevent skin contact. People with any symptoms of herpes should abstain from sexual activity with uninfected partners.

During an outbreak, practitioners often recommend that people clean the areas with warm water and then keep the active lesions as dry as possible after this. One way to help prevent spread of the virus is to dry the area with a hairdryer on a low or cool setting instead of using a towel.

All causes of HSV reactivation are unknown, but several triggers have been identified and are summarized in Table 18-1. Changes in the immune system the week before

TABLE 18-1. Potential Triggers That May Reactivate Herpes Simplex Virus

HSV-1

- Ultraviolet light
- Immunodeficiency
- Stress, depression, anxiety (chronic)
- Poor sleep
- Trauma to mucosa
- Cold, windy, or dry weather
- Hot food or biting lips
- Food allergy
- Fever

HSV-2

- Immunodeficiency
- Stress, depression, anxiety (chronic)
- Poor sleep
- Food allergy
- Trauma to genital mucosa
- Menses (usually 5–12 days before onset)

HSV, herpes simplex virus.

and during menstruation can play a role in HSV-1 reactivation.[5] Concurrent infections such as viral upper respiratory infections or other febrile illnesses can cause outbreaks, and this association led to the common names cold sores and fever blisters.

Trauma Prevention

Local injury to the face, lips, eyes, or mouth can lead to reactivation. Exposure to wind, ultraviolet light, and sunlight are also well-known triggers. Preventing mucosal injury from chapping or sunburn is important in the prevention of outbreaks. Use of lip balm to prevent injury, and specifically the ingredient zinc sulfate (discussed later in the chapter), can help heal and prevent recurrent herpes infections.

Stress and Sleep

Sleep deprivation from poor sleep habits or lifestyle factors can increase a person's chance of herpes recurrence. Stress and uncontrolled anxiety can often lead to recurrences as well. These two factors should be addressed in patients with recurrent outbreaks of herpes.

Nutrition

Increased Lysine and Decreased Arginine

Generally, a well-balanced diet high in fruits and vegetables is recommended as healthy. Specifically for people infected with HSV, a diet avoiding foods high in arginine and including foods high in lysine is often recommended for reducing herpes outbreaks. Table 18-2 provides a list of foods high in lysine and arginine. Tissue culture studies have demonstrated a beneficial effect on viral replication when the amino acid ratio of arginine to lysine favors arginine. The opposite, elevation of lysine to arginine, suppresses viral replication and inhibits cytopathogenicity of HSV.[6] Results of clinical studies using this theory of avoiding arginine-rich foods have not been conclusively positive.

TABLE 18-2. Dietary Considerations in Herpes Simplex Viral Infection

Foods to Avoid (High Arginine Levels)

- Chocolate
- Peanuts
- Almonds
- Cashews
- Sunflower seeds
- Gelatin

Foods to Include (High Lysine Levels)

- Vegetables
- Beans
- Fish
- Turkey
- Chicken

Lysine supplementation is reviewed later in the chapter. Lysine intake can be increased by increasing consumption of lysine-rich foods, such as legumes and animal proteins and reducing intake of lysine-poor foods such as grains and refined sugars. Emphasizing foods that are not processed or cooked in ways that limit available lysine (boiling or poaching preserves lysine, whereas grilling, broiling, or frying destroys it) also improves lysine nutritional status. Making these dietary changes may obviate the need for lysine supplementation in some cases.[7]

Refined Carbohydrates

Ingestion of large amounts of refined carbohydrates impairs certain parameters of immune function. In rats, the progressive addition of sucrose to the diet caused a dose-dependent reduction in the capacity to produce antibodies.[8] In healthy humans, acute ingestion of 75 g of glucose significantly depressed cell-mediated immune function after 30 and 60 minutes.[9] Although the relationship between refined carbohydrate intake and susceptibility to HSV has not been investigated, many patients notice that herpetic lesions recur when they eat too many sweets. In some cases, ingestion of even small amounts of refined sugar appears to trigger an exacerbation. Restriction of refined carbohydrate intake should therefore be considered on a case-by-case basis.

Food Allergies

Although the potential association between food allergy and recurrent HSV infection has not been studied, patients often report that outbreaks become less common after they identify and avoid specific foods. Repeated ingestion of allergenic foods could theoretically strain the immune system and potentially increase chances of HSV reactivation. Consider a trial of an elimination diet if food allergies are thought to play a role (see Chapter 84, Food Intolerance and Elimination Diet).

Supplements

Vitamin C

In early scientific studies in the 1930s, ascorbic acid was shown to inactivate a wide range of viruses in vitro, including HSV.[10] Oral and intravenous vitamin C, along with a vitamin C paste, was found to help alleviate HSV outbreaks

in patients with acquired immunodeficiency syndrome (AIDS) in the 1980s.[11] In a small double-blind trial, patients with HSV outbreaks received 200 mg ascorbic acid and 200 mg water-soluble flavonoids (apparently from citrus) three times daily for 3 days or a placebo. The mean time until remission of symptoms was 57% shorter in the active treatment group than in the placebo group (4.2 versus 9.7 days; $P < .01$). Treatment was most effective when it was initiated during the prodromal stage.[12]

Thus, supplementation with vitamin C, with or without flavonoids, appears to be a worthwhile treatment for herpes simplex when supplementation is used early in an outbreak. Anecdotal evidence suggests that the antiviral effect of vitamin C is more pronounced at higher doses. For treatment of an acute episode, patients may consider increasing the daily consumption of vitamin C by eating fruits high in the vitamin and supplementing according to bowel tolerance for 5 to 10 days.

Zinc

Several studies have indicated that topical zinc preparations may be effective at shortening duration of outbreaks of HSV infection and preventing recurrence. One study of patients with frequent recurrences of HSV used a topical solution of 0.025% to 0.05% zinc sulfate. During an acute episode, zinc was applied daily until the lesions were gone. Treatment of healed lesions was continued once weekly for 1 month, then twice a month. During a follow-up period of 16 to 23 months, none of the patients experienced a recurrence of lesions. Results also showed that application of a 0.05% zinc sulfate solution, before and during sun exposure, at the site of previous HSV infections decreased relapses induced by sun exposure.[13]

Oral zinc seems to be helpful as well. Taking 23 mg zinc sulfate and 250 mg vitamin C, each twice daily for 6 weeks, appeared to reduce the duration and severity of HSV outbreaks during the supplementation period.[14]

Dosage

Topical zinc sulfate 0.025% to 0.05% is applied daily for acute outbreaks. Oral zinc sulfate, 23 mg daily (with 250 mg of vitamin C) twice daily for 6 weeks, may reduce the duration and severity of outbreaks.

Precautions

Long-term oral zinc supplementation may require a copper supplement to prevent zinc-induced copper deficiency.[15]

Lysine

A review of clinical trials showed that lysine supplements seem to be more effective for preventing a herpes outbreak than for reducing the severity and duration of an outbreak.[16] One such clinical trial included 114 patients (52 completed the trial) with recurrent orofacial herpes or genital herpes, or both. Patients were randomly assigned to receive, in double-blind fashion, 1 g lysine hydrochloride three times daily or placebo for 6 months. Among those who completed the trial, the proportion of patients who reported the treatment to be effective or very effective was 74% in the lysine group and 28% in the placebo group ($P < .01$). Lysine was significantly more effective than placebo in terms of frequency and severity of lesions and healing time.[17]

According to anecdotal reports, lysine supplementation accelerates the healing of acute herpes simplex outbreaks. Short-term administration of 1 to 3 g lysine daily has been found to reduce the duration of attacks, and higher doses are more effective than lower doses.[18] In a double-blind trial, however, administration of 1 g lysine at the first sign of infection, followed by 500 mg twice daily for a total treatment period of 5 days, had no significant effect on the healing rate.[19] Although anecdotal reports suggest that higher doses of lysine may be effective during acute outbreaks, no controlled trials have confirmed this.

Dosage

For prevention, 1 g, three times daily for 6 months, is taken.

Precautions

Gastrointestinal side effects such as diarrhea and abdominal pain have been reported with high doses (more than 10 g/day). A modest rise in low-density lipoprotein has been reported.

Topical Vitamin E

Topical application of vitamin E seems to relieve pain and aid in the healing of oral herpetic lesions (gingivostomatitis or herpetic cold sores). One study used topical cotton saturated with vitamin E oil (20,000 to 28,000 units/oz) placed over a dried lesion for 15 minutes.[20] In some cases, a single application was beneficial, but large or multiple lesions responded better when they were treated three times daily for 3 days. In another study, the content of a vitamin E capsule was applied to lesions every 4 hours. Prompt and sustained pain relief occurred, and the lesions healed more rapidly than expected.[21]

Dosage

Empty the contents of a vitamin E capsule (*d*-alpha-tocopherol) onto a cotton stick and apply to crusted sores every 8 hours for 3 days.

Mind-Body Therapy

Antecedent stress has commonly been thought to instigate HSV outbreaks. However, this relationship has not always been clearly delineated in the literature. Some investigators have postulated that stress is induced by the recurrence itself and not causative.[22] In a 2009 review article, however, psychosocial stress was in fact shown to increase HSV recurrence significantly.[23] Further evidence for the link between stress and HSV recurrence was shown by a reduction in HSV-2 antibody titers in patients after cognitive-behavioral therapy.[24] Because high levels of circulating HSV antibodies have been correlated with HSV recurrence, this signifies a positive effect. Another interesting correlate has shown depressive symptoms to increase the rate of HSV recurrence.[25] Thus, it stands to reason that a focus on modalities to lower stress level and to treat depression when present would decrease the incidence of HSV outbreaks.

Relaxation Training

Relaxation exercises can be incorporated into a daily routine and also used to manage situational stress (see Chapter 93, Relaxation Techniques).

Meditation

Meditation can be an excellent way for patients to manage chronic stress. Encouraging the receptive patient to incorporate a meditative practice into daily life can have far-reaching health benefits (see Chapter 98, Recommending Meditation).

Botanicals

Lemon Balm

Lemon balm *(Melissa officinalis)*, an herb from the mint family, is typically known for its calming properties. It is also a potent antiviral herb and has been used to treat herpes infections for many years. Studies have demonstrated its effect when used topically as a 1% cream or ointment of a 70:1 leaf extract applied two to four times a day. Topical application should be started with prodromal symptoms and continued for 2 to 3 days after the lesions have healed. One double-blind placebo-controlled study ($N = 66$) demonstrated significant improvement in discomfort, number of lesions, and size of lesions when compared with controls.[26]

Dosage

Lemon balm 1% cream or ointment of 70:1 extract applied to lesions two to four times daily from the start of symptoms to 2 to 3 days after healing.

Precautions

Lemon balm is likely safe and without long-term risk.

Siberian Ginseng

Siberian ginseng *(Eleutherococcus senticosus)* is an adaptogenic plant. Its root has been used to form a standardized extract containing 0.3% eleutheroside (Elagen). When taken orally, this extract was found to decrease frequency, duration, and severity of HSV-2 outbreaks.[27]

Dosage

Siberian ginseng extract standardized to contain eleutheroside E 0.3% is taken in a dose of 400 mg per day.

Precautions

Siberian ginseng can cause slight drowsiness, anxiety, irritability, melancholy, mastalgia, and uterine bleeding. These symptoms are often seen with doses higher than normal. It should be used with caution in patients with cardiovascular disease because hypertension, palpitations, and tachycardia can occur. Long-term use of Siberian ginseng has been associated with nerve inflammation and subsequent muscle spasm.

Rhubarb and Sage

A cream composed of 23 mg/g each of rhubarb *(Rheum officinale and Rheum palmatum)* and sage *(Salvia officinalis)* topically has been shown to be as effective as acyclovir cream.[28]

Dosage

Apply a cream containing 23 mg/g each of rhubarb and sage extracts every 2 to 4 hours while awake. Start treatment within 1 day of prodromal symptoms and continue for 7 days.

Precautions

Oral use of rhubarb may have significant side effects, but topical use appears to be safe. Rhubarb-containing products should not be used for longer than 8 days.

Propolis

Propolis is a resin-like substance collected by bees from a variety of plant structures. One study demonstrated the benefit of propolis in the treatment of HSV lesions with a 3% ointment applied four times a day.[29]

Dosage

An ointment of 3% propolis is applied to HSV lesions four times a day.

Precautions

Some allergic reactions have been reported with oral propolis use. Patients with bee allergies should also use caution with propolis. One case report noted acute renal failure in a patient using oral propolis who improved when propolis was stopped. Topical propolis may contain cosmetics that could induce eczematous contact dermatitis.

Sangre de Grado

Sangre de Grado is a tree indigenous to the Amazon of South America. Its resin contains SP-303, which has been used orally in the treatment of diarrhea. One study showed its benefit in reducing HSV lesions in the genital and perianal region in patients with AIDS. These patients used a standardized extract containing SP-303.[30,31]

Dosage

An ointment of 15% SP-303 (derived from Sangre de Grado) is applied topically to lesions three times a day for 21 days.

Precautions

SP-303 used topically can cause pain and burning.

Aloe Vera

Some data indicate that aloe vera 0.5% extract cream, applied topically three times a day, hastens healing time compared with aloe vera gel or placebo.[32]

Dosage

Aloe vera 0.5% extract cream is applied topically three times a day for 2 weeks.

Precautions

Topical aloe is generally well tolerated. Some burning, itching, or local dermatitis can be experienced.

Pharmaceuticals

Antivirals are the mainstay in conventional medicine for the treatment of primary and recurrent HSV infections. By inhibiting DNA polymerase in virally infected cells, these drugs work to interfere with viral replication. The greatest effects are seen when the drugs are prescribed within 48 to 72 hours of the initiation of symptoms from an outbreak. If a patient is experiencing new lesions after this time frame, however, initiation of an antiviral may still be warranted.

Studies demonstrated that the use of acyclovir can decrease the duration of lesions, fevers, and odynophagia, as well as reduce viral shedding compared with placebo.[33]

Early treatment does not seem to decrease the risk for recurrent infection.[34]

Caution is advised in patients with renal disease because antiviral medications can worsen renal function, especially when these drugs are used with other nephrotoxic substances.

Primary Herpes Infection

Options include the following:
Acyclovir: 400 mg orally three times per day or 200 mg orally five times per day for 7 to 10 days[35]
Famciclovir: 500 mg orally three times daily for 7 to 10 days
Valacyclovir: 1000 mg orally twice daily for 7 to 10 days[36]

Famciclovir and valacyclovir offer less frequent dosing but are more expensive.

Recurrent Herpes Infection

Patients who experience minimal symptoms and infrequent recurrences may not need treatment at all. Those with more significant symptoms may benefit from antivirals when the drugs are started at the onset of prodrome symptoms (itching, burning, tingling).

Topical antiviral treatment has shown to have a modest benefit and may be helpful for certain patients. One study demonstrated a decrease in healing time, duration of pain, and viral shedding. [37] Topical options are as follows:
Acyclovir cream or ointment: applied six times a day for 7 days[38]
Penciclovir cream: applied every 2 hours while awake for 4 days[37]

Oral options include the following:
Acyclovir: 200 or 400 mg five times daily for 5 days [39]
Famciclovir: 750 mg twice daily for 1 day or 1500 mg as a single dose[40]
Valacyclovir: 2 g twice daily for 1 day[41,42]

Single-day dosing with famciclovir or valacyclovir can offer greater patient convenience and lower cost compared with 5 days of acyclovir.[42]

Pharmaceutical Prophylaxis

Prophylactic treatment should be prescribed on an individual basis and depends on the severity of symptoms with outbreaks or underlying conditions. In general, suppressive therapy is recommended if a patient has six or more recurrences per year. Practitioners should discontinue prophylactic antiviral medications once a year to see whether continuation is necessary.

Options include the following:
Acyclovir: 400 mg orally twice a day[43]
Valacyclovir: 500 mg orally once a day[44]

Prevention Prescription

- Follow safe sexual practices, with the use of condoms and avoidance of oral sex if infectious status is unknown.
- Avoid contact with vesicular fluid to others or other body areas.
- Avoid trauma to the skin (physical trauma, rough intercourse, sunburns).
- Maintain a regular sleep-wake cycle with 8 hours of sleep daily.
- Avoid known food triggers.
- Eat lysine-rich food (vegetables, beans, fish, chicken, and turkey).
- Avoid excessive arginine-rich foods (chocolate, peanuts, almonds, cashews, sunflower seeds, and gelatin).
- Make lifestyle choices to reduce stress levels.
- Prevent and treat depression.
- Consider antiviral medications if outbreaks are frequent or you are immunosuppressed.

Therapeutic Review

Acute Treatment

Supplements

- Zinc sulfate
  - Topical solution 0.025% to 0.05%: applied daily at the start of an outbreak, then once weekly for 1 month, then twice a month
  - Oral: 25 mg zinc added to 250 mg of vitamin C each twice a day for 6 weeks
- Vitamin C: 200 to 250 mg three times a day for 3 days
- Lysine: 1 g three times a day
- Vitamin E oil (20,000 to 28,000 units/oz): applied topically to crusted lesions for 15 minutes three times a day for 3 days

Botanicals

- Lemon balm 1% cream or ointment (70:1 extract): applied two to four times daily at onset of symptoms to 2 to 3 days after healing
- Siberian ginseng (eleutheroside E 0.3% standardized extract): 400 mg by mouth daily (higher doses and long-term use can lead to significant adverse effects)
- Rhubarb and sage extract cream containing 23 mg/g each: applied topically every 2 to 4 hours for 7 days

Continued

- Propolis 3% ointment: applied topically 4 times a day (use caution if patient has a bee allergy) 
- Sangre de Grado (SP-303) 15% ointment: applied topically to lesions three times a day for 21 days 
- Aloe vera 0.5% extract cream: applied topically three times a day for 2 weeks 

Pharmaceuticals

- Primary infection 
  - Acyclovir: 400 mg orally three times daily or 200 mg orally five times daily for 7 to 10 days
  - Famciclovir: 500 mg orally three times daily for 7 to 10 days
  - Valacyclovir: 1000 mg orally twice daily for 7 to 10 days
- Recurrent infection
  - Topical 

  Acyclovir cream or ointment: applied 6 times a day for 7 days

  Penciclovir cream: applied every 2 hours while awake for 4 days
  - Oral 

  Acyclovir: 200 to 400 mg five times daily for 5 days

  Famciclovir: 750 mg twice daily for 1 day or 1500 mg as single dose

  Valacyclovir: 2 g twice a day for 1 day

Prevention of Recurrences

Lifestyle

- Avoid trauma to genital and oral mucosa.
- Use sun protection.
- Encourage 8 hours of sleep each night.

Nutrition

- Encourage seven to eight servings of fruits and vegetables a day.
- Increase lysine-rich foods (see Table 18-2). 
- Decrease arginine-rich foods (see Table 18-2). 
- Consider an elimination diet. 

Mind-Body Therapy

- Make lifestyle changes to reduce chronic stress, anxiety, and depression. Educate patients on techniques for relaxation such as breath work and meditation. Treat depression when present. 

Supplements

- Zinc
  - Topical: 0.05% solution before and during sun exposure at the site of previous HSV infection 
  - Oral: 25 mg twice a day (supplement with copper if long-term use) 
- Lysine: 1 g three times a day 

Botanicals

- Siberian ginseng (eleutheroside E 0.3% standardized extract): 400 mg a day (high doses and long-term use can lead to significant adverse effects) 

Pharmaceuticals

- Acyclovir: 400 mg orally twice daily
- Valacyclovir: 500 mg orally once a day 

KEY WEB RESOURCES

University of Maryland Medical Center. http://www.umm.edu/patiented/articles/what_herpes_simplex_000052_1.htm.

This Web site provides a comprehensive overview of herpes simplex. Treatment options are outlined for conventional therapy, as well as complementary and alternative approaches.

American Academy of Dermatology. http://www.aad.org/public/publications/pamphlets/viral_herpes_simplex.html.

This Web site provides educational information for both clinical and nonclinical readers.

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References are available at expertconsult.com.

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Chapter 19

Chronic Hepatitis

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Pathophysiology

Hepatitis is the Latin term for liver inflammation. It is characterized by hepatonecrosis and inflammatory cell infiltration. Viral and toxic agents are the most common causes of hepatitis. *Acute hepatitis* describes a process enduring less than 6 months. Hepatitis is deemed chronic when it is present for longer than 6 months. The ongoing inflammatory process may lead to fibrosis and eventually cirrhosis, with a concomitant increased risk of hepatocellular carcinoma.

Chronic hepatitis has various causes, in isolation or combination (Table 19-1). Most people with chronic hepatitis develop the disease gradually without an acute clinical illness or obvious symptoms. The condition is generally insidious and slowly progressive, declaring itself clinically only after cirrhosis develops with concomitant symptoms. Cases of chronic hepatitis diagnosed before the development of hepatic symptoms are often the result of incidental findings, especially unexpectedly elevated liver enzymes on routine biochemical panels.

The most common cause of chronic viral hepatitis in the United States is hepatitis C, accounting for approximately 50% to 75% of all cases.[1–3] Given its high prevalence and the associated implications for clinical practice, chronic hepatitis C (CHC) is the focus of this section. Integrative treatments aimed at controlling chronic hepatic inflammation and its sequelae, which underlie the pathologic process of CHC, are applicable to other conditions that share a similar pathophysiology.

The histologic hallmarks of hepatitis are hepatic necrosis and mononuclear infiltration (lymphocytes, macrophages, and plasma cells). These parameters are directly assessed with liver biopsy. Specimens are graded according to portal and lobular inflammatory activity and are staged based on the degree of fibrosis or the presence of cirrhosis. The hepatitis C virus (HCV) is hepatotropic but minimally cytopathic. A corollary of this observation is that HCV viral load does not affect the natural history of the disease in a given individual.[4,5] The detrimental effects of chronic HCV infection are predominantly a consequence of the associated chronic inflammatory process, which causes marked oxidative stress resulting from an overabundance of free radicals. In the presence of ongoing hepatonecrosis, connective tissue is laid down as the body attempts repair. An accumulation of extracellular connective tissue leads to fibrosis, which progresses predictably (Table 19-2). Cirrhosis is the final stage of the fibrotic process, characterized by diffuse hepatocyte damage, nodular regeneration, and aberrant architecture accompanied by impaired hepatocyte function and impeded portal blood flow.

Advanced fibrosis and cirrhosis are associated with increased risk for the development of hepatocellular carcinoma. Each year, 1% to 3% of people with HCV-related cirrhosis develop liver cancer.[6] The incidence of liver cancer in the United States tripled from 1975 to 2005, with the most significant increases occurring in black, white, and Hispanic men 50 to 59 years old.[7] Although 1-year, cause-specific survival for hepatocellular carcinoma increased from 25% to 47% from 1992 to 2004, more than half of all newly diagnosed patients succumb within the first 12 months after diagnosis.[7]

Liver biopsy remains the gold standard for making a histopathologic diagnosis of chronic hepatitis. Biochemical, serologic, and nucleic acid testing are the mainstays of etiologic diagnosis. Histologic information is particularly important for hepatitis C management decisions because fibrotic stage is often a key factor in such deliberations. Overall, approximately 5% to 25% of people with CHC develop cirrhosis over a period of 25 to 30 years.[8–10] Observational prospective studies and outcome modeling projections indicate that the risk of liver disease progression toward severe fibrosis or cirrhosis is minimal at 10 to 15 years in patients with persistently normal alanine aminotransferase (ALT) levels, approximately 5% to 10% in patients with elevated ALT and no fibrosis on initial liver biopsy, but greater than 30% to 40% in those with elevated ALT and portal fibrosis.[8,11]

A study of patients with newly diagnosed hepatitis C found that up to 20% of those patients with evidence of

TABLE 19-1. Common Causes of Chronic Hepatitis

ETIOLOGIC CATEGORY	SPECIFICS
Hepatitis viruses	Hepatitis C Hepatitis B (± hepatitis D)
Toxins and medications	Ethanol Methyldopa Isoniazid Nitrofurantoin Amiodarone
Autoimmune disease	Autoimmune hepatitis
Inborn metabolic disorders	Wilson disease Hemochromatosis Alpha$_1$-antitrypsin deficiency
Acquired metabolic disorders	Nonalcoholic steatohepatitis
Biliary diseases	Primary and secondary biliary cirrhosis Primary sclerosing cholangitis Biliary tree anomalies
Cryptogenic	—

TABLE 19-2. Stages of Liver Fibrosis

STAGE	CHARACTERISTICS
0	No fibrosis
1	Confined to enlarged portal zones
3	Architectural distortion (septal fibrosis, bridging) without obvious cirrhosis
4	Probable or definite cirrhosis

cirrhosis on liver biopsy were not suspected of having cirrhosis, based on clinical and laboratory findings.[12] Liver enzyme levels do not predictably correlate with liver histologic features. A 2006 study of 480 patients with CHC who had persistently normal ALT levels found that nearly two thirds of patients had evidence of portal fibrosis on liver biopsy, and roughly 1 in 10 patients had bridging fibrosis.[13] Laboratory panels that include multiple biologic markers of hepatic fibrosis, such as platelet count, hyaluronic acid, procollagen type 3 N-terminal peptide, and tissue inhibitor of matrix metalloproteinase-1, perform relatively well in predicting the presence or absence of advanced fibrosis or cirrhosis among patients with CHC who have no physical or other laboratory evidence of cirrhosis. These tests lack sensitivity and specificity with midrange fibrosis, however, and therefore cannot be used to track fibrosis progression.[6,14,15]

Although patients with clinical or laboratory evidence of frank cirrhosis can have an accurate diagnosis without liver biopsy, the reverse logic is untrue (i.e., cirrhosis cannot be ruled out based on clinical and laboratory assessments alone). In the absence of clinical evidence of cirrhosis, the only way to assess a patient's liver histologic features with a high degree of certainty is with liver biopsy. Histologic features other than fibrotic stage (e.g., steatosis and iron accumulation) may also have predictive value for disease progression and response to interferon-based regimens.[16,17] Nonhistologic factors associated with accelerated disease progression and poor outcomes are shown in Table 19-3. Notably absent from this list are HCV genotype and viral load, factors that do not predict disease progression. Both these factors, however, correlate with the probability of response to interferon-based therapy.

TABLE 19-3. Nonhistologic Factors Associated With Increased Risk of Development of Cirrhosis Among People With Chronic Hepatitis C

- Genotypic male
- Heavy alcohol consumption
- Coinfection with human immunodeficiency virus and/or hepatitis B virus
- Elevated serum alanine aminotransferase[160]
- Obesity[6]
- Age older than 35 yr at the time of initial infection

Reducing Free Radicals

The primary care provider has an important role in promoting constitutional, hepatic, and immunologic health and wellness. The interplay of host and virologic factors that potentially influence CHC disease progression and may be affected by integrative interventions falls into two primary arenas: oxidative stress and immunologic function.[18–30] Chronic inflammation leads to an overabundance of oxygen-derived free radicals. The influence of free radicals in a given inflammatory reaction depends on the balance between the production and inactivation of these reactive metabolites.[18] To the extent that one can influence the balance favorably toward decreased oxidative stress, one can potentially limit or reduce damage caused by an overabundance of free radicals.

Enhancing Liver Detoxification

When considering therapy for chronic hepatitis, the practitioner should keep in mind the liver's detoxification function. The liver is the interface between the digestive tract and the rest of the body, and it orchestrates metabolic homeostasis. Blood delivered from the digestive tract is filtered and processed by the liver. Endogenous waste products and pollutant xenobiotics are detoxified and excreted into the bile. A two-phase detoxification process neutralizes and eliminates these chemicals. For optimal function of the hepatic detoxification system, the phases must be balanced and supported by adequate dietary intake to provide the necessary system elements. Phase I of the detoxification pathway is chemical neutralization, which is accomplished predominantly by the cytochrome P-450 system. This system is a versatile family of heme-derived enzymes that catalyze redox reactions on a wide variety of endogenous and exogenous substrates. When a chemical is neutralized by cytochrome P-450 enzymes, free radicals are produced, which can damage hepatocytes. Free radicals are removed by antioxidants in the liver; one of the most important is glutathione, which is also used in phase II of the detoxification process. High-level toxin exposure can deplete hepatic glutathione and thus hamper both phases of the detoxification process.

TABLE 19-4. Substances That Support Phase II Detoxification

DETOXIFICATION PATHWAY	REQUIRED NUTRIENTS
Glutathione conjugation	Dietary glutathione Vitamins B_2, B_6, and C *N*-Acetylcysteine Glycine, cysteine, glutamine, and methionine Zinc, copper, manganese, and selenium
Amino acid conjugation	Glycine, taurine, glutamine, arginine, and ornithine Magnesium
Methylation	*S*-Adenosylmethionine Vitamin B_{12} and folic acid Choline Molybdenum
Sulfation	Dietary sulfur-rich foods B vitamins Taurine, methionine, cysteine, and glutathione Zinc, copper, manganese, selenium, and molybdenum
Acetylation	Vitamins B_1, B_2, B_5 (pantothenic acid), and C Acetyl coenzyme A
Glucuronidation	Glucuronic acid and glutamine Magnesium Vitamins B_3 and B_6

Phase II of the detoxification process is elimination, which typically involves a conjugation reaction that renders the toxin water soluble and enables excretion of the toxin complex through bile or urine. The six phase II detoxification pathways are glutathione conjugation, amino acid conjugation, methylation, sulfation, acetylation, and glucuronidation.[31] Many experts consider glutathione conjugation to be the most important of these pathways. In summary, glutathione serves as both a potent antioxidant and an essential substrate for phase II detoxification. Table 19-4 lists substances needed to support the phase II detoxification pathways (see Chapter 104, Detoxification).

Patients with chronic hepatitis should be vaccinated against hepatitis A and B to decrease the risk of superinfection and acute fulminant hepatitis.

Integrative Therapy

The choice of therapeutic modalities used in an integrative approach to CHC management depends on numerous factors, including the patient's liver status, goals, and comorbid conditions. Regardless of the specific modalities chosen, the fundamental goals of integrative CHC management are to:

1. Decrease hepatic inflammation and thereby limit disease progression
2. Support and enhance hepatic detoxification capacity
3. Support healthy immune function
4. Decrease the risk of cirrhosis and hepatocellular carcinoma
5. Support and enhance quality of life

Pharmaceuticals

The National Institutes of Health Consensus Conference Statement on the Management of Hepatitis C[32] states that all patients with CHC are potential candidates for antiviral therapy. Current pharmacologic, state-of-the-art treatment for CHC is combination therapy with pegylated interferon alfa (peginterferon) and ribavirin. The American Association for the Study of Liver Diseases Practice Guideline on the Diagnosis, Management, and Treatment of Hepatitis C[6] recommends combination therapy for patients with bridging fibrosis or compensated cirrhosis on liver biopsy. The relative and absolute contraindications to interferon-based therapy are numerous, however, and include ongoing alcohol dependence, hepatic decompensation, and certain comorbid medical and neuropsychiatric conditions. Thus, many patients with CHC are ineligible for interferon-based treatment or fall outside this histologically defined group. Additionally, the side effect profiles of peginterferon and ribavirin are such that many patients decline or postpone aggressive pharmacologic therapy.

Deciding which patients should consider therapy with peginterferon plus ribavirin must be done on a case-by-case basis. Paradoxically, evidence indicates that patients with low-stage fibrosis are more likely to clear HCV in response to combination therapy compared with patients with advanced fibrosis or cirrhosis. Yet these are the same patients in whom the risk of progression to cirrhosis is lowest. Table 19-5 summarizes factors predictive of response to interferon-based therapy for CHC.

A challenge in pharmaceutical treatment is that patients who are most likely to respond to therapy are also least likely to progress to cirrhosis.

The decision to start therapy requires consideration of the patient's goals, liver status and likelihood of disease progression, comorbidities, and potential risks and benefits. Watchful waiting with supportive management, including periodic liver biopsy (every 4 to 5 years), is considered both safe and prudent for patients with minimal fibrosis on initial liver biopsy. At the other extreme, patients with decompensated hepatic cirrhosis are ineligible for interferon-based therapy and should be referred for liver transplant evaluation.

CHC is a highly variable disease. Although certain factors can be used to predict the most likely natural history of the disease, the clinical course in a given individual is inherently unpredictable. Accordingly, no clear consensus exists among gastroenterologists and hepatologists regarding absolute criteria for deciding which patients should be treated with interferon-based therapy. The challenge is to identify those patients for whom the formidable undertaking of interferon-based therapy is most likely to prove holistically healing. An overly aggressive or inappropriately passive approach can prove detrimental to a patient, depending on his or her circumstances.

TABLE 19-5. Factors Predictive of Viral Response to Interferon-Based Therapy for Hepatitis C Virus

FACTOR	ASSOCIATION WITH VIRAL RESPONSE
HCV genotype	Genotypes 2 and 3 significantly more responsive to peginterferon alfa plus ribavirin than genotypes 1 and 4*
HCV viral load	Probability of a viral response reduced by high pretreatment viral load (600,000 units/mL or more)[43]
Liver fibrosis stage	Fibrosis stage on liver biopsy inversely predictive of the likelihood of viral response; absence of bridging fibrosis or cirrhosis significantly positively predictive
Ethnicity	People of European or Asian ethnicity more likely to experience a viral response than are those of African or Hispanic ethnicity
Hepatic steatosis	Likelihood of a viral response adversely affected by the presence and severity of steatosis
Body mass index	Likelihood of a viral response negatively influenced by elevated body mass index
Insulin resistance	Probability of a viral response possibly reduced by insulin resistance
Age (among adults)	Overall, age inversely related to likelihood of a viral response

HCV, hepatitis C virus.
*In a study of more than 6000 patients with chronic hepatitis C in the United States, the genotype distribution was 73% genotype 1, 14% genotype 2, 8% genotype 3, 4% mixed genotype, and less than 1% for genotypes 4, 5, and 6.[162]
HCV genotype and viral load have predictive value with respect to the likelihood of response to interferon-based therapy. However, these factors are not predictive of liver fibrosis or disease progression.

Peginterferon Alfa

Interferons are a family of potent cytokines produced in response to viral infection and various other stimuli. Interferons are associated with complex antiviral, immunomodulatory, and antiproliferative actions. Interferon-stimulated genes inhibit viral replication and cell proliferation. Pegylation technology links interferon to the inactive, water-soluble polymer polyethylene glycol, which shields the molecules from proteolytic enzymes and prolongs the half-life of the drug. Two peginterferons have been approved by the U.S. Food and Drug Administration for the treatment of CHC: peginterferon alfa-2a (Pegasys) and peginterferon alfa-2b (Peg-Intron).

Dosage

Peginterferon alfa-2a dosing, in combination with ribavirin, for the treatment of CHC is 180 mcg/week subcutaneously. The recommended dose of peginterferon alfa-2b, administered in combination with ribavirin, is 1.5 mcg/kg/week subcutaneously.

Precautions

The most common side effects of peginterferons are flulike symptoms such as fatigue, lethargy, myalgia, and headache. Other potentially serious side effects include depression, anxiety, suicidal ideation, hypothyroidism, bone marrow suppression, and anorexia.

Ribavirin

Ribavirin is a guanosine analogue that has shown activity against a variety of RNA and DNA viruses in vitro and in vivo. Ribavirin alone has little in vivo effect against HCV. The combination of peginterferon alfa and ribavirin, however, has been definitively shown to lead to superior, durable response rates compared with monotherapy with either agent.[33,34] Four companies in the United States market ribavirin, which is administered orally twice daily.

Dosage

The dosage recommendation for ribavirin in combination with pegylated interferon depends on body weight, genotype, and whether peginterferon alfa-2a or alfa-2b is used. For HCV genotypes 1 and 4, the recommended dose of peginterferon alfa-2a is 1000 mg/day orally in two divided doses for patients weighing 75 kg or less and 1200 mg/day for those weighing more than 75 kg. If using peginterferon alfa-2b, the recommended dose of ribavirin is 800 mg/day for patients weighing less than 65 kg, 1000 mg/day for those weighing 65 to 85 kg, 1200 mg/day for those weighing 85 kg to 105 kg, and 1400 mg/day for patients weighing more than 105 kg. For HCV genotypes 2 and 3, the recommended dose of ribavirin with peginterferon alfa-2a or alfa-2b is 800 mg/day orally in two divided doses, regardless of body weight.

Precautions

Ribavirin is associated with two serious side effects: hemolytic anemia and birth defects. Other side effects of ribavirin include cough, dyspnea, insomnia, pruritus, rash, and anorexia.

Peginterferon plus Ribavirin Treatment and Response

The duration of combination peginterferon-based therapy for HCV varies by genotype. The standard duration of treatment is 48 weeks for HCV genotypes 1 and 4, and 24 weeks for genotypes 2 and 3.[6] Monitoring of HCV viral load after the initiation of therapy determines virologic response and may influence the duration of therapy. Early virologic response (EVR), a 100-fold or greater reduction in HCV viral load after the first 12 weeks of treatment, is predictive of sustained virologic response (SVR),[35,36] defined as undetectable HCV RNA 6 months after completion of therapy. In the absence of EVR, it is highly unlikely that continued antiviral treatment will successfully clear HCV. Treatment discontinuation is recommended in the absence of EVR.[6,33,37]

Rapid virologic response (RVR), defined as undetectable HCV using a molecular assay with a lower detection limit of 50 units/mL at week 4 of therapy, is highly predictive of SVR.[38,39] Among patients with RVR and difficulty tolerating treatment, consideration may be given to shortening the duration of therapy to 24 weeks for patients with HCV genotype 1, and to 12 to 16 weeks for those with genotypes 2 and 3, respectively.[39–42] Early discontinuation of treatment, however, increases the risk of relapse on completion of therapy.

SVR rates vary by HCV genotype. Approximately 80% of people with genotypes 2 and 3 who receive peginterferon plus ribavirin achieve SVR compared with roughly 50% of people with genotype 1.[33,37,43,44] Results of studies evaluating the long-term durability of SVR indicate that late relapse is rare and liver histology typically improves with time.[45,46] Among patients with marked pretreatment hepatic fibrosis, a low level of risk for the development of hepatocellular carcinoma persists, especially among those with preexisting cirrhosis.

Hepatitis C genotypes 1 and 4 are associated with the poorest response to therapy.

Hepatitis A and B Vaccination

Anyone with documented chronic hepatitis who was not previously immunized and is without serologic evidence of immunity should be vaccinated for both hepatitis A and hepatitis B. Superinfection with a second hepatitis virus in a patient already chronically infected with another of the hepatitis viruses may cause acute fulminant disease. In the absence of an acute fulminant episode, new infection superimposed on preexisting chronic liver disease may accelerate disease progression and negatively affect prognosis.

Supplements

Glutathione

Glutathione is a potent antioxidant with many crucial functions, including detoxification and cytotoxic T lymphocyte (CTL) activation.[47] Most glutathione in the body is produced intracellularly in the liver from the amino acids cysteine, glutamate, and glycine. Glutathione levels are frequently below normal in people with alcoholic hepatitis and CHC.[48–50] One study found that patients with CHC who had the lowest glutathione levels had the highest viral loads and greater degrees of liver damage, compared with patients with the highest glutathione levels.[50]

The absorption of intact glutathione from dietary sources appears to be limited; glutathione is hydrolyzed by intestinal gamma-glutamyl transferase (GGT). Similarly, a study of oral glutathione supplementation found no increase in circulating levels.[51] Optimal glutathione levels are achieved by consuming a diet rich in foods with high levels of sulfur-containing amino acids (e.g., asparagus, avocados, broccoli, spinach, garlic, and unprocessed meats) and may be enhanced by nutritional supplements that promote glutathione production, such as vitamins C and E, *N*-acetylcysteine (NAC), selenium, silymarin, and curcumin.

Glutathione is not absorbed well when taken orally. The best way to increase glutathione levels is to eat sulfur-containing foods (asparagus, avocados, broccoli, spinach, garlic) and supplement with nutrients that enhance production, including vitamin C, vitamin E, *N*-acetylcysteine, selenium, silymarin, and curcumin.

Vitamin C

Vitamin C is a powerful antioxidant and antiinflammatory agent, functions that may help limit the chronic inflammation and oxidative stress associated with CHC. In a 2008 study, investigators noted an inverse relationship between plasma vitamin C levels and aspartate aminotransferase (AST) among patients with CHC.[52] Evidence indicates that vitamin C also has in vivo immunomodulatory and anticarcinogenic functions. Finally, vitamin C has been found to preserve intracellular reduced glutathione concentrations and improve overall antioxidant protection capacity.[53]

Dosage

Vitamin C 200 to 250 mg twice daily (recommendations vary widely). The Institute of Medicine of the National Academies notes that the tolerable upper intake limit (UL) for vitamin C is 2000 mg/day.[54]

Precautions

Vitamin C modulates iron absorption and transport. High doses of vitamin C should be avoided by persons with hemochromatosis or other conditions with the potential for iron overload. High doses of vitamin C are also contraindicated in patients with a history of kidney stones or renal insufficiency. Excessive doses of vitamin C may result in bloating and diarrhea.

Vitamin E

Vitamin E is a fat-soluble antioxidant that also supports optimal glutathione levels. Research data on vitamin E in the setting of chronic hepatitis are mixed. A small study of patients with CHC found that nearly half of the participants taking 800 units daily experienced improvement of liver enzyme levels.[55] A separate study in which CHC patients took 945 units of vitamin E, 200 mcg of selenium, and 500 mg of vitamin C daily found no effect on serum ALT, HCV viral load, or oxidative markers after 6 months of treatment.[56] Some data indicate that vitamin E may have a role in interruption of the fibrotic process.[57,58]

Dosage

Dose is 400 International Units (IU)/day of d-alpha tocopherol.

Precautions

High doses of vitamin E may potentiate the effects of antithrombotic drugs (including aspirin), anticoagulants, and some herbs (e.g., garlic and ginkgo). Patients with vitamin K deficiencies (e.g., liver failure) should avoid high doses of vitamin E. The recommended UL for vitamin E is 1500 IU/day.

N-*Acetylcysteine*

NAC is a derivative of the amino acid L-cysteine. It is a reducing agent and an antioxidant. NAC is more stable than L-cysteine and may be better absorbed. Acetylcysteine (Mucomyst)

is used therapeutically as an inhaled mucolytic and an oral antidote for acetaminophen poisoning. By increasing hepatic glutathione levels, NAC counters the marked depletion that characterizes acetaminophen poisoning. NAC is available over the counter as a dietary supplement, which is rapidly absorbed. It is a precursor in glutathione production and has been found to raise serum levels, although not as effectively as vitamin C.[59] Long-term safety of this product in otherwise healthy people is yet to be proved. One study found that doses greater than 1.2 g/day may have prooxidant effects.[60] The findings of studies examining the effects of NAC in people with CHC are conflicting; some studies show no benefit, and others report normalization of liver enzyme levels.[61–64] In animal models, NAC was found to relieve oxidative stress and dampen the hepatic inflammatory response associated with nonalcoholic steatohepatitis.[65,66] Because of the unestablished safety profile of NAC and because of its cost, support for optimal glutathione levels are best achieved using other supplements, such as vitamins C and E, silymarin, and selenium.

Dosage
NAC 800 mg/day

Precautions
Doses of NAC greater than 1.2 g/day may have prooxidant effects. Reported adverse reactions after oral administration include nausea, vomiting, diarrhea, headache, and rash. Renal stone formation has been reported, albeit rarely; patients taking NAC should be encouraged to drink six to eight glasses of water daily. Gastrointestinal symptoms may be reduced by taking NAC with meals.

Selenium
Selenium is an essential micronutrient. Selenium enters the food chain through incorporation into plant proteins; the concentration present in plant matter is a function of the selenium content of the soil. In the United States, the Eastern Coastal Plain and the Pacific Northwest have the lowest soil selenium concentrations. Selenium has antioxidant activity by virtue of its role in the formation and function of selenium-dependent glutathione peroxidases. It may also have antiinflammatory, immunomodulatory, anticarcinogenic, and detoxification actions in the body. Selenium deficiency appears to be linked to humoral immune suppression. Low immunoglobulin G (IgG) and IgM titers have been reported in association with selenium deficiency; antibody titers have been found to increase with selenium supplementation.[67] Although its role has not been fully elucidated, selenium also appears to be essential for healthy cell-mediated immunity.

In one study, selenium levels were found to be significantly reduced among people with hepatitis C. Patients with CHC who did not have cirrhosis had selenium levels 20% lower than normal, and those patients with cirrhosis had levels 40% lower than normal.[68] Once cirrhosis develops, the degree of serum selenium deficit does not reliably predict disease severity.[69] Patients with chronic hepatitis may benefit from the observed anticarcinogenic effects of selenium supplementation. A large study examining selenium levels in 7342 men with chronic hepatitis B or C and the development of hepatocellular carcinoma found selenium levels were lowest in the men with CHC. Participants with the highest selenium levels were 38% less likely to develop hepatocellular carcinoma than were participants with the lowest selenium levels.[70] Another large-scale study of more than 130,000 people in China found a similar protective effect.[71]

Dosage
The dose is 200 mcg/day in the form of high-selenium yeast or L-selenomethionine.

Precautions
At doses of less than 900 mcg/day, adverse reactions are uncommon. The most frequently reported symptoms associated with acute or chronic selenium toxicity (selenosis) include hair and nail brittleness and loss, rash, fatigue, irritability, nausea, and vomiting. High doses of selenium can decrease gastrointestinal absorption of vitamin C.[72]

S-Adenosylmethionine
S-Adenosylmethionine (SAMe) is a metabolite of the essential amino acid L-methionine. In Europe, SAMe is used medicinally for the treatment of depression, liver disorders, osteoarthritis, and fibromyalgia. It is available over the counter in the United States. SAMe is found in virtually all body tissues. It has a crucial biochemical role, by donating a methyl group in transmethylation reactions. Methylation is one of the key pathways in phase II of the hepatic detoxification system. Transmethylation is also essential in the biosynthesis of DNA, RNA, phospholipids, proteins, epinephrine, melatonin, creatine, and other essential molecules.

The hepatoprotective effects of SAMe are relatively well established. A placebo-controlled, 2-year study of patients with alcoholic cirrhosis found that 1200 mg/day significantly improved survival and delayed the need for liver transplantation.[73] A laboratory model of hepatocellular carcinoma found that SAMe had opposing hepatoprotective effects on normal hepatocytes and proapoptotic effects on hepatoma cells.[74] Clinical trials are under way to determine the possible therapeutic role of SAMe for CHC and for the prevention of hepatocellular carcinoma among patients with cirrhosis. In an open-label pilot study of 29 patients with CHC who had not responded to previous interferon-based combination therapy, coadministration of SAMe and betaine along with peginterferon alfa-2b and ribavirin improved EVR compared with combination therapy alone. SVR, however, was achieved in only 10% of patients receiving the experimental protocol.[75] Studies among patients with chronic viral hepatitis and other chronic liver conditions have found that SAMe helps alleviate symptoms such as itching, jaundice, and fatigue and reduces liver enzymes and bilirubin levels.[76,77]

Depression is a common problem in patients with CHC. SAMe has been used for more than 3 decades in Europe for the treatment of depression. A literature review concluded that the proof of concept is solid, but additional study data are needed before SAMe can be confidently recommended as first-line or adjuvant therapy for depression.[78]

SAMe is expensive and easily oxidized, thus making it an impractical supplement for many patients. In addition, small trials suggested that the oral bioavailability of SAMe may be low. Some clinicians recommend a combination of methionine, trimethylglycine, vitamin B_{12}, and folic acid to support the body's ability to synthesize endogenous SAMe. The high cost of SAMe, its relative chemical instability, and lack of conclusive data to support its use in chronic viral hepatitis

preclude recommendation for regular use. In patients with alcohol-related liver disease (alone or in combination with other etiologic factors), however, SAMe supplementation may be advisable.

Dosage
For liver disease, the dose is typically 800 mg twice daily on an empty stomach. Because of its instability with oxidation, SAMe should be individually wrapped in blister packs.

Precautions
Mild gastrointestinal upset, anxiety, hyperactive muscle movement, and insomnia have been reported as side effects of SAMe use. Patients with depression and bipolar disorder should be closely monitored while taking SAMe.

Alpha-Lipoic Acid
Alpha-lipoic acid (ALA) is a fatty acid antioxidant. It is a key metabolite in mitochondrial energy production and acts as a potent free radical scavenger in both aqueous and lipophilic environments. ALA is used as a drug in many European countries, primarily to treat liver disorders and neuropathy. ALA's effect of raising cellular glutathione levels is thought to be important in CHC because patients may suffer from a relative glutathione deficiency.[79,80] ALA also helps recycle and regenerate other antioxidants, including vitamins E and C.[81] Animal models indicate that ALA may impede fibrosis progression associated with chronic hepatitis by reducing the production of reactive oxygen species.[82,83]

ALA is costly and has not been well studied in clinical trials among people with chronic viral hepatitis. Therefore, routine use is not recommended. In patients with unexplained spikes in liver enzymes, however, ALA may be advisable to reduce oxidative stress.

Dosage
ALA 500 to 600 mg/day

Precautions
No side effects have been reported at doses of up to 1000 mg/day.

Glutamine
Glutamine is a conditionally essential amino acid and is the most abundant amino acid in the body. Although the body normally synthesizes adequate amounts of glutamine, endogenous production may be inadequate during periods of metabolic stress. Glutamine is crucial to many metabolic functions, including protein and glutathione synthesis, energy production, acid-base balance, maintenance of optimal antioxidant status, intestinal integrity, immune function, gluconeogenesis, nitrogen transport, and neurotransmitter, nucleotide, and nucleic acid synthesis. Glutamine has been shown to regulate the expression of several genes and to activate several proteins.[84] l-Glutamine is an immunonutrient and is the preferred substrate for energy production in enterocytes and lymphocytes. One study noted that glutamine influences the production of some T-cell–derived cytokines and is thereby important for optimal lymphocyte proliferation.[85] Notably, lymphocytes are unable to produce glutamine. Glutamine deficiency can result in inadequate production of glutathione. If glutamine stores are depleted by ongoing immune system demands, glutathione production will be inadequate. With its many functions, glutamine is an important nutritional supplement when any question exists that metabolic stress may render endogenous synthesis inadequate.

Dosage
Glutamine 2 to 4 g/day during periods of metabolic stress or poor dietary intake. The supplement should be taken between meals.

Precautions
Glutamine supplementation should be approached with caution in patients with hepatic or renal insufficiency.[86]

Zinc
Zinc is an essential nutritional element. It has many important biochemical roles in the body, including acting as an essential cofactor in healthy immunologic function and supporting antioxidant systems. A small, randomized trial of polar zinc supplementation among patients with CHC who were undergoing therapy with peginterferon alfa-2b plus ribavirin found significantly lower ALT levels at 12 weeks among the intervention group.[87] The investigators postulated that the observed effect possibly resulted from enhanced antioxidant activity fueled by the supplemental zinc. Although zinc deficiency is relatively uncommon in developed countries, it may come into play in patients with poor nutritional intake. Routine zinc supplementation is unnecessary for many patients with CHC but should be considered in patients who may be nutritionally deprived because of disease-related symptoms.

Dosage
Zinc 15 mg/day. The recommended UL for zinc is 40 mg/day.

Precautions
Long-term ingestion of high doses of zinc may deplete copper stores, interfere with iron function, and lead to microcytic anemia. Ingestion of large amounts of zinc (more than 30 mg/day) may cause acute toxicity with nausea, vomiting, diarrhea, anorexia, abdominal cramps, a metallic taste, headache, and drowsiness.

Iron
Patients should avoid iron overload. Increased hepatic iron stores (primarily associated with common heterozygous hemochromatosis mutations) are associated with higher grades of inflammation and more severe hepatic fibrosis in patients with CHC, compared with patients without iron overload.[88,89] Patients with reduced iron levels who were treated with interferon had an improved response, as measured by reduction in serum ALT.[90] Iron supplements should be avoided among patients with CHC except in cases of documented deficiency. Iron-binding supplements may be beneficial in patients with increased serum iron.

Botanicals

Milk Thistle (Silybum marianum)
The use of milk thistle for liver disease dates back to the Roman Empire, when this plant was mixed with honey and used for "carrying off bile." Much remains undiscovered

about milk thistle (silymarin), but research has uncovered several mechanisms by which milk thistle may benefit patients with chronic liver disease.

In laboratory models, silymarin has been shown to protect hepatocytes from toxins by stabilizing the cell membrane against free radical attack.[91] A clinical example of this therapeutic use of silymarin is its use in death cap mushroom *(Amanita phalloides)* poisoning. The amatoxins in the mushrooms are taken up by hepatocytes and interfere with messenger RNA and protein synthesis, typically leading to acute fulminant hepatitis. Pooled data from case record studies involving 452 patients with *A. phalloides* poisoning show a highly significant difference in mortality in favor of silybin (the primary isomer contained in silymarin).[92] Investigators believe that silibin binds to the hepatocyte cell membrane and thus prevents toxin penetration. Milk thistle has been found to protect against other toxins, including pesticides, drugs, and halogenated cyclic hydrocarbons.[93]

Silymarin is a potent antioxidant. It was reported to raise liver and intestine glutathione levels by 50% in animal studies[94] and to increase the levels of the antioxidant enzymes superoxide dismutase, glutathione peroxidase, and catalase in a separate animal model.[95] Silymarin also has antifibrotic properties. Among silymarin users in the Hepatitis C Antiviral Long-Term Treatment against Cirrhosis (HALT-C) trial, researchers found reduced fibrosis progression but no significant difference in clinical outcome, compared with nonusers.[96] A randomized double-blind 12-month trial of 177 patients with CHC, however, found that although patients taking silymarin supplementation reported improved symptoms and general well-being, no effect was noted on HCV viremia, serum ALT, or serum and ultrasound markers for hepatic fibrosis.[97] Combination treatments with milk thistle as a principal component are being evaluated. In a small study of patients with CHC who were treated with a 3-month course of a concoction of silibin phospholipids and vitamin E, researchers found a significant reduction in aminotransferase levels.[98] Other clinical studies of the effects of silymarin on chronic liver disease have yielded mixed results.[99–101] A 2005 Cochrane Review of 13 randomized trials examining milk thistle concluded that "our results question the beneficial effect of milk thistle for patients with alcoholic and/or hepatitis B or C virus liver diseases and highlight the lack of high-quality evidence to support this intervention."[102]

In summary, research data indicate that many actions of silymarin may theoretically be beneficial to patients with chronic hepatitis. The clinical data to support this supposition, however, are lacking with regard to chronic viral hepatitis. Given that milk thistle has no known serious adverse effects, many clinicians believe that the potential for benefit justifies the recommendation to use this herbal supplement, despite the lack of robust clinical evidence to support this recommendation.

Dosage

Milk thistle 300 mg three times a day or 210 mg of silymarin three times daily. The standard dose of milk thistle is based on the silymarin content, which is 70% of the bulk herb (300 mg of milk thistle = 210 mg of silymarin). Silymarin-phosphatidylcholine is absorbed more effectively than regular standardized milk thistle and requires less frequent dosing (240 mg twice daily for active treatment). Alcohol extracts should be avoided in patients with hepatitis.

Precautions

Side effects of milk thistle are rare. Reported adverse reactions include stomach pain, nausea, vomiting, diarrhea, headache, rash or other skin reactions, and joint pain. Allergic reactions may occur in patients with hypersensitivity to ragweed or plants in the daisy family.

The potential for interaction between silymarin and peginterferon plus ribavirin has not been thoroughly studied in clinical trials. Some clinicians advise patients to stop taking milk thistle while they are treated with interferon-based therapy to eliminate the possibility of unknown herb-drug interactions.

Licorice Root (Glycyrrhiza glabra)

The licorice plant has been used medicinally since the Scythians introduced it to the ancient Greeks; it has been used in Europe since the Middle Ages. Licorice root preparations have been an accepted treatment for hepatitis in Japan since the 1960s. Glycyrrhizin (an aqueous extract of licorice root) acts primarily as an antiinflammatory and cytoprotective agent; it does not have antiviral properties.[103] Most clinical studies showing benefit have used a form of intravenous glycyrrhizin called Stronger Neo-Minophagen C (SNMC: 0.2% glycyrrhizin, 0.1% cysteine, and 2% glycine). In a multicenter double-blind trial conducted in Japan, investigators found that long-term daily treatment with SNMC among patients with viral hepatitis led to a significantly reduced incidence of cirrhosis and hepatocellular carcinoma.[104] A review article published in 2005 noted that SNMC "improves mortality in patients with subacute liver failure, and improves liver functions in patients with subacute hepatic failure, chronic hepatitis, and cirrhosis with activity. SNMC does not reduce mortality among patients with cirrhosis with activity."[103] A Cochrane Review of medicinal herbs for HCV infection concluded that glycyrrhizin did not demonstrate significant beneficial effects.[105]

The clinician is faced with a decision whether to recommend licorice root for patients with chronic hepatitis. Although promising animal model data and years of experience support its use, clinical data showing efficacy are scant. An open discussion with each patient is advised wherein the clinician presents the information available and helps the patient make an individualized treatment decision.

Dosage

Oral forms of licorice root are available over the counter in the United States. The recommended dosage depends on the form taken: 250 to 500 mg three times a day of the solid dry powder; 1 to 2 g three times a day of the powdered root; or 2 to 4 mL three times a day of the fluid extract.

Precautions

High doses of glycyrrhizin can lead to an aldosterone effect with potassium loss, water retention, and hypertension. Use can potentiate the effects of diuretics, certain cardiac medications (e.g., digitalis), and corticosteroids. Glycyrrhizin should be used with caution in people with hypertension, ascites, renal insufficiency, or cardiac insufficiency. A diet high in potassium-rich foods is recommended for patients taking a licorice root preparation. Blood pressure and potassium levels should be monitored regularly.

Schisandra (Schisandra chinensis)

Schisandra has been used in China for more than 1000 years to treat liver disorders and other maladies. The medicinal substances are derived from the fruit of the plant and include schisandrine A, B, and C and several gomisins. Schisandra is a potent free radical scavenger, a characteristic that may explain the hepatoprotective effects observed with this botanical. Gomisin A, an active ingredient in schisandra, has been found to promote hepatocyte growth factor, limit lipid peroxidation, and inhibit apoptosis in acute hepatic injury animal models.[106,107] Gomisin A also acts as an anti-inflammatory by preventing the release of arachidonic acid in macrophages in vitro.[108] Laboratory evidence suggests that gomisin A may have anticarcinogenic effects.[109,110] Published clinical trial data examining the use of schisandra in patients with chronic hepatitis are lacking.

Dosage

Schisandra extract 100 mg twice daily.

Precautions

Schisandra lignans have been reported to induce phase I drug metabolism[111] and competitively inhibit the methylation pathway of phase II detoxification in animal models.[112] Caution should be used if medications metabolized by the cytochrome P-450 system are given with schisandra. Side effects are uncommon and include dyspepsia, anorexia, and urticaria.

Astragalus (Astragalus membranaceus)

Astragalus is an important herb used in Chinese medicine for its effects on the immune system. In vitro studies found that astragalus promotes B-cell proliferation and antibody production and enhances CTL activity.[113] It also acts as a potent antioxidant by increasing superoxide dismutase and decreasing lipid peroxide activity. Astragalus was reported to have protective effects against toxins in animal models.[114] Astragalus injection solution has an inhibitory effect on experimental hepatic fibrogenesis, possibly because of its antioxidant properties.[115] A small trial among patients with chronic hepatitis B found that astragalus supplementation was associated with decreased serum fibrosis markers and liver enzymes.[116] A meta-analysis that included clinical trials from the English and Chinese literature concluded that astragalus and certain other traditional Chinese botanicals may have activity against hepatocellular carcinoma.[117] Whether these agents may have a chemoprotective role for patients with chronic viral hepatitis who are at risk for hepatocellular carcinoma remains a matter of conjecture.

Dosage

Astragalus powder 4 to 7 g daily (most commonly used in combination with other herbs)

Precautions

Doses greater than 28 g/day may cause immune suppression. Because of its immunostimulatory effects, astragalus should be avoided in patients receiving immunosuppressive therapy and in those with autoimmune disease. Astragalus may contain selenium; ingestion of large amounts over time may lead to selenosis. Astragalus may potentiate the effects of antithrombotic and anticoagulant medications. Side effects of this herb are uncommon.

Herbal Concoctions and Traditional Chinese Medicine

China has a high prevalence of chronic viral hepatitis. Traditional Chinese medicine (TCM) has long described healing remedies for chronic liver maladies. Since the cultural revolution of the 1950s, an integrative form of medicine has been used in China that combines the tenets of both TCM and modern pathophysiology and phytopharmacology.

Chinese medicine relies on individualized constitutional diagnosis and treatment in parallel with biochemical, histologic, and radiologic diagnostic methods. Because constitutional diagnostic methods are used in formulating a treatment plan, individualized herbal concoctions containing several botanicals, each prescribed to address a specific imbalance, are commonly used. Herbal concoctions for chronic hepatitis are likely to include varying doses and combinations of the botanicals discussed earlier in addition to others. Herbal concoction prescriptions are altered according to a patient's changing signs and symptoms. A referral to a qualified TCM practitioner with experience in treating chronic hepatitis may be beneficial for patients who opt to forego interferon-based therapy.

Mind-Body Therapies

Research is beginning to catch up with clinical experience regarding the negative effects of psychosocial stress on health, including liver health. Elucidating the exact mechanisms by which the mind and body interact in the spectrum of health and disease is an arena of active research and an area of healing that has only recently been appreciated from a pathophysiologic perspective.

Two classes of compounds studied in relation to stress and disease are glucocorticoids and catecholamines. Stress activates the hypothalamic-pituitary-adrenal axis and leads to increased glucocorticoid secretion. The sympathetic nervous system is similarly activated by stress, which increases levels of catecholamines.[118] Both groups of substances cause specific cytokine responses that influence the inflammatory response.

A small study in Japan found an association between chronic psychosocial stress related to type 1 personality and increasing hepatitis C severity.[119] Stress has been shown to induce interleukin-6 and tumor necrosis factor-alpha within the liver, thus augmenting the hepatic inflammatory response.[120] Evidence suggests that repetitive stress may aggravate chronic inflammatory diseases to a greater extent than acute stressors.[121] Thus, mind-body therapies that alleviate psychosocial stress may enhance the liver-specific and overall health of people living with chronic hepatitis.

Therapeutic modalities that enhance balance and increase a patient's sense of control, meaning, and purpose may decrease the degree to which psychosocial stress contributes to a patient's disease process. Having a chronic illness is a stressor in and of itself. Whatever we can do to help patients minimize or alleviate this and other stressors in their lives is healing in the broadest and truest sense (see Chapter 93, Relaxation Techniques).

Examples of modalities that may help alleviate stress and enhance peacefulness include meditation, prayer, journaling, counseling, support groups, behavioral therapy, hypnosis, and visualization, as well as art, music, and dance

therapy. Relaxation techniques such as deep breathing, biofeedback, and others may also merit discussion. People find respite from the stressors in their lives in many different ways. Practitioners should be mindful of this and tailor recommendations accordingly. Offer suggestions that suit your patient's personality, culture, and belief system. For example, the thought of sitting still for 30 minutes of daily meditation may induce rather than alleviate the anxiety of a goal-oriented type A individual. People with a driving nature may be better suited to more active modalities such as walking or jogging, tai chi, or yoga.

Lifestyle Interventions

Measures to Reduce Toxin Exposure

Exposure to exogenous toxins increases hepatic workload and oxidative stress. When the liver is already in a state of chronic inflammation, this additional burden may exacerbate ongoing injury and accelerate disease progression.

Reduce Toxins in the Diet

Oral intake of toxic xenobiotics can be minimized by avoiding prepackaged, ready-to-eat foods, processed meats, and canned foods. Fresh fruit and vegetables are best in terms of nutritional value and minimizing intake of unwanted chemicals. Encourage organically grown foods, but keep in mind that such products may not be affordable for some patients. Washing fresh fruit and vegetables with a brush under running water helps remove pesticides. Filtered water can also reduce the amount of hepatotoxins ingested.

Avoid Alcohol

Alcohol abstinence is one of the most important recommendations a clinician can make for patients with chronic hepatitis. Alcohol intake in patients with HCV has been associated with accelerated fibrosis, increased risk of cirrhosis, and reduced response to interferon-based therapy.[122] No "safe" threshold for alcohol intake has been established for people with chronic hepatitis.[6] Patients with an active dependence on alcohol are ineligible for interferon-based therapy; a 6-month period of abstinence is recommended by most clinicians. Clinicians must be prepared to offer patients who have an alcohol problem information about local services available to provide these patients with psychosocial support in becoming alcohol free. Family members may also need to engage in the process. Alcohol in over-the-counter products (e.g., mouthwash, cold preparations, and tinctures) is also to be avoided (see Chapter 81, Alcoholism and Substance Abuse).

Avoid Tobacco Products

All tobacco products (chewing tobacco, cigars, pipes, and cigarettes) introduce a wide array of toxins into the body and should be avoided. Smoking reduces glutathione levels through the burden of detoxifying nicotine and neutralizing the free radicals produced by the toxins in tobacco. Smoking increases the risk of hepatocellular carcinoma,[123,124] and it reduces response rates to interferon-based therapy.[125]

Avoid Unnecessary Drugs and Supplements

Pharmaceuticals, botanicals, and supplements that are metabolized by the liver can dramatically increase the xenobiotic burden on the liver. Additionally, some of these products have hepatotoxic potential (Table 19-6). All products with hepatotoxic potential should be avoided or prescribed with caution and closely supervised.

TABLE 19-6. Common Pharmaceuticals and Botanicals With Hepatotoxic Potential

TYPE	SPECIFIC AGENTS
Pharmaceuticals	Acetaminophen Alpha-methyldopa (Aldomet) Amiodarone (Cordarone) Carbamazepine (Tegretol) Diclofenac (Voltaren, Cataflam) Fluconazole or ketoconazole (Diflucan, Nizoral) Hydralazine (Apresoline, Novo-Hylazin) Ibuprofen (Advil, Motrin, Nuprin) Nitrofurantoin (Macrodantin) Phenytoin (Dilantin) Sulfa medications (especially Septra or Bactrim) Amoxicillin (Amoxil) Chlorpromazine (Thorazine) Ciprofloxacin (Cipro) Duloxetine (Cymbalta) Statins/HMG-CoA reductase inhibitors (Caduet, Crestor, Lescol, Lipitor, Mevacor, Pravachol, Simcor, Vytorin, Zocor)
Botanicals	Barberry *(Berberis vulgaris)* Comfrey *(Symphytum officinale)*: should never be taken internally Golden ragwort *(Senecio aureus)* Groundsel *(Senecio vulgaris)* Huang qin *(Scutellaria baicalensis)* Kava kava *(Piper methysticum)* Pennyroyal *(Mentha piperita officinalis)* Sassafras *(Sassafras albidum)* Senna *(Cassia senna)* Valerian *(Valeriana officinalis)* Wall germander *(Teucrium chamaedrys)* Wood sage *(Teucrium scorodonia)* Ma-huang *(Ephedra equisetina)* Jin bu huan *(Lycopodium serratum)*

Street drugs increase the toxic burden on the liver. Recreational drug use is an important topic to discuss with all patients with chronic hepatitis. Many patients with CHC believe that smoking marijuana is a good way to alleviate symptoms associated with the disease and side effects of interferon-based therapy. In reality, cannabis use dramatically increases the toxin burden on the liver and has been reported to significantly accelerate hepatic fibrosis progression.[126] Additionally, cannabis use may contribute to steatosis, which is independently associated with CHC progression.[127] Patients may be hesitant to mention their marijuana use. Asking about marijuana use in the same manner that you inquire about other lifestyle issues opens the door to a candid discussion.

Avoid Environmental and Occupational Exposure to Toxins

Pesticides, herbicides, and other toxic chemicals can damage hepatocytes and elevate liver enzyme levels.[128–130] Protective gear approved by the Occupational Safety and Health Administration is necessary for people whose work exposes

them to chemicals, solvents, fumes, pesticides, or herbicides. Home exposure to paint and lacquer, glues, epoxy, and other toxins should be minimized.

Exercise

Exercise enhances portal blood flow, decreases fatigue,[131] and improves overall well-being. Further, exercise may alleviate depression,[132] a common finding in patients with chronic liver disease, especially CHC. Finally, moderate exercise has been shown to improve the immune response.[133,134] Encourage a realistic exercise program that takes into account the patient's current activity level and interests and progresses gradually. Patients who are sedentary and avoidant of "exercise" may respond well to a broadened view: anything that gets one up and moving constitutes exercise.

Nutrition

The adage, "you are what you eat," describes a literal truth. The liver is integral to metabolic homeostasis and is the master processor of all nutritional intake. One's diet can make these jobs easier or more difficult. In general, a diet rich in a wide variety of fresh fruit and vegetables supplies the liver with needed nutrients to support its synthetic and detoxification functions. Adequate high-quality protein intake is needed to support the liver's synthetic functions and the immune system. Low dietary fat helps prevent or counter hepatic steatosis, a condition that accelerates disease progression. Avoiding excessive carbohydrate intake helps stabilize glucose metabolism, which is often disturbed in patients with chronic liver disease secondary to insulin resistance.

Encourage Healthy Body Weight

Hepatic steatosis has been reported to increase the rate of hepatic fibrosis in patients with CHC.[135,136] Although patients with genotype 3 disease are more prone to steatosis than are patients with other HCV genotypes, an elevated body mass index is an independent predictor of nonalcoholic steatosis.[137] Further, patients with CHC and significant steatosis have lower response rates to interferon-based therapy, compared with patients without steatosis.[138,139] Overweight and obese patients should be encouraged to engage in a sensible, sustainable weight reduction program that combines moderately reduced caloric intake with increased caloric burn through heightened activity. Fasting and fad diets, especially those that restrict protein or encourage high fat intake, should be discouraged.

> Steatohepatitis is more common with genotype 3 disease and is associated with a lower response rate to interferon-based therapy. Management of metabolic syndrome, high triglycerides, and obesity should be a priority.

Encourage Regular Consumption of Cruciferous Vegetables

Cruciferous vegetables are members of the cabbage family of plants and include cabbage, broccoli, cauliflower, Brussels sprouts, kale, mustard greens, collard greens, kohlrabi, rutabaga, turnips, bok choy, arugula, horseradish, radish, wasabi, and watercress. These vegetables are good sources of vitamin C, selenium, folate, carotenoids, lignans, and flavonoids. Prolonged, high heat can destroy some of the phytochemicals in vegetables. Encourage patients to cook vegetables lightly or eat them raw, when possible and appetizing.

Cruciferous vegetables contain high concentrations of indole-3-carbinol, which can increase the activity of certain phase I and II detoxification enzymes.[140,141] This increase in the activity of biotransformation enzymes is the likely mechanism behind the anticarcinogenic effects associated with consumption of cruciferous vegetables.

Encourage Regular Consumption of Fruit

Fruit is a rich source of vitamins C, E, and K, folate, selenium, magnesium, potassium, carotenoids, flavonoids, lignans, terpenoids, and fiber. Eating adequate amounts of a wide variety of fruit helps ensure that the liver has an optimal supply of the substrates needed for detoxification and biosynthesis. Berries, such as cranberries, blueberries, blackberries, and raspberries, contain high concentrations of antioxidants. Peaches, mangoes, and melons are also rich in antioxidants. Citrus fruit (e.g., oranges, tangerines, lemons, and limes) contains high concentrations of the phytochemical D-limonene, a strong inducer of phase I and II of the detoxification system.[142]

Avoid Foods That Inhibit the Detoxification System

Foodstuffs that inhibit the detoxification system warrant special mention. Grapefruit contains naringenin, which inhibits the cytochrome P-450 3A4 enzyme of the phase I detoxification system.[143] Capsaicin (the compound responsible for the spiciness of hot peppers), eugenol from clove oil, and quercetin from onions also slow phase I detoxification. Patients with chronic liver disease are best advised to limit their intake of these foodstuffs.

Encourage Adequate Protein Intake

Adequate protein intake is essential for healthy immune function and detoxification. Liver disease and chronic inflammation increase the body's need for protein, especially in the presence of cirrhosis. Furthermore, phase II of the detoxification system is especially vulnerable to inadequate protein intake.

Complete proteins contain all the essential amino acids. Healthful sources of complete proteins include eggs, lentils, nuts, lean meats, fish, poultry, and soy. Recommended daily protein intake (in grams) is calculated by multiplying body weight (in pounds) by a factor 0.5 to 0.7.

Encourage Healthful Dietary Fat Intake

Fats are easily misunderstood because of confusing terminology. When counseling patients about healthful dietary fat intake, focus on two major points:

1. Limit dietary fat to no more than 30% of caloric intake; 20% is better, and 10% may be best for someone on a weight reduction program.
2. Limit intake of omega-6 polyunsaturated fats and trans fats.

Research has shown that high-fat diets, especially in combination with reduced protein and carbohydrates, increase the risk of steatosis and progression to cirrhosis among patients with chronic hepatitis.[144,145] Hence, patients with chronic hepatitis should be encouraged to limit their overall fat intake.

Advising patients about what fats to eat is somewhat more complicated. Most primary care clinicians are accustomed to promoting the intake of unsaturated fats instead of saturated fats for cardiovascular health. However, patients with chronic liver disease have additional pathophysiologic concerns to be addressed. Unsaturated fats are more volatile (polyunsaturated fats more so than monounsaturated fats) and prone to oxidation than are saturated fats. The oxidative stress in the liver is already high in patients with chronic hepatitis; the additional stress of large quantities of unsaturated fats may exacerbate hepatocyte injury. Particularly important is a reduction in the intake of polyunsaturated omega-6 fatty acids (e.g., safflower oil, sunflower oil, corn oil). Encourage use of predominantly monounsaturated fats such as olive, canola, and peanut oils for cooking. Omega-3 fatty acids should also be encouraged to help reduce inflammation because these oils are known to reduce tumor necrosis factor, a proinflammatory cytokine.[146] Finally, all patients should be advised to avoid trans fats (anything that lists hydrogenated or partially hydrogenated fat on the food label) (see Chapter 86, The Antiinflammatory Diet).

Encourage Dietary Fiber

Dietary fiber helps bind toxins in the gut, thus resulting in excretion through the bowel without hepatic processing. To promote fiber intake, encourage a diet rich in fruit, vegetables, and whole grains. Consider supplementing with a soluble fiber such as methylcellulose or psyllium.

Consume Green Tea

Catechin polyphenols in green tea have antioxidant, antiangiogenesis, and antiproliferative properties that may help reduce inflammation in patients with chronic hepatitis and may potentially slow disease progression and attenuate the risk for hepatocellular carcinoma.[147,148] A study of 124 patients with viral hepatitis who were treated with 3 g of catechins versus placebo resulted in significantly lower AST, ALT, and serum bilirubin levels. Compared with other types of viral hepatitis, people with non-A non-B (presumed HCV) hepatitis showed the greatest response.[149]

Dosage

Prescribe 2 or 3 cups of green tea daily.

Precaution

Many patients think if a little is good, more must be better, but, of course, that is not always the case. Be aware that cases of fulminant hepatitis have been reported after consumption of highly concentrated dry extracts of green tea.[150,151] Caution patients against the use of green tea extracts.

Therapies to Consider

The association of hepatitis B virus (HBV) and HCV with hepatocellular carcinoma has been firmly established. In January 2005, HBV and HCV were added to the list of known human carcinogens in the U.S. Department of Health and Human Services *Report on Carcinogens,* 11th edition.[152] Although the link is clear, the carcinogenic transformation process is poorly understood. Nucleic acid damage by reactive nitrogen and oxygen species is believed to contribute to inflammation-related carcinogenesis in patients with chronic hepatitis.[153] Hepatocyte regeneration in the milieu of chronic inflammation may predispose to such nucleic acid damage. Evidence indicates that virus-specific mechanisms also contribute to hepatocyte carcinogenic transformation.[154,155] Based on the knowledge that the risk of developing hepatocellular carcinoma increases in parallel with the degree of hepatic fibrosis, agents with antifibrotic properties may be useful in delaying progression to cirrhosis and its concomitant risk for hepatocellular carcinoma.

Colchicine

Colchicine, an alkaloid isolated from the autumn crocus, was reported to resolve cirrhotic nodules and extracellular fibers in an animal model.[156] A small study of patients with cirrhosis and ascites reported that survival was three times greater in those taking colchicine versus placebo over 11 years.[157] However, a large, multicenter clinical trial comparing low-dose peginterferon with colchicine as maintenance therapy for patients with CHC and advanced fibrosis or cirrhosis found no significant difference between the treatment groups.[158] Study participants were virologic nonresponders to previous therapy with interferon plus ribavirin. Notably, 49% of the enrolled patients did not complete the 4-year trial. Because colchicine is not standard therapy, clinicians should consult with a gastroenterologist before this treatment is initiated.

Dosage

Colchicine 0.6 mg twice daily

Prevention Prescription

Hepatitis B Primary Prevention

- Administer the hepatitis B vaccine.
- Use universal body fluid precautions.

Hepatitis C Primary Prevention

- Injection drug users: do not share needles or other drug paraphernalia.
- Do not share personal care items that may be contaminated with blood, including toothbrushes, razors, and manicure and pedicure equipment.
- Do not get a tattoo with an unsterilized stylus; be certain that new ink and new or sterilized ink pots are used.
- If you have multiple sexual partners, avoid contact with blood during sexual activity, and use latex condoms correctly and consistently at every sexual encounter.
- Use universal body fluid precautions.

Hepatitis C Secondary Prevention

- Abstain from alcohol.
- Abstain from tobacco products, street drugs, and unnecessary medications and supplements.
- Avoid environmental toxins, including pesticides, herbicides, and other toxic chemicals.
- Achieve and maintain a healthy body weight.
- Exercise regularly.
- Establish and maintain ongoing health care to include monitoring for disease progression and screening for the development of hepatocellular carcinoma.

Therapeutic Review

Screening

Because people with chronic hepatitis C (CHC) are likely to be asymptomatic and may not have consistently elevated liver enzymes, all patients should be routinely screened for hepatitis C risk factors.[10] The following list of questions can help elucidate a patient's relative risk for hepatitis C:

- Did you receive any blood or blood products (e.g., packed cells, whole blood, plasma, platelets, clotting factors, gammaglobulin) before 1992?
- Have you ever undergone kidney dialysis?
- Have you had an organ transplant (especially before 1992)?
- Have you ever, even once, injected street drugs?
- Have you ever, even once, shared drug paraphernalia (e.g., needles, cookers, straws)?
- Have you ever been accidentally stuck with a used medical needle?
- Do you have human immunodeficiency virus (HIV)?
- Have you ever held a job (e.g., police officer, fire fighter, emergency medical technician, paramedic, medical or dental worker) or participated in a sport (e.g., hockey, rugby, boxing, football, and other contact sports) that exposed you to blood?
- Did your mother have hepatitis C when you were born?
- Have you ever been incarcerated?
- Have you been in military combat?
- Are you living with or have you ever lived with someone known to have hepatitis C?
- Have you ever shared personal care items that may have been contaminated with blood (e.g., razors, toothbrushes, manicure or pedicure equipment) with others?
- Have you ever had a piercing or tattoo in a noncommercial facility?
- Have you ever had unprotected sex with someone known to have hepatitis C?
- Have you ever had unprotected sex with someone who is or was an injection drug user?

Sexual transmission of hepatitis C is uncommon, especially among people in a long-term, monogamous relationship.[117] However, patients with a history of sexually transmitted infections and multiple, short-term sexual relationships are at increased risk.[159] Sexual behavior that involves contact with blood is the source of potential hepatitis C virus (HCV) exposure (e.g., anal intercourse, fisting, and other practices that can cause bleeding).

Laboratory Testing

Patients with one or more risk factors and those patients who specifically request testing should be screened for hepatitis C by using an enzyme immunoassay for HCV antibodies.[10] A positive serologic test result indicates exposure to the virus but not necessarily active infection. Approximately 25% to 35% of adults infected with HCV spontaneously clear the virus. The remaining 65% to 75% become chronically infected. Patients with a positive antibody screen should be tested for HCV RNA to determine whether they are currently infected. HCV genotype testing is recommended for any patient considering interferon-based therapy because genotype affects the planned duration of treatment and the probability of successful viral clearance.[161]

Although liver biopsy was once considered a standard component of the initial evaluation of patients with CHC, the American Association for the Study of Liver Diseases now recommends that physicians consider obtaining a liver biopsy only if the patient or provider believes that the information will contribute to therapeutic decision making or will provide desired prognostic information.[10] For patients who prefer not to undergo a liver biopsy or who have a contraindication to the procedure, panels of serum markers for fibrosis (e.g., Fibrotest, Fibrosure) may help evaluate the fibrotic state of the liver. These tests are reasonably accurate at differentiating the extremes of the fibrotic spectrum (i.e., little to no fibrosis versus cirrhosis). However, current accuracy of these tests to determine the degree of fibrosis between the extremes of the spectrum is limited.

The following therapeutic review addresses management after a diagnosis of CHC has been made and liver histologic features have been evaluated, directly or indirectly.

Patients With Newly Diagnosed CHC Who Have No Physical, Laboratory, or Histologic Evidence of Advanced Fibrosis or Cirrhosis and Who Are Not Undergoing Interferon-Based Therapy

- Laboratory
  - Obtain baseline markers of liver status (aspartate aminotransferase [AST], alanine aminotransferase [ALT], albumin, bilirubin, and platelet count) and alfa-fetoprotein level.
  - Consider HCV genotype testing to aid in management decisions.
  - Monitor the AST/ALT ratio at least biannually.
- Radiology
  - Obtain a baseline ultrasound study of the liver.
- Lifestyle
  - Reduce toxin exposure (e.g., tobacco, environmental toxins).
  - Urge abstention from alcohol and illicit drug use.

Continued

- Reduce dietary toxins; encourage organic foodstuffs if feasible.
- Encourage achieving and maintaining a healthy body weight.
- Promote regular exercise.
- Counsel patients about how to reduce the risk of spread of chronic viral hepatitis to others.
- Refer for alcohol or drug dependence counseling and treatment as needed.

- Nutrition
  - Fruits and vegetables
    - Increase intake of fruits and vegetables (especially cruciferous vegetables) to six or seven servings daily. 
    - Limit grapefruit and other inhibitors of the detoxification system. 
  - Dietary fats
    - Limit fat intake (no more than 30%; aim for 10% to 20%). 
    - Eliminate trans fats (hydrogenated and partially hydrogenated oils). 
    - Use olive, canola, or peanut oil in cooking. 
    - Increase intake of omega-3 fatty acids (cold-water fish, nuts, flaxseed). 
    - Decrease intake of omega-6 fatty acids (vegetable oils). 
  - Dietary fiber
    - Increase fiber intake. 
    - Consider supplementation with methylcellulose or psyllium if dietary fiber intake is inadequate. 
  - Dietary protein
    - Ensure adequate protein intake (recommended grams of intake = pounds of body weight × 0.5 to 0.7) 
- Pharmaceuticals
  - Vaccinate patients without immunity to hepatitis A and B. 
- Mind-Body Therapy
  - Encourage lifestyle choices that reduce psychosocial stress.
  - Explore relaxation and meditative techniques tailored to the patient's personality, belief system, and culture to help reduce stress.
- Supplements
  - Selenium: 200 mcg daily 
  - Iron-free multivitamin with minerals: daily 
  - B-complex vitamin: daily 
  - Vitamin C: 200 to 250 mg twice daily 
  - Vitamin E (d-alpha tocopherol): 400 units daily 
  - Precautions: Avoid iron supplementation and excess vitamin A.
- Botanicals to Consider
  - Silymarin phosphatidylcholine: 240 mg twice daily 
  - Licorice root: 200 to 500 mg dry powder three times daily or 1 to 2 g powdered root three times daily or 2 to 4 mL of fluid extract three times daily 
  - Schisandra: 100 mg of extract twice daily 
  - Astragalus: 4 to 7 g of powder daily 
- Monitoring
  - See the patient at least twice yearly to monitor for signs of progression or extrahepatic manifestations of disease.
  - Monitor the AST/ALT ratio; a ratio greater than 1 indicates probable disease progression to advanced fibrosis or cirrhosis.[120] Refer for a gastroenterology or hepatology consultation.
  - Consider repeat liver biopsy every 4 to 5 years.
- Consultations
  - An infectious disease consultation and comanagement are highly recommended for patients coinfected with HCV and HIV.
  - A gastroenterology or hepatology consultation is recommended for patients coinfected with HCV and HBV and for patients with HCV and other comorbid hepatic conditions.

Patients With Newly Diagnosed CHC Who Have Physical, Laboratory, or Histologic Evidence of Advanced Fibrosis or Cirrhosis

Recommendations are the same as previously described, with the following additions:

- Laboratory
  - Order HCV genotype testing to aid in treatment planning.
  - Order baseline HCV viral load to aid in treatment planning.
- Lifestyle
  - Same as previously described
- Nutrition
  - A nutrition consultation is recommended for patients with cirrhosis.
- Mind-Body Therapy
  - Same as previously described

TABLE 19-7. Contraindications to Pegylated Interferon plus Ribavirin Therapy

TYPE OF ABNORMALITY	SPECIFIC CRITERIA
Hematologic abnormalities	Anemia (hemoglobin less than 12 g/dL in female patients and less than 13 g/dL in male patients), especially patients with hemoglobinopathies Leukopenia (less than 1500 × 10^3/μL) Thrombocytopenia (less than 100 × 10^3/μL)
Neuropsychiatric conditions	Unstable depression or other major psychiatric disorder Active alcohol dependence Illicit drug use that interferes with the patient's ability to commit to regular treatment
Comorbidities	Unstable cardiac arrhythmia or cardiovascular disease Uncontrolled cerebrovascular disease or seizure disorder Uncontrolled diabetes mellitus Diabetic retinopathy Renal failure Active autoimmune disease
Hypersensitivity	Hypersensitivity to interferon or ribavirin
Other	Pregnancy or lactation Decompensated cirrhosis Unwillingness or inability to practice reliable contraception

- Pharmaceuticals
  - Recommend peginterferon alfa plus ribavirin treatment for patients without contraindications to this therapy (Table 19-7). A2
  - For patients with relative contraindications, prepare and execute a management plan to resolve the contraindications.

Monitoring Patients Receiving Peginterferon plus Ribavirin

- Office visits
  - Monitor patients who are receiving therapy at least every 4 weeks for treatment side effects, including depression.
  - Treat side effects aggressively to improve compliance, minimize discomfort, and avoid dose reductions. Encourage patients to call between visits if problems arise.
- Laboratory testing
  - Monitor hemoglobin levels monthly for evidence of hemolytic anemia secondary to ribavirin.
  - Consider determining the HCV viral load at week 4 of treatment to determine whether the patient has had a rapid virologic response (RVR). This information may help determine the minimum duration of therapy if the patient has difficulty tolerating the planned course of treatment.
  - Obtain an HCV viral load measurement at week 12 of treatment to determine whether an early virologic response (EVR) has occurred. In patients without at least a 100-fold drop in HCV viral load (compared with baseline), discontinue therapy. For genotype 1 disease with EVR, continue therapy for a total of 48 weeks. For genotype 2 or 3 disease with EVR, continue therapy for a total of 24 weeks.
  - Check the HCV viral load at the completion of a full course of therapy to determine end-of-treatment response. Patients with detectable HCV RNA at the end of treatment are deemed nonresponders. Those without detectable HCV RNA at the end of treatment are viral responders.
  - End-of-treatment responders should have an HCV RNA test every 6 months for the first year and yearly thereafter for 5 years to detect possible relapse.
- Botanicals
  - Because the potential interactions among peginterferon, ribavirin, and botanicals have not been evaluated, consider discontinuing all herbal supplements during interferon-based therapy or monitor the patient closely for new or unexpected symptoms or reactions.
- Consultations
  - A nutrition consultation is recommended for patients with cirrhosis.
  - If botanicals are to be continued during interferon-based therapy, consider consulting with a Chinese medicine specialist experienced in the management of patients with CHC who are receiving interferon-based therapy.
  - An infectious disease consultation and comanagement are highly recommended for patients coinfected with HCV and HIV.
  - A gastroenterology or hepatology consultation is recommended for patients coinfected with HCV and HBV and for patients with HCV and other comorbid hepatic conditions.
  - For patients with compensated cirrhosis, a hepatology consultation is strongly recommended before treatment. Interferon-based therapy can push patients with compensated cirrhosis into decompensation.

Patients With Newly Diagnosed CHC and Moderate Fibrosis to Compensated Cirrhosis Who Have Contraindications to or Decline Interferon-Based Therapy

Management of these patients is generally the same as for patients with minimal fibrosis, with a few exceptions. Monitor carefully with periodic biochemical C2

Continued

testing (AST, ALT, total protein, albumin, bilirubin, white blood cell count, and platelet count). Monitor for development of hepatocellular carcinoma with alfa-fetoprotein testing every 6 months and hepatic ultrasound at least once yearly. Botanical therapy may be advised in these patients. 

Additional supplements (not previously mentioned in the recommendations for patients with minimal fibrosis) should be considered to reduce hepatic inflammation, boost hepatic antioxidant capacity, promote robust immune function, and support the detoxification pathway (i.e., glutamine, alpha-lipoic acid, N-acetylcysteine, and *S*-adenosylmethionine). 

Patients With CHC and Decompensated Cirrhosis

Refer for a hepatology consultation and possible liver transplant evaluation.

Patients With CHC Who Were Previously Treated Unsuccessfully With Standard Interferon plus Ribavirin (Nonresponse and Relapse)

Patients previously treated with standard interferon plus ribavirin or just with interferon who were nonresponders or who relapsed after completion of therapy can be successfully retreated with peginterferon alfa plus ribavirin. Response rates are generally not as high as in treatment-naive patients, especially among previous treatment nonresponders. 

The FDA recently approved the protease inhibitors telaprevir (Incivek) and boceprevir (Victrelis), which can be added to peginterferon and ribavarin as triple therapy for patients with genotype 1 CHC. The addition of one of these protease inhibitors increases the probability of response to peginterferon and ribavirin in this difficult-to-treat population. 

KEY WEB RESOURCES

For Clinicians

American Association for the Study of Liver Diseases (AASLD). *Practice Guidelines, Diagnosis, Management, and Treatment of Hepatitis C: An Update*. http://www.aasld.org/practiceguidelines/Documents/Bookmarked%20Practice%20Guidelines/Diagnosis_of_HEP_C_Update.Aug%20_09pdf.pdf.	This 2009 update document reviews the relevant peer-reviewed literature and provides evidence-based practice guidelines, which have been endorsed by AASLD, the Infectious Diseases Society of America, and the American College of Gastroenterology.
Centers for Disease Control and Prevention. *Viral Hepatitis*. http://www.cdc.gov/hepatitis.	The CDC viral hepatitis hub provides extensive information for clinicians about the various forms of viral hepatitis, including downloadable publications for your practice, access to articles in *Morbidity and Mortality Weekly Report,* and online study and training resources.

For Patients

National Institute of Diabetes and Digestive and Kidney Diseases. *What I Need to Know about Hepatitis C*. http://digestive.niddk.nih.gov/ddiseases/pubs/hepc_ez/.	This site provides a user-friendly overview of hepatitis C basics, which may be particularly useful for patients with newly diagnosed disease.
American Liver Foundation. http://www.liverfoundation.org.	This site provides online informational materials and webcasts designed for patients and caregivers living with chronic liver disease.
Hepatitis Foundation International. http://www.hepfi.org.	The Foundation is a North American advocacy group that provides an online library of information about various forms of chronic hepatitis, news, and research updates, largely targeted to patients and caregivers.

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References are available at expertconsult.com.

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Chapter 20

Urinary Tract Infection

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Pathophysiology and Epidemiology

Urinary tract infections (UTIs) are common, with an estimated lifetime incidence of approximately 53% in women and 14% in men.[1] The higher prevalence in women is thought to be related to urethral length. For those who have had a prior infection, the risk of another increases dramatically. One study found a recurrence rate of 44% within 1 year for those women with a history of UTI.[2] The most common pathogens include gram-negative organisms, in particular *Escherichia coli (E. coli)*, which accounts for 80% of infections.[3] Many recurrent infections may actually represent reinfection with the same organism.[4] Despite clearing the bacteria from the urine, the colon may act as a reservoir for pathogenic bacteria.

Simple UTI, or cystitis, involves bacterial colonization of the bladder. Complicated UTIs usually involve structural or anatomic factors, underlying disease states such as diabetes that hinder treatment, or drug-resistant bacterial strains. Ascending infections into the kidneys are not uncommon, particularly with complicated UTIs; pyelonephritis requires urgent medical attention to avoid damage to renal structures and sepsis. Factors that increase the likelihood of disease progression may include delay of treatment, unrecognized infection, asymptomatic bacteriuria in pregnancy, anatomic factors, and systemic diseases that lower immune function, such as diabetes and others. Asymptomatic bacteriuria does not require treatment outside of pregnancy, although debate exists about the utility of treating this condition in patients with diabetes. Although bacteriuria is more common in diabetic patients,[5] treatment has not been shown to alter outcomes.[6] The U.S. Preventive Services Task Force (USPSTF) recommends screening for bacteriuria in pregnancy (A recommendation) and against screening in others (D recommendation).[7] Rapid treatment of pregnant women with clinically diagnosed UTI or asymptomatic bacteriuria is essential because of the high risk of pyelonephritis.

Clinical Presentation

Most episodes of lower UTI manifest with some combination of dysuria, urinary urgency, and frequency. Gross hematuria, suprapubic discomfort, and cloudy urine are not uncommon. Symptoms of fever, myalgia, or low back or flank pain should prompt consideration of pyelonephritis. A history of dysuria, urinary frequency, and absence of vaginal discharge indicates a 90% probability of UTI.[8] Physical examination findings may consist of suprapubic tenderness; however, a physical examination is not required in the evaluation of UTI.

Laboratory testing frequently is isolated to urinalysis. Urinalysis may reveal positive nitrite, positive leukocyte esterase (LE), or hematuria. The presence of nitrite with either LE or hematuria has a positive predictive value of 92%, but a negative predictive value of only 76% when all three values are negative.[9] Urine culture is not required for diagnosis and treatment of simple UTI but may be helpful for recurrent symptoms, to exclude other causes such as interstitial cystitis or when concern exists for a drug-resistant organism. If culture is performed, the finding of more than 100,000 colony-forming units (CFUs) of one organism supports the diagnosis.

The differential diagnosis of dysuria includes *Chlamydia trachomatis* cervicitis and interstitial cystitis, among other disorders in women. Prostatitis and urethritis should be excluded in the treatment of men with UTI. Treatment by telephone for patients with recurrent infection is generally considered acceptable. Many practices have a nurse triage protocol that allows recommendations, including prescriptions to be provided without an office visit. Frequent complicated UTIs or pyelonephritis in women or UTIs in men may benefit from further evaluation by a urologist or further imaging.

Risk Factors

Several factors that may predispose an individual to recurrent UTIs vary across the age spectrum (Table 20-1). Younger women who are sexually active, have a history

TABLE 20-1. Risk Factors for Urinary Tract Infection

YOUNG WOMEN	OLDER WOMEN	MEN	GENERAL
Higher frequency of intercourse	Diabetes	Lack of circumcision	Foreign bodies
History of UTI as child	History of premenopausal UTI	Penetrative anal intercourse	Nephrolithiasis
Condom use	Urge incontinence	Female partner with UTI	Catheters
Spermicide use	Sexual activity	Prostatic hypertrophy	Family history of recurrent UTI
Diaphragm use	Incomplete bladder emptying		Decreased fluid intake
Pregnancy	Cystocele		
Delayed urination			
Lack of voiding after intercourse			

UTI, urinary tract infection.

of UTIs as children, use condoms (particularly those with spermicidal lubrication), or use diaphragms are at higher risk.[10,11] Frequency of sexual intercourse is an independent risk factor.[10] UTIs have an inverse relationship to voiding after intercourse.[12] Tight clothing and soap preference have not been shown to be related to UTI recurrence in case control trials, although tampon use and soda consumption may be related.[13] Delayed urination in college-age women seems to be significantly related to infection risk.[14] Physiologic changes of pregnancy are associated with a significant increase in UTI.

Postmenopausal women with recurrent UTIs are more likely to be affected by diabetes, a history of premenopausal UTIs, urge incontinence, sexual activity, incomplete emptying of the bladder, or the presence of a cystocele.[15,16]

Some risk factors cross all age ranges, including a family history of recurrent UTIs and foreign bodies such as renal stones and catheters. A family history of recurrent UTIs may be associated with increased risk resulting from the relationship of specific phenotypes and bacterial adherence to the bladder wall.[17]

Risk factors that predispose men to simple UTIs include penetrative anal intercourse, a female partner with UTI, and lack of circumcision.[18] Obstructive symptoms, such as those related to prostatic hypertrophy, predispose patients to complicated UTI.

Integrative Therapy

Nutrition

In general, a diet high in fruits and vegetables, whole grains, and healthy fats will promote good health and may strengthen the immune system. In addition, some foods and food components are thought to have a direct impact on the frequency of UTI.

Bladder Irritants

Many clinicians believe that certain foods cause irritation of the bladder and therefore increase the risk of UTI in some individuals, although case-control studies evaluating dietary factors have not supported this assertion.[12] Possible irritants include caffeine, simple sugars or starches, tobacco and alcohol, and some food additives. For patients with recurrent UTIs, a trial elimination diet to avoid these substances may result in a reduction in the frequency of infections.

Garlic and Onions

Garlic has been used as an antimicrobial agent throughout history for a wide range of conditions. Studies have evaluated its effect on a broad range of organisms, including viral, bacterial, fungal, and parasitic infections. It appears to be active against common urinary pathogens.[19] The most active ingredient in garlic is thought to be the sulfur-containing compound, allicin.[20] Nearly 100 compounds present in garlic may act synergistically, however. In animal models of urinary pseudomonas, garlic appeared to decrease bacterial counts and prevent renal damage.[21] Human trials of garlic for UTI are lacking. Garlic may be useful for acute or recurrent infections.

Chopping or mashing the garlic clove 10 minutes before eating or cooking it seems to maximize the release of allicin, thus increasing effectiveness. Raw consumption is preferred to cooking, because the highest allicin content may be found in raw garlic. Cooked garlic, however, may also have significant health benefits.

Onions also contain allicin and may be helpful in the treatment of UTIs and the prevention of urinary pathogens, although no trials have been conducted. Onions contain many compounds thought to promote health, including flavonoids such as quercetin.

Fluids

Many practitioners recommend significant fluid intake to flush the urinary system, in hopes of preventing UTIs. This practice, however, has not been consistently proved in the literature. Several studies showed an association with decreased fluid intake and susceptibility to UTI,[22,23] while others did not support this finding.[10,12] One review suggested that the issue may be more the combination of fluid intake, frequent voiding, and complete bladder emptying that makes a difference over simply drinking larger volumes.[24] This recommendation is not harmful, and it may be helpful.

Supplements

Probiotics

Because of the colonic bacterial reservoir of pathogenic strains likely involved in recurrent UTIs,[4] it is a logical extension to maximize intestinal health. Probiotic treatments have been evaluated in several studies, although consistent results are lacking. Theoretically, *Lactobacillus* strains provide a barrier in the vagina and on the perineum to prevent bladder colonization. They out-compete pathogenic strains and

affect their adhesion.[25] A systematic review in 2009 found five studies that evaluated *Lactobacillus* strains for prevention of UTI, with no consensus.[26] The most efficacious strains in the literature appear to be *Lactobacillus rhamnosus* GR-1 and *Lactobacillus fermentum* RC-14.[27] Several studies showed *Lactobacillus* GG to be less effective.[27] Optimal dosing is unclear but is likely to be at least in the range of 1 billion CFUs. Probiotics can be given orally or vaginally.

Dosage

One billion CFUs daily of *L. rhamnosus* or *L. fermentum*. These probiotics will likely be mixed with other strains in a particular product. The products with these strains are limited in number but are increasingly available.

Precautions

The risk of probiotics in immunocompetent individuals is exceedingly small.

Vitamin C (Ascorbic Acid)

Vitamin C may have a role in the prevention of recurrent UTI. In a single-blind randomized trial of pregnant women, 100 mg of ascorbic acid cut UTI rates by more than half over 3 months (29.1% versus 12.7%).[28] In a case control study, intake of vitamin C correlated with protection against UTI in college age women, however the amounts taken were not noted.[12]

Dosage

Optimal dosage is unknown. Consider 100 mg daily for prevention.

Precautions

Diarrhea may occur in patients taking high doses of vitamin C.

D-Mannose

D-Mannose is a simple sugar found in fruits. It is not broken down in the bloodstream, and it is concentrated in the bladder, where it prevents bacterial adherence to the bladder wall. The cellular receptors of uroepithelial cells to which bacteria such as *E. coli* bind are made of D-mannose.[29] When taken as a supplement, D-mannose binds to the bacterial receptors blocking the bacteria's ability to adhere to the epithelial cell wall.[29] Animal studies showed efficacy in decreasing bacteriuria within 1 day.[30]

The safety of D-mannose was studied in long-term studies of mice, and no evidence of harm was found.[31] D-Mannose has been used in humans for a rare carbohydrate-deficient glycoprotein syndrome. No trials have been done to evaluate the efficacy of D-mannose in humans when it is taken for UTI either as treatment for acute infection or as prophylaxis. D-Mannose shows promise as a potentially safe supplement for treatment of UTI.

Dosage

D-Mannose powder, ¾ to 1 teaspoon one to two times daily, is taken for prevention; and ¾ to 1 teaspoon three times daily is indicated for active treatment.

Precautions

Loose stools and abdominal bloating may occur. High doses over prolonged periods may be nephrotoxic.

D-Mannose is thought to inhibit urinary tract infection by encouraging binding of bacteria to this sugar instead of the bladder wall and thus enhancing evacuation through the urine.

Botanicals

Cranberry (Vaccinium macrocarpon)

Cranberry juice and powder have successfully been used to prevent UTI. The use of cranberry dates back to Native American tribes who used it for urinary conditions. Historically, cranberry was thought to work by acidifying urine, yet studies have shown effects with minimal change in urine pH.[32] The presumed active compounds, proanthocyanidins (PACs), may inhibit bacterial adhesion to the bladder wall and decrease bacterial virulence.[33] In a small trial, a dose of 72 mg of PAC was effective against *E. coli.* This effect appears to be dose dependent,[33] although the optimal dose is unknown.

In one randomized controlled trial, cranberry juice was compared with powder and placebo in sexually active women.[34] Both cranberry groups reduced recurrent UTI by approximately 30%. The doses used in this study were 250 mL of cranberry juice three times daily and concentrated cranberry juice tablets twice daily. The size of the tablets used was not disclosed. Another trial used only 30 mL of cranberry-lingonberry concentrate daily and reported a 20% risk reduction for UTI recurrence.[35] The small studies that have shown success with tablets have used 400 to 800 mg twice daily.[36,37] The size and design of these studies may limit extrapolation to a larger population. Another trial randomized women to 500 mg of cranberry extract or 100 mg of trimethoprim and found equal efficacy in prevention of UTIs.[38]

A 2008 Cochrane Review looked at 10 randomized trials using cranberry juice or capsules and found some evidence that cranberry juice may decrease the frequency of UTI in susceptible women.[39] This review found a high dropout rate, however, likely related to difficulty adhering to daily juice consumption.[39] The optimal dose could not be determined by these studies. Cranberry is not effective in patients with neurogenic bladder.

Although cranberry products are frequently used to treat acute infection, these qualities have not been researched.[40]

Dosage

For prevention of UTI, the dose is 16 oz (500 mL) of unsweetened cranberry juice daily or cranberry extract, 500 mg daily to 400 to 800 mg twice daily.

Precautions

Moderate interaction with warfarin is possible.

Many cranberry beverage products on the market contain only a small amount of cranberry juice and a significant amount of sweeteners. This may have a minimal impact on the urinary tract and potentially a negative impact on overall health.

Uva Ursi (Arctostaphylos uva ursi)

Uva Ursi, or bearberry, leaf has long been used for urinary symptoms, although few human data have evaluated efficacy. The active compound is thought to be arbutin, which is converted into hydroquinone.[41] Alkaline urine is thought to be necessary for efficacy. In vitro studies have suggested activity against typical pathogens.[42]

One preliminary trial showed effectiveness in preventing recurrent UTI when uva ursi was combined with dandelion root and leaf.[43] In this trial, women took an extract for 1 month and then were followed for 1 year. During that time, 18% of women in the placebo group (27 individuals total) and 0% in the treatment group (30 individuals) had a UTI. Unfortunately, because of potential toxicity when uva ursi is used long term, it cannot be recommended for UTI prophylaxis. This toxicity may be related to the component hydroquinone and the inhibition of melanin,[44] although tannins may also play a role. The most common side effects include nausea and gastrointestinal distress. Rarer and more serious side effects may include hepatotoxicity, retinal disease,[44] seizure, cyanosis, and death. These risks are more pronounced with high doses and prolonged use. Many experts recommend limiting use to acute infections for no more than 1 week and restricting use to five times per year.[45]

Dosage

Uva ursi is taken as 3 g of dried herb daily or as an infusion (3 g of dried herb steeped in 150 mL of cold water for 12 to 24 hours), 1 cup 4 times daily; the hydroquinone derivative dose is 400 to 840 mg up to four times daily.

Precautions

Uva ursi is not safe in pregnancy, in children, or for long-term use. Uva ursi can turn urine greenish brown, which can interfere with urinalysis. It is potentially hepatotoxic with prolonged use.

Berberine

Berberine is an alkaloid found in certain plants. Common in the traditions of traditional Chinese medicine, Ayurvedic medicine, and Native American healing, plant species that contain berberine include goldenseal *(Hydrastis canadensis),* Oregon grape *(Berberis aquifolium),* bayberry *(Berberis vulgaris),* coptis *(Coptis chinensis)*, and tree turmeric *(Berberis aristata).* A few studies have been done on this compound. Some have used specific plants, and others have used isolated berberine. In vitro studies showed that berberine sulfate causes inhibition of *E. coli* adhesion to epithelial cells.[46] Studies using berberine for other indications did not show toxicity or significant side effects.[47]

Goldenseal (Hydrastis canadensis)

Goldenseal is a woodland herbaceous plant native to North America. Few data support its use in UTI, but the root has been used for antimicrobial purposes. One study of goldenseal extract showed in vitro activity against several common urinary pathogens.[48] No studies have been conducted in vivo. Concern exists about overharvesting and dwindling populations of goldenseal in the forests of eastern North America.

Dosage

The optimal dose is unknown. A common dose of goldenseal is 0.5 to 1 g three times daily of the dried root.

Precautions

Berberine (including goldenseal) is not considered safe in pregnancy or for infants because of the risk of kernicterus.[49] It may also effect the cytochrome P-450 system and subsequently the serum levels of other substances.

Other Herbal Preparations

Other traditional herbal preparations that have been used for UTIs include stinging nettles, marshmallow root, echinacea, burdock, slippery elm, dandelion, and lovage. Some of these, such as *Echinacea angustifolia,* have been studied in other conditions. For example, although echinacea has been identified as an immune stimulator, it has not been studied in UTI. Other herbal preparations have little research on any clinical uses.

Pharmaceuticals

Antibiotics

Simple cystitis in women may be treated with a 3-day regimen of any of several antibiotics, including trimethoprim-sulfamethoxazole and ciprofloxacin. Other acceptable antibiotics include nitrofurantoin and amoxicillin. Optimal therapy often depends on antibiotic resistance rates in the individual's community. Complicated UTIs require a longer course. Pregnant women and those with chronic disease such as diabetes should be treated for 7 days. Men with UTI are also usually treated for 7 days, and prostatitis should be excluded.

Recurrent UTIs may be treated with prophylactic antibiotics daily or postcoitally. Either approach has been shown to decrease the frequency of infection. Prophylactic antibiotics are usually continued for 6 to 12 months before a trial off the drugs. In a Cochrane Review, 6- and 12-month regimens appeared to be equal in efficacy.[50] Postcoital antibiotics appear to be as effective against recurrent UTIs as daily therapy for those individuals with symptoms related to intercourse.[50]

Dosage

Trimethoprim-sulfamethoxazole, one tablet double strength (DS) (160/800 mg) twice daily for 3 days; ciprofloxacin, 250 mg twice daily for 3 days; nitrofurantoin extended release (ER), 100 mg twice daily for 7 days.

Prophylactic doses are usually given once daily at the same dose used for treatment. Common choices include ciprofloxacin, nitrofurantoin, and trimethoprim-sulfamethoxazole daily.[51] Postcoital doses are given as one tablet at the time of intercourse.

Precautions

Frequent or long-term use of antibiotics may be associated with medication side effects and risk of disruption of normal bacterial flora.

Phenazopyridine

Phenazopyridine (Pyridium) can provide pain relief from dysuria and bladder spasms. It is available over the counter and by prescription.

Dosage
The dose is 100 to 200 mg twice daily for 2 days.

Precautions
This medication turns urine and tears a dark orange that can interfere with urinalysis and can stain contact lenses.

Estrogen
Systemic estrogen replacement does not appear to have an effect on the frequency of UTIs in postmenopausal women,[52] although topical estrogens may be beneficial for postmenopausal women with recurrent UTIs.[53] In one randomized trial, 0.5 mg of vaginal estriol nightly for 2 weeks followed by twice weekly for 8 months compared with placebo resulted in a significant reduction in UTI frequency (0.5 versus 5.9 episodes per patient year). Vaginal estriol was found to be less effective than daily nitrofurantoin (Macrodantin) in preventing recurrent UTI.[54]

Dosage
The dose is 0.5 mg vaginal estriol nightly for 2 weeks, followed by twice weekly.

Precautions
Vaginal estrogen may be absorbed systemically at high doses, thus prompting the need for endometrial protection. In general, the safest approach is to use the lowest effective dose for the least amount of time needed.

Other Therapies to Consider

Behavioral Changes
Certain behaviors have been thought to be associated with an increased risk of UTI. Many of these behaviors are associated with irritation of the urethra or reflux of urine back into the bladder from the urethra. These include sexual intercourse, wearing of tight clothing, holding of urine, and use of irritants such as bubble bath, douche, or other products. Many of these have no evidence base, but addressing them has little risk of harm.

Acupuncture
In one randomized trial of acupuncture compared with no treatment, women with a history of recurrent UTIs had a 50% reduction in UTIs compared with the control group (73% versus 52% with no UTIs over 6 months).[55] The treatment group received biweekly acupuncture sessions over 4 weeks and were followed for 6 months. Bladder residuals were reduced in the treatment group to 50% compared with baseline, and no change was noted in the control group. An earlier study by the same research team showed similar results, with partial response after sham acupuncture as compared with a no-treatment control.[56]

Mind-Body Skills
Although no specific mind-body skills have been evaluated in the prevention or treatment of UTI, mental health and spiritual health are important components of overall health, including the immune system. These mind-body components, along with other foundations of health, such as nutritional status, adequate sleep, and physical activity, are essential to optimal health. Attention to techniques to improve them, whether yoga, mindfulness, social connectedness, or other strategies, will likely help limit susceptibility to infectious processes.

Biofeedback
In the subgroup of women who suffer from dysfunctional voiding, pelvic floor therapy appears to decrease recurrent UTIs.[57] Dysfunctional voiding is defined as increased external sphincter activity during voluntary voiding. This occurs in individuals without neurologic deficit.

Prevention Prescription

- Encourage a plant-based diet high in garlic and onions.
- Urge removal of possible bladder irritants such as caffeine, alcohol, and simple sugars.
- Encourage adequate fluid intake.
- Monitor stress, and focus on foundations of health such as optimal diet, physical activity, sleep, and mental and spiritual health.
- Encourage frequent voiding and avoidance of holding urine.
- Consider changing method of birth control if frequent UTIs occur after use of spermicides, condoms, or diaphragms.
- Recommend urination after intercourse.

Therapeutic Review

This is a summary of therapeutic options for UTI both for acute treatment and for prevention. If a patient presents with severe symptoms or has a history suggestive of a complicated UTI, an initial course of antibiotics would be beneficial. For the patient who has mild to moderate symptoms, a ladder approach may be appropriate. Patients should be counseled to seek further care if their symptoms worsen or do not resolve.

Acute Infection

Nutrition
- Encourage garlic consumption. C 1

Supplements
- D-Mannose: ¾ to 1 teaspoon three times daily C 1

Botanicals
- Cranberry 16 oz of unsweetened juice daily or extract 500 mg bid C 1

Continued

- Uva ursi: hydroquinone derivative 400-840 mg up to 4 times daily or 3 grams of dried root daily

Pharmaceuticals

- Trimethoprim-sulfamethoxazole: one double-strength tablet twice daily for 3 days
- Nitrofurantoin extended release: 100 mg twice daily for 7 days
- Ciprofloxacin: 250 mg twice daily for 3 days
- Phenazopyridine: 200 mg twice daily for 2 days

Recurrent Infections

Removal of Exacerbating Factors

- Eliminate use of spermicides, and try a change of birth control method.
- Recommend urinating after intercourse.

Nutrition

- Encourage garlic consumption.
- Encourage adequate fluid intake.

Supplements

- Probiotics: 1 billion CFUs daily of *Lactobacillus rhamnosus* or *L. fermentum*
- Vitamin C: 100 mg daily

Botanicals

- Cranberry: 16 oz of unsweetened juice daily or extract, 500 mg twice daily
- Uva ursi
- Other herbal products that have potential benefit, including berberine-containing plants and echinacea

Pharmaceuticals

- Trimethoprim-sulfamethoxazole: one double-strength tablet daily
- Nitrofurantoin: 100 mg daily
- Ciprofloxacin: 250 mg daily

Other Therapies

- Biofeedback for those with dysfunctional voiding
- Acupuncture

KEY WEB RESOURCES

National Center for Complementary and Alternative Medicine (NCCAM) Dietary and Herbal Supplements page. http://nccam.nih.gov/health/supplements

National Kidney and Urologic Diseases Information Clearinghouse. http://kidney.niddk.nih.gov/index.htm

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References are available at expertconsult.com

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Chapter 21

Recurrent Yeast Infections

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Pathophysiology and Epidemiology

Approximately 55% to 75% of all women experience vulvovaginal candidiasis (VVC) during their lifetime, and up to 40% to 50% of them will have recurrent episodes.[1] Approximately 8% of women will have recurrent vulvovaginal candidiasis (RVVC), as defined by four or more episodes in a year.[2] By age 25 years, half of all college women will have experienced at least one physician-diagnosed case of VVC.[3] African American women are more frequently affected than are others.[4,5]

VVC is extremely rare in premenstrual years and increases in reproductive age. It also tends to be less frequent in postmenopausal women, although women who are undergoing estrogen therapy generally have higher frequency of VVC.[6]

VVC is a spectrum of conditions with variable number of organisms and a variable degree of symptoms. Most highly symptomatic women have a large number of organisms with florid exudative vaginitis or thrush, most likely resulting from a combination of reduced local protective cellular responses and increased immediate hypersensitivity reaction. Other women have minimal symptoms with large numbers of organisms, most likely secondary to reduced local protective immune responses. Still other women are highly symptomatic with a small number of organisms and without thrush, most likely because of an immediate hypersensitivity response.[7]

Candida albicans, the most common pathogen implicated in RVVC, causes approximately 90% of cases. Other species include *Candida glabrata* (second most common), *Candida parapsilosis, Candida krusei, Candida tropicalis, Candida lusitaniae, Saccharomyces cerevisiae, and Trichosporon* species.[8] However, approximately 20% to 25% of asymptomatic women are colonized by *Candida* in their vagina, as shown by culture.[9] *Candida* also seems to be part of the normal vaginal flora and is in equilibrium with other bacterial and vaginal defense mechanisms.[10] *Candida* in blastophore form is consistent with asymptomatic colonization, and germinated yeast with hyphae are more common in symptomatic VVC.[7,11] Symptomatic cases of VVC and RVVC appear to be caused by host factors (aggressive innate response by polymorphonuclear neutrophils) rather than by the virulent properties of the organism.[12] Recurrence appears to result from relapse rather than reinfection, in response to a change in normal protective host defensive mechanisms at the vaginal mucosa.[7]

Typical symptoms of VVC include vulvovaginal pruritus (50%), vulvar swelling (24%), and dysuria (33%).[13] Vaginal discharge can be variable, from thin and watery to thick and resembling cottage cheese. Other common symptoms include vaginal soreness, irritation, vulvar burning, and dyspareunia. Examination may show vulvar and labial erythema, edema, and often fissures and peripheral pustulopapular lesions. The cervix is usually normal, often with vaginal mucosal erythema and an off-white discharge.[11]

The diagnosis is based on normal vaginal pH (4.0 to 4.5), clinical findings and symptoms, and positive microscopic findings with 10% potassium hydroxide (KOH). Cultures should be obtained in patients with symptomatic cases and negative KOH findings.[11,13] In recurrent cases, cultures must be obtained.[14] The sensitivity of microscopy is 50% at best,[15] however, and approximately 49% of culture results can be negative.[16] Polymerase chain reaction (PCR) is more sensitive than culture, but costs may be prohibitive.[17] Often, the diagnosis is based on clinical findings, vaginal pH, positive microscopic findings, and yeast cultures. In resistant cases, cultures are useful for isolating candidal species other than *C. albicans* to target the treatment.[14]

Classification of VVC is based on whether the infection is complicated or uncomplicated (Table 21-1).[8,14] Most cases of uncomplicated VVC respond well to a standard course of oral or topical antifungal therapy. In complicated VVC, the clinical situation may be complicated by the risk factors. To achieve a cure, all those factors must be addressed.

TABLE 21-1. Classification of Vulvovaginal Candidiasis

Uncomplicated
• Sporadic or infrequent VVC • Mild to moderate VVC • Most likely *Candida albicans* • Normal, nonpregnant, nonimmunocompromised women
Complicated
• Recurrent (four or more episodes per year) • Severe VVC • Non-*Candida albicans* • Aberrant host (e.g., uncontrolled diabetes, immunocompromised or pregnant women, debilitation)

VVC, vulvovaginal candidiasis.

Risk Factors

The following are considered to be risk factors for complicated VVC.

Nutritional

- Increased ingestion of sweets[14,18]
- Consumption of foods rich in simple carbohydrates[18]
- Decreased milk consumption[19]
- Increased caloric intake, with daily intake of carbohydrates greater than 223 g, and certain fibers[20]

Contraception

- Oral contraception[3,4] (higher risk with high estrogen content[21,22])
- Diaphragm[16,23]
- Intrauterine device[21,22]
- Sponge[21,22]
- Spermicide[4]

Sexual Behavior

- Receiving orogenital sex more than twice in 2 weeks (the most consistent evidence)[4,18,19,24–28]
- Anal intercourse[25]
- Female masturbation with saliva[18,19]
- Age at first intercourse[18,19,25] and frequency of vaginal intercourse[4,18,21,27,28] (conflicting evidence)
- High number of lifetime sex partners[21]
- Sexual intercourse during menstruation[21]
- Male factors: male masturbating with saliva in the past month and lower age of first intercourse[19] (Uncircumcised male patients have a higher risk than do circumcised men.[29])

Hygiene Products

- Douching[21,26,27]

Host Factors

- Immunosuppression/human immunodeficiency virus infection
- Diabetes
- Impaired glucose tolerance in nondiabetic patients[30]
- High body mass index[30]
- Race: blacks > whites > Asians[4]
- Antibiotic use[21,31] (Colonized women are more at risk.[32])
- Noncompliance with medications during previous infection[33]
- Prior diagnosis of VVC in the previous year[4]
- Pregnancy state, as a result of high concentrations of pregnancy hormones[34]

Psychosocial Factors

- High stress and psychosocial factors[35,36]
- Smoking[35]
- Decreased satisfaction in life[36]
- Poor self-esteem[36]

Receiving orogenital sex and using any form of contraceptive, having a high body mass index, having impaired glucose tolerance, consuming excessive sweets, and having high stress levels constitute some of the risk factors for recurrent vulvovaginal candidiasis.

In addition, women with persistent pruritus may benefit from the addition of antihistamines to main therapy.[37] Some studies have shown that cutaneous systemic hyposensitization of *Candida* antigen may benefit women with RVVC as an alternative approach to antifungal agents.[38,39] Treating male partners has no benefit in VVC recurrence rates.[40–42]

Integrative Therapy

Because RVVC is difficult to treat, incorporating complementary therapies with conventional treatment may be prudent.

Nutrition and Supplements

Given that increased caloric intake and increased consumption of sweets and simple carbohydrates are risk factors for RVVC, a low-fat, low-calorie diet rich in complex carbohydrates with avoidance of simple carbohydrates and sweets is recommended.

Yogurt (Containing Lactobacillus*)*

Probiotics are supplements that contain live bacteria. They colonize the gut and promote healthy normal flora. Yogurt containing *Lactobacillus acidophilus,* taken orally or intravaginally, has been found effective against VVC. One study found that daily ingestion of 8 oz of yogurt containing

L. acidophilus decreased both colonization and infection by *Candida*.[43] Another study showed that daily ingestion of 150 mL of yogurt containing *L. acidophilus* could increase vaginal colonization of *L. acidophilus*, but not necessarily decrease the incidence of VVC, as compared with pasteurized yogurt.[44]

Dosage

The dose is 8 oz of yogurt orally once or twice daily. It can be applied intravaginally with a tampon.

Probiotics

Lactobacillus is considered to be part of the normal vaginal and intestinal flora and may play a large role in the control of microflora and maintenance of the normal state by producing many metabolites that may deter the growth of pathogens, including *Candida*.[45] Among several known species of *Lactobacillus, Lactobacillus* GR-1 and *Lactobacillus fermentum* RC-14 have the ability to inhibit or kill yeast.[46,47] They provide resistance against *Candida* by preventing germination by producing bacteriocins and hydrogen peroxide.[48] Women with VVC are shown to have decreased numbers of *Lactobacillus* that produce hydrogen peroxide (*L. acidophilus, Lactobacillus gasseri,* and *Lactobacillus vaginalis*) and increased numbers of non–hydrogen peroxide–producing *Lactobacillus* (*Lactobacillus iners*) in their vaginal flora.[49] Other subspecies of *Lactobacillus* that produce hydrogen peroxide include *Lactobacillus jensenii* and *Lactobacillus crispatus*.[50] One study showed that approximately eight species of *Lactobacillus* have a protective effect against vaginal candidiasis.[51]

The optimum dosage of *L.* GR-1 and *L. fermentum* RC-14 is considered to be 10^9 organisms.[52]

Several clinical studies showed mixed results regarding effectiveness of various species of *Lactobacillus* in the treatment of RVVC. One pilot study showed resolution of RVVC with twice-daily vaginal suppositories containing 10^9 organisms of *Lactobacillus rhamnosus* GG.[53] Weekly intravaginal application of *L. acidophilus* was also found to be prophylactic against VVC in HIV-infected women.[54] However, a large randomized controlled double-blind study found that preparations containing *L. rhamnosus* and *Bifidobacterium longum* oral capsules and *L. rhamnosus*, *Lactobacillus delbrueckii*, *L. acidophilus,* and *Streptococcus thermophilus* vaginal pessary taken orally, vaginally, or both during and after the antibiotic administration (for nongynecologic infection) did not prevent VVC in women.[55] The amount of viable organisms was not mentioned in the study, and the duration of treatment after the course of antibiotics was only 4 days. Further large studies involving multiple species of hydrogen peroxide–producing *Lactobacillus* are needed to evaluate the effect on RVVC because *Lactobacillus* show host specificity and colonization potential.

Dosage

The dose is not standardized. Recommend using commercially available capsules containing at least 10^9 organisms of multiple species of *Lactobacillus* that produce hydrogen peroxide, such as *L. acidophilus, Lactobacillus* GR-1, *L. fermentum* RC-14, *L. rhamnosus* GG, *L. gasseri,* and *L. vaginalis*. These capsules can be taken orally or intravaginally on a daily basis for RVVC.

Precautions

None of the foregoing studies noted any harm or undesirable side effects of *Lactobacillus* used either topically or orally.

> Yogurt or probiotics that contain multiple species of *Lactobacillus* may inhibit the growth of *Candida* species. Oral or topical use of one or two *Lactobacillus* species may not be helpful in preventing recurrent vulvovaginal candidiasis because these species may not have specific action against the organism causing the infection.

Gentian Violet

Gentian violet is a dye and is an old antifungal remedy that is effective as a cure for RVVC.[56] A 0.25% to 0.5% aqueous solution can be applied at home daily for a week, or a 1% solution can be applied in the clinic weekly up to three times.[57] A 1% solution used daily for a week can successfully treat RVVC caused by *C. glabrata*.[58] Most of the commercial products have been discontinued.

Dosage

The best way to use gentian violet is to coat the vaginal wall with a swab or soak a tampon in the solution and insert it intravaginally overnight.[59]

Precautions

Gentian violet causes permanent staining of clothes that is almost impossible to remove, and some patients may develop vulvar irritation after application.[57]

Pharmaceuticals

Fluconazole

For uncomplicated infections, topical treatments are as effective as oral treatments, but most women prefer oral treatments with fluconazole for convenience.[40]

Complicated VVC is very difficult to treat and often requires twice the duration of the usual course of treatment; some patients require treatment for weeks or months.[14] One standard treatment is to use fluconazole, 150 mg once every 72 hours for 9 days, followed by maintenance therapy of 150 mg weekly.[14,60] Some patients may need to be treated for 14 days, followed by maintenance therapy. Occasionally, recurrent infections are caused by multiple species, especially *C. glabrata,* which is often resistant to itraconazole (74%) and to fluconazole (16%).[61] *C. glabrata* often requires an increased dose of fluconazole.[61] For recurrent infections, a maintenance regimen with 150 mg of oral fluconazole can be used on a weekly basis for 6 months, followed by 6 months of observation, with disease-free rates at 6, 9, and 12 months of 91%, 73%, and 43%, respectively.[62] Long-term maintenance treatment can reduce the rate of recurrence, but it is difficult to achieve a long-term cure.

Boric Acid and Combination Therapy

Intravaginal application of 600 mg of boric acid once daily for 14 days is effective for *C. glabrata,* with 70% success rate.[60] However, boric acid is associated with fetal anomalies and should not be used in pregnant women or in women who are trying to become pregnant.[60] It should not be taken

orally, either.[63] If boric acid fails to cure an infection, topical nystatin or flucytosine (17%) once daily for 14 days can be used. If that fails, a combination regimen consisting of topical boric acid, flucytosine, or nystatin, with oral itraconazole, is recommended.[64] In severe cases, low-potency topical corticosteroids may be used for symptom relief.[60]

Recurrent infections that do not respond to standard therapies may be caused by more than one species of *Candida,* and some of these species may be resistant to imidazoles and triazoles. Some patients may need long-term maintenance therapy, and some may require combination regimens.

Botanicals

Garlic (Allium sativum)

Results of in vitro studies showed that garlic has anticandidal properties.[65–68] Oral preparations of both fresh garlic extract and freeze-dried extracts are equally effective. The active ingredient, allicin, is known to inhibit both germination of spores and growth of hyphae.[69] No human studies have been conducted.

Dosage

The dosage for garlic has not been well established for VVC. However, one can take commercially available freeze-dried extracts of garlic up to 500 mg two to three times a day orally. Another treatment is to wrap a clove of garlic in unbleached gauze and crush it before inserting it into the vagina and leaving it there overnight. This treatment is repeated for 6 nights.[70]

Precautions

Topical applications of garlic can be uncomfortable because it can irritate the mucosa.

Tea Tree Oil (Melaleuca alternifolia)

Tea tree oil is native to Australia, and its main ingredient is terpin-4-ol. Results of in vitro studies have shown that tea tree oil has antifungal activities,[71–75] comparable to those of ketoconazole, econazole, and miconazole.[72] In vitro studies also found tea tree oil effective against fluconazole-resistant *Candida* species.[76] Human studies of tea tree oil for treatment of VVC are lacking.

Dosage

A preparation of 5% to 10% tea tree oil is applied topically daily. Alternatively, one to two drops of tea tree oil (commercially available, nonessential oil) can be placed in a gelatin capsule. The remainder of the capsule is filled with calendula oil or vegetable oil or water. Two capsules can be placed intravaginally overnight for up to 6 nights.[77]

Although most of the commercially available tea tree oils do not mention its concentration, patients can make their own preparations from tea tree essential oil. To make 5% tea tree oil, simply add 5 drops of tea tree essential oil to 5 mL of base oil (vegetable oil, coconut oil, or calendula oil) and mix thoroughly. Similarly, adding 10 drops to 5 mL of base oil will make a 10% mixture.

Precautions

Tea tree oil is known to cause allergic dermatitis. A skin patch test is recommended before use.[63] Tea tree essential oil should not be applied directly to the vaginal mucosa. It can cause severe irritation and damage because it is highly concentrated.

Mind-Body Approaches and Stress Management

Relaxation methods, meditation, deep breathing, yoga, guided imagery, and self-hypnosis can be used to manage stress and enhance mental and spiritual well-being, thereby improving immune response in patients who experience high levels of stress.

Risk Factor Reduction

Behavioral approaches can be used to reduce the risk factors listed previously. One may not be able to reduce all the risk factors, but addressing as many risk factors as possible may help prevent RVVC. Some of the behavioral approaches include avoidance of orogenital sex and douching, optimal glycemic control in diabetes, weight loss, exercise, and smoking cessation in individuals who warrant it. Unhurried sexual intercourse and extra lubrication for women who have a history of RVVC may help prevent damage to vaginal epithelium and, in turn, may prevent recurrence.[78] Wearing well-ventilated clothing can be beneficial.[11] In patients with severe recurrent cases, discontinuing contraceptives may be recommended. Strict compliance with an antifungal regimen must be emphasized.

Reducing risk factors for vulvovaginitis may prevent recurrence.

Prevention Prescription

- Avoid receiving oral sex for recurrent infections.
- Practice unhurried intercourse with extra lubrication to avoid trauma to the vaginal mucosa.
- Avoid using saliva for masturbation.
- Wear well-ventilated clothing.
- Consider discontinuing oral contraceptives with high doses of estrogen.
- Avoid douching.
- Avoid eating simple carbohydrates and sweets.
- Achieve optimal glycemic control in diabetes.
- Follow a diet and exercise program (useful with high body mass index and impaired glucose tolerance for prevention).
- Stop smoking.
- Treat depression, with effective stress management in recurrent cases.
- Ensure daily ingestion of yogurt containing multiple strains of *Lactobacillus.*
- Ensure a daily intake of garlic.

Therapeutic Review

Recurrent vulvovaginal candidiasis (RVVC) is often difficult to cure and may require an integrative approach along with conventional therapy. Some of the integrative approaches include nutrition and supplements, mind-body work, and risk factor reduction, along with longer-term pharmacotherapy.

Mind-Body Therapy

- Deep breathing, relaxation, yoga, and meditation may be useful in highly stressed individuals to prevent recurrences by enhancing immune function. C-1

Nutrition and Supplements

- Ingestion of 8 oz of yogurt containing multiple active species of *Lactobacillus* on a daily basis (Look for the "Live Active Culture" seal on the label, which requires 10^8 viable lactic acid bacteria per gram.) B-1
- Use of probiotics containing multiple active species of *Lactobacillus* (10^9 organisms) on a daily basis B-1

Botanicals

- Tea tree oil (5% to 10%) may be used topically in patients who are not allergic to it. C-1
- Fresh garlic cloves nightly intravaginally or 500 mg of garlic extract may be used orally two to three times daily. C-1

Pharmaceuticals

- For uncomplicated VVC:
  - Fluconazole: 150 mg orally once A-2
  - Clotrimazole vaginal (Gyne-Lotrimin): 200-mg suppository or 2% cream nightly for 3 days A-2
- For potentially resistant *Candida* strains, consider:
  - Terconazole vaginal (Terazol): 80-mg suppository or 0.8% cream nightly for 3 to 7 days A-2
- For complicated VVC:
  - Oral fluconazole: 150 mg every 72 hours for 9 to 14 days A-2
  - Oral ketoconazole: 200 mg once or twice daily orally for 14 days A-2
  - Boric acid: 600 mg intravaginally daily for 14 days B-2
- For RVVC and resistant VVC:
  - Maintenance therapy with fluconazole: 100 or 150 mg once a week long term A-2
  - Combination therapy with topical boric acid, nystatin or flucytosine (17%), and oral itraconazole: may be needed for some patients with recurrent and resistant cases B-2

KEY WEB RESOURCES

womenshealth.gov	U.S. Department of Health and Human Services Office on Women's Health
http://www.womenshealth.gov/faq/vaginal-yeast-infections.cfm	Patient education information
http://www.floracopeia.com; http://www.mountainroseherbs.com/aroma/ess.html	For purchasing high-quality tea tree essential oil

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References are available at expertconsult.com.

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Chapter 22

Lyme Disease

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Pathophysiology and Epidemiology

Lyme disease is a multisystem infection caused by the spirochetal bacterium *Borrelia burgdorferi.*[1] *B. burgdorferi* sensu stricto is the only species known to cause human infection in the United States, whereas pathogenic species in Europe include *B. burgdorferi* sensu stricto, *Borrelia garinii*, and *Borrelia Afzelii,* among others. Seven pathogenic species have been identified in Asia.[1]

In 1977, Lyme disease was characterized by Steere et al and named for the geographic area (Lyme, Old Lyme, and Haddam, Connecticut) where 39 patients presented with arthritic symptoms of previously unknown cause,[2] although individual cases of Lyme borreliosis were described in Europe in the early twentieth century.[1,3]

Lyme disease is the most common vector-transmitted disease in the United States. Approximately 20,000 cases of Lyme disease are reported to the Centers for Disease Control and Prevention (CDC) each year, although the CDC notes that these rates reflect both overdiagnosis of cases and overall underreporting.[4] Most (95%) reported cases occur in the northeastern and midwestern areas of the United States in 12 states (Connecticut, Delaware, Maine, Maryland, Massachusetts, Minnesota, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, and Wisconsin). Figure 22-1 illustrates the distribution of Lyme disease in the United States.

Lyme borreliosis also occurs in some Asian countries and throughout Europe.[1] Connecticut has the highest incidence of Lyme disease in the United States (122 cases per 100,000).[5] The incidence in the other states where Lyme disease is most endemic is 29.2 cases per 100,000.[4]

The principal vectors for transmission of *B. burgdorferi* in the United States are nymphal deer ticks *(Ixodes scapularis)* during the late spring or summer months.[6] Infected ticks need to be attached for at least 24 to 48 hours to be able to transmit the organism.[6] Bites from *Ixodes* ticks are usually painless and are often unrecognized. Figure 22-2 illustrates stages of the life cycle of the deer tick.

Ixodes ticks may also transmit *Anaplasma phagocytophila* (the agent of human granulocytic anaplasmosis [HGA]), *Babesia microti*, other *Borrelia* species, and viruses, either separately or in conjunction with *B. burgdorferi.*[7] The impact of coinfections on the clinical course of Lyme disease is not well defined,[7] although persons with coinfections may present with more symptoms and fever and chills.[8]

Infected persons do not transmit Lyme disease to others. No epidemiologic or clinical data currently confirm sexual or congenital transmission of *B. burgdorferi* between humans.[9]

Clinical Course

Lyme disease is classified into three stages: early localized Lyme disease, early disseminated Lyme disease, and late Lyme disease.[9] Early localized Lyme disease is characterized by a rash (erythema migrans) appearing at the site of the tick bite typically between 7 and 14 days following the bite.[9] Erythema migrans is usually asymptomatic but may become pruritic. Systemic symptoms sometimes may accompany the rash and include fever, myalgia, headache, fatigue, and localized lymphadenopathy.[9]

Early disseminated Lyme disease may manifest as multiple sites of erythema migrans, usually appearing 3 to 5 weeks following the tick bite. Neurologic findings, including meningitis and cranial nerve palsies, may be present along with fatigue, flulike symptoms, and syncopal episodes.[9]

Late Lyme disease is characterized by arthritis, usually affecting the large joints, including the knee, and this arthritis can be monarticular or oligoarticular. Neurologic complications may develop, including polyneuropathy, encephalitis, and encephalopathy.[9,10]

Persons suffering from chronic persistent symptoms often present with debilitating and severe symptoms. Patients should not be dismissed or disregarded because the pathophysiology of their symptoms is unknown. Effective symptomatic treatments can significantly improve quality of life.

FIGURE 22-1
Epidemiology of Lyme disease. The distribution of Lyme disease corresponds to the distribution of the *Ixodes* ticks that transmit *Borrelia burgdorferi*. (From the Centers for Disease Control and Prevention, Division of Vector-Borne Diseases. *Lyme Disease Transmission*. <http://www.cdc.gov/lyme/transmission/index.html>; 2011 Accessed 27.07.11.)

FIGURE 22-2
Various stages of the life cycle of the deer tick *Ixodes scapularis,* the vector for Lyme disease in the northern United States. The larval stage is shown on the *left,* followed by the nymphal stage, the adult female, and the adult male on the *right.* Most infections are transmitted from ticks at the nymphal stage. (From Murray TS, Shapiro ED. Lyme disease. *Clin Lab Med.* 2010;30:311.)

Chronic Persistent Symptoms, Chronic Lyme Disease, and Medically Unexplained Symptoms

Fatigue, arthralgia, and myalgia may persist after initial treatment for Lyme disease. Steere and Glickstein[11] reported that 10% of patients with Lyme arthritis develop persistent synovitis that can last for months or years after initial antibiotic treatment. The impact of persistent symptoms is great. The effect on health-related quality of life is reported to be comparable to or more severe than congestive heart failure and type 2 diabetes.[12]

In a cohort in Westchester County, New York, Asch et al[13] found that 53% of patients reported persistent symptoms following initial treatment for Lyme disease. These investigators noted that antibiotic treatment within 4 weeks of initial infection was associated with a greater likelihood of full symptom resolution.[13] In a pediatric cohort, 23% of children developed refractory arthritis after initial treatment.[14] These children were subsequently treated with nonsteroidal antiinflammatory drugs, intra-articular steroid injections, or disease-modifying antirheumatic drugs (DMARDs). None developed chronic arthritis or recurrent infections.[14] Polymerase chain reaction (PCR) testing of joint fluid can detect *B. burgdorferi* DNA for several weeks after spirochetes are killed,[15] and thus PCR may not be a good test for effectiveness of treatment. Chandra et al[16] found significantly higher levels of antineural antibody reactivity in persons with persistent Lyme symptoms compared with post-Lyme healthy and normal healthy controls, a finding suggesting that chronic symptoms may be related to a differential immune response.

Chronic Lyme disease is a label used for a constellation of nonspecific symptoms such as fatigue, night sweats, sore throat, lymphadenopathy, arthralgia, myalgia, palpitations, abdominal pain, nausea, diarrhea, sleep disturbance, poor concentration, irritability, depression, back pain, headache, and dizziness, with or without serologic or clinical evidence of previous infection by *B. burgdorferi.*[17–19] The diagnosis of chronic Lyme disease is nebulous; no standard definition exists, although the disorder is understood to be distinct from post-Lyme disease syndrome or late Lyme disease, in which arthralgia and other symptoms persist after documented *B. burgdorferi* infection.[20]

Patients are frequently diagnosed with chronic Lyme disease based on nonstandard interpretations of serology or other testing that has limited validity and reliability or, more often, based on clinical symptoms alone.[20] Chronic Lyme disease is diagnosed throughout the United States, including in areas where Lyme disease is not endemic.[19,21,22] Often, persons self-diagnose using lists of multiple nonspecific symptoms found on the Internet. Treatment usually includes regimens of multiple antibiotics, often administered parenterally, frequently continuing for months or years, in opposition to standard guidelines for treatment of Lyme disease.[20] This approach is far longer in duration and is associated with substantially greater risks than standard treatment for any other spirochetal infection and virtually all infectious agents treated with antibiotics. Chronic Lyme disease regimens often result in considerable out-of-pocket expenses (often amounting to tens of thousands of dollars per year), patient distress, and potential harm,[23] as well as increasing the risk of selecting for antibiotic-resistant bacteria.[19] Some investigators attribute chronic symptoms to drug-resistant reservoirs of *B. burgdorferi,* including atypical intracellular cystic or spherical forms.[24,25] However, no research has correlated the presence of these reservoirs with persistent symptoms, nor has the eradication of these been associated with improvement in symptoms.[26]

One survey found that 2.1% of Connecticut-based primary care physicians diagnose and treat chronic Lyme disease, whereas most were unsure or did not believe in the existence of chronic Lyme disease.[2] The predominant infectious disease, pediatric, and neurology organizations discount chronic Lyme disease as a distinct clinical entity, whereas other academic, professional, and advocacy organizations argue the contrary. The issue has become politicized, with acrimonious debate among academic organizations and advocacy groups.[27]

The symptoms of chronic Lyme disease can resemble other medically unexplained symptoms (also known as functional somatic syndromes) including chronic fatigue syndrome, irritable bowel syndrome, fibromyalgia, sick building syndrome, and chronic unexplained pain,[28,29] as well as neurologic conditions such as amyotrophic lateral sclerosis[30] or multiple sclerosis.[31] The lack of clear pathophysiology in medically unexplained conditions often results in extensive and expensive diagnostic workups and significant iatrogenic complications.[32,33] As in many chronic conditions in which persons are suffering from pain, psychiatric comorbidities are prevalent and are often overlooked.[2,33–35] At least 13% of outpatient visits are attributable to medically unexplained symptoms.[33,36] Suffering is often exacerbated by a self-validated or provider-validated cycle that attributes common somatic complaints to serious conditions.[35] Significant symptomatic and objective overlap occurs in these conditions, as well as high rates of concurrence of different syndromes.[35,37,38] In one sample, nearly half the patients with chronic Lyme disease were diagnosed with fibromyalgia.[39] Many syndromes manifest with similar constellations of nonspecific symptoms such as muscle weakness, arthralgias, and general fatigue.[40] Patients with these conditions regularly seek out complementary and alternative medicine (CAM) therapies and providers.[41–44]

Diagnosis

Lyme disease is diagnosed using historical and physical findings; serologic testing is used to support the diagnosis in persons without erythema migrans. Early Lyme disease is generally diagnosed based on the presence of erythema migrans; persons at this early state are usually seronegative because erythema migrans appears before an adaptive immune response develops.[45] In a case series in Maryland, 87% of patients with early Lyme disease presented with erythema migrans[46]; Of the Lyme disease cases reported to the CDC between 2003 and 2005, 70% manifested with erythema migrans.[4] The Food and Drug Administration (FDA) does not recommend serologic testing in early Lyme disease because of the low sensitivity of tests in early manifestations.[47]

Be careful to assess the diagnostic workup of any new patient who presents with chronic persistent symptoms attributed to Lyme disease. Patients often diagnose themselves by using unreliable symptom checklists found on the Internet.

The CDC criteria for Lyme disease are (1) erythema migrans alone or (2) at least one late manifestation in addition to laboratory confirmation of infection. Laboratory confirmation, by this definition, includes isolation of *B. burgdorferi* from a clinical specimen or the presence of immunoglobulin M (IgM) or immunoglobulin G (IgG) antibodies to *B. burgdorferi* in serum or cerebrospinal fluid.[48] The CDC recommends a two-tier process when testing blood for evidence of Lyme disease. Initial testing using an enzyme-linked immunosorbent assay (ELISA) or immunofluorescent assay (IFA) is followed by a Western blot for confirmation.[48] It is important to note that the CDC criteria for Lyme disease are not intended for use by clinicians to make a diagnosis of Lyme disease. Rather, they are intended for national surveillance data,[49] though the majority of cases in practice do fulfill this definition.[45]

ELISA testing is associated with many false-positive results,[50] hence the need for confirmation of a positive or equivocal ELISA result by Western blot. A negative ELISA result, conversely, does not warrant further serologic testing.[20,48] Western blot testing is more specific; that is, it will likely be positive when a person is truly infected. IgM antibodies appear first, typically within 1 to 2 weeks of initial infection. IgG antibodies appear later; usually within 2 to 6 weeks after the onset of erythema migrans. At least 90% of persons with late Lyme disease have positive IgG antibodies.[51] These may remain elevated following successful antibiotic treatment and symptom resolution.[45] Steere et al[8] reported that 16% of a large cohort had systemic symptoms of Lyme disease without initially presenting with erythema migrans and later demonstrated positive serologic findings.[8] Persons who fit into this rubric should have objective symptoms such as arthritis or facial palsy, as opposed to arthralgia.

Enzyme-linked immunosorbent assay (ELISA) testing is associated with many false-positive results,[50] hence the need for confirmation of a positive or equivocal ELISA result by Western blot. A negative ELISA result, conversely, does not warrant further serologic testing.

The sensitivity of two-tier testing is greatest in late Lyme disease; in the acute phase of erythema migrans, sensitivities range from 29% to 40% and increase to 97% in persons with arthritis (with specificity at 99%).[1] Considerable variability exists between the different commercial assays that are cleared by the FDA, especially for the detection of IgM antibodies.[1] Screening persons who do not have evidence of Lyme disease for possible exposure to Lyme disease is not recommended.[45] Seropositivity indicates past exposure and does not prove an active infectious process,[52] and it should not be used to diagnose active Lyme disease. Serologic testing is most useful in persons with a high pretest probability: persons in whom Lyme disease is likely, based on history and clinical presentation. In this population, positive serologic results support the diagnosis of Lyme disease. In late Lyme disease, a positive IgG test result nearly always occurs. In persons with low prior probability of Lyme disease, serologic testing has more false-positive results.

Testing of ticks for *B. burgdorferi* is generally not reliable for determining whether antibiotic therapy should be initiated.[53] Strict use of the standard diagnostic criteria minimizes false-positive test results, but atypical presentations are missed.[54] Less stringent diagnostic criteria incorporating broader clinical symptoms have been proposed and are in use by a minority of clinicians.[55] No literature is available assessing the diagnostic accuracy of these alternative criteria.

Unconventional Testing

Some unconventional (not FDA-cleared) direct-to-practitioner laboratory tests claim to improve on standard Lyme disease assessment and diagnosis methods. To review them all is beyond the scope of this chapter. These are often propriety tests developed and marketed by a single

laboratory. These tests are regularly paid for out of pocket by patients, often with extensive markups by practitioners. Besides the marketing materials from the laboratories themselves, few independent data have assessed the validity of these tests. Literature from one representative test included an advertisement for the test that superficially resembled a peer-reviewed journal article. The article promoted incorporating the laboratory's novel testing into existing diagnostic algorithms and claimed that the novel tests have relevance by "…clarifying clinically ambiguous cases, and confirming therapeutic success." No data justifying these claims were presented, although the choices of immunologic markers appeared reasonable.

The alternative tests appear to report positive results at higher rates than do conventional serologic testing. Despite the documented shortcomings of conventional serology that can lead to false-negative results and the appeal of tests that claim more sensitivity, the alternatives cannot be endorsed at this time. It is unknown whether the higher rates of positive results from alternative tests are caused by more true-positive findings or whether the results are (1) affected by selection effects (in which people more likely to be infected are sent to alternative laboratories); (2) less precise or accurate than conventional testing, (3) false positive, (4) affected by confirmation bias, or (5) a combination thereof. Unfortunately, no independent data are available that assess these factors.

Because of the high out-of-pocket cost, and the uncertain benefit of these tests, none of these unvalidated tests[56] can be recommended without documenting adequate human testing, at minimum ensuring the following: (1) high sensitivity and specificity in diagnosing Lyme disease according to established criteria, (2) minimal intrasample variability, assessed independently[5,57,58]; and (3) comparative effectiveness in relation to and in addition to standard ELISA and Western blot testing.

Integrative Therapy for Acute Lyme Disease

Persons with Lyme disease typically seek CAM for three major reasons. Some seek CAM therapies in addition to conventional therapies—a *complementary* or *integrative* approach. Some believe that conventional therapies are ineffective or dangerous and are seeking more "natural" *alternatives* to mainstream therapies. Some patients present after learning about chronic Lyme disease through the Internet or from advocacy groups promoting treatment protocols employing a myriad mixture of long-term antimicrobials (often parentally),[55,59] nutritional supplements, botanicals, and other unconventional therapies such as hyperbaric oxygen[60] or antifungals.[61]

In many conditions, complementary and alternative medicine (CAM) patients and providers are promoting less invasive therapies than the mainstream standard of care. Lyme disease is an unusual case in which CAM patients and providers are often seeking more invasive and elaborate interventions than conventionally provided.

Because the evidence that differentiates chronic Lyme disease from other medically unexplained conditions is unclear, this section focuses on acute Lyme disease, as defined and diagnosed using standard criteria.[20]

Risk Reduction

Reducing the risk of tick bites in endemic areas and proper removal of ticks within 48 hours following a bite are the most effective means to reduce the incidence of Lyme disease (see the Prevention Prescription box).

No major lifestyle interventions such as specific diets or exercise regimens have been shown to reduce risk of contracting Lyme disease.[62] "Immune-boosting" formulas or other natural products have not been shown to affect the incidence of Lyme disease.

Pharmaceuticals

Lyme disease is best treated with antibiotics. Treatment within 4 weeks of symptom onset is strongly associated with complete recovery.[13] Coinfections (HGA/ehrlichiosis, babesiosis) should be addressed as warranted. Persons experiencing symptoms of late Lyme disease with neurologic, rheumatologic, or cardiac manifestations should be treated by an appropriate specialist. No credible alternatives exist to prompt antibiotic treatment; the risks of inadequate treatment are progression to more severe symptoms and greater risk of long-term sequelae.

Antibiotics

Doxycycline is first-line therapy in early Lyme disease. It is effective for the treatment of erythema migrans, as well as for HGA, which may be concurrent with early Lyme disease.

Dosage for Adults[20]

Doxycycline: 100 mg twice per day for 14 days (range, 10 to 21 days)
Amoxicillin: 500 mg three times per day for 14 days (range, 14 to 21 days)
Cefuroxime axetil: 500 mg twice per day for 14 days (range, 14 to 21 days)

Precautions

Doxycycline should not be used in children younger than 8 years of age or in pregnant or lactating women. Amoxicillin and cefuroxime axetil are also effective for the treatment of early Lyme disease and can be used in children younger than 8 years of age.[20,42]

In persons with early Lyme disease with neurologic manifestations (meningitis or radiculopathy), oral doxycycline[63] or parenteral ceftriaxone is recommended for adults. Cefotaxime and penicillin G are effective alternatives.[20]

Dosage and Precautions for Lyme Disease With Neurologic Manifestations

Doxycycline: 200 mg per day for 14 days
Ceftriaxone: 2 g once per day intravenously for 14 days (range, 10 to 28 days)
Cefotaxime: 2 g intravenously every 8 hours
Penicillin G: 18 to 24 million units per day, divided into doses given every 4 hours for patients with normal renal function

Late Lyme arthritis can be treated with somewhat longer regimens than used in early Lyme disease. Some persons may not respond or may require intravenous antibiotics. For recurrent or persistent arthritis, the Infectious Disease Society of America recommends additional 4-week courses of oral antibiotics for persons whose symptoms have improved with initial oral treatment and intravenous therapy for persons not experiencing substantial improvement with oral antibiotics.[20]

Doxycycline can increase photosensitivity. Avoid exposure to sunlight, sunlamps, or tanning beds while using doxycycline. A sunscreen (minimum SPF 15) can also be helpful. Do not take iron supplements, multivitamins, calcium supplements, antacids, or laxatives within 2 hours before or after taking doxycycline.

Supplements

Probiotics

Antibiotic-associated diarrhea occurs in approximately 25% of patients.[64] Probiotic therapy can mitigate this side effect.[65] Because probiotic effects vary by indication and strain, prescriptions need to be strain specific. The strains most likely to be effective in treating antibiotic-associated diarrhea are *Lactobacillus* GG, *Lactobacillus sporogenes*, and *Saccharomyces boulardii.*[65] Some evidence supports the use of *S. boulardii* in treating *Clostridium difficile*–associated colitis.[66]

Dosage

The dose is 5 to 40 billion colony-forming units (CFUs)/day,[65] throughout the duration of antibiotic treatment.[67]

Precautions

Probiotics are generally safe, but case reports of endocarditis and sepsis in immunocompromised patients exist.[68] In addition, caution should be exercised in patients with a central venous catheter or those who have compromised intestinal mucosa.[64]

Integrative Therapy for Chronic Persistent Symptoms

Assessing whether Lyme disease was adequately treated and whether the patient actually had objective evidence of Lyme borreliosis is important. Persons without an initial diagnosis of Lyme disease that is based on objective criteria should be discouraged from pursuing a diagnosis of chronic Lyme disease. Persistent symptoms may not be caused by continued active borreliosis; rather, such patients can be treated with symptomatic and antiinflammatory measures. Antibiotic-refractory arthritic symptoms may also be autoimmune or attributed to persistent infection.[15]

For persons with unexplained symptoms who have a low prior probability of Lyme disease, the value of alternative testing is minimal because true-positive results are rare. If test results are positive, psychological benefits can be derived from a diagnosis supporting a defined medical process, whether or not the diagnosis is accurate. This potential benefit may be outweighed by the high possibility of negative externalities from identifying with cases of severe, lifelong debilitation (prevalent in the popular media),[69,70] coupled with highly invasive and potentially harmful treatments of unclear benefit. Clearly, benefit exists in a true positive identification of Lyme disease with subsequent treatment resulting in symptomatic relief, reducing the likelihood of long-term sequelae.

Certain unconventional methods are purported to treat acute or, more often, persistent infection. Some of these methods, purporting to detect "vibrations" in the body (e.g., the Rife machine) or electrodiagnostic devices (e.g., the Vega test) have no scientific basis and no validity in treating Lyme disease or any other disorder. Some elaborate alternative protocols exist,[7,72] but they have not been systematically assessed in controlled trials. Other common herbal therapies with some evidence of antimicrobial activity that are safe include *Artemisia annua*, olive leaf, goldenseal *(Hydrastis canadensis),* and grapefruit seed extract, although they have not demonstrated antispirochetal activity. Some other common interventions in Lyme disease protocols include chaparral *(Larrea divaricata)*[73] and colloidal silver,[74] which have significant risks of toxicity and harm; these should be actively discouraged.

The following are a sampling of integrative therapies that can be antiinflammatory or analgesic with a high potential benefit-to-risk ratio. Given the paucity of clinical trials assessing CAM interventions in persons with persistent symptoms following Lyme borreliosis, the therapies chosen here are safe and have demonstrated efficacy in inflammatory conditions or medically unexplained conditions that symptomatically resemble chronic Lyme disease. A more comprehensive list of potential therapies can be found in Chapter 46, Fibromyalgia, and Chapter 47, Effective Treatment of Chronic Fatigue Syndrome, Fatigue Fibromyalgia, and Muscle/Myofascial Pain: A Comprehensive Medicine Approach.

Acknowledging and addressing the real suffering and debilitating symptoms of patients is critical,[69,70] regardless of whether the cause of their symptoms is clear or ambiguous. The benefits of a salutogenic patient-practitioner relationship are described in Chapter 3, The Healing Encounter.

Pharmaceuticals

Antiinflammatory Treatments

Nonsteroidal antiinflammatory drugs (NSAIDs), intra-articular steroid injections, and DMARDs have all been used to treat persistent symptoms associated with Lyme disease.[14]

Antibiotics

Four randomized controlled trials were carried out on patients with post-Lyme disease syndrome who underwent long-term antibiotic regimens.[12,19,75–77] Krupp et al[75] demonstrated improvements in fatigue in persons treated with intravenous ceftriaxone after 28 days compared with placebo, without improvement in cognitive function or a laboratory measure of infection. Six of the 52 patients who began the interventions (11.5%) discontinued the study because of adverse events; of these, 4 patients (3 receiving placebo) required hospitalization for line sepsis.[75] None of the other studies demonstrated significant benefit for long-term antibiotic treatment in patients with ongoing subjective symptoms following standard treatment of initial Lyme disease.[12]

Case reports documenting symptomatic relief using long-term antibiotic therapy are common.[78] Cameron[79] reported significant improvements in quality of life in patients experiencing persistent Lyme disease symptoms when they were treated with amoxicillin for 3 months, although this study was criticized for several methodologic flaws that may render its conclusions moot.[80] Certain antibiotics, including macrolides and tetracyclines, used to treat Lyme disease exhibit antiinflammatory effects,[81] whereas beta-lactams[82] and tetracyclines[83] exhibit neuroprotective effects. Thus, symptomatic relief with antibiotics can be achieved through pharmacologic actions other than antimicrobial effects.

Precautions

The risks of long-term antibiotic therapy are well documented and include anaphylaxis, biliary complications resulting in cholecystectomy,[84] fatal sepsis,[23] and infection of intravenous catheters.[19] Longer courses of antibiotics increase the risk of adverse events.[15] NSAIDs, DMARDs, and intra-articular injections also pose considerable risk and may be undesirable if treatments with a better risk-to-benefit ratio exist.

If the presence of persistent borreliosis cannot be established using objective criteria, nonpharmacologic therapies are initially recommended for symptomatic relief. Pharmaceuticals can be considered if nonpharmacologic means do not provide adequate relief. Antibiotics should be used only if active borreliosis is confirmed.

Gabapentin

In an open pilot study in 10 patients with neuroborreliosis, all 10 patients were treated with gabapentin (starting at 300 mg/day and increasing to a maximum tolerated dose). Weissenbacher et al[85] reported that pain symptoms improved in 90% of patients, and sleep quality and general health improved in 50% of patients.

Dosage

The dose is 300 mg/day, titrating up to a maximum tolerated dose within 4 to 12 weeks. In the study by Weissenbacher et al,[85] the average dose associated with pain reduction was 700 mg, with a maximum doses between 500 and 1200 mg.

Precautions

Gabapentin is associated with various adverse effects, including depression and increased risk of suicide.[86] Abrupt discontinuation of gabapentin can cause withdrawal symptoms.[85]

Botanicals

The herb *Uncaria tomentosa* (cat's claw) is prominent in numerous alternative protocols for Lyme disease.[71] It has antioxidant, antiinflammatory, and immunostimulant activity.[87] No evidence exists for specific antispirochetal activity. In a randomized trial in persons with rheumatoid arthritis, a specific extract of *Uncaria tomentosa* demonstrated efficacy in reducing painful joints.[88]

Dosage

An extract free of tetracyclic oxindole alkaloids is taken at 60 mg daily in three divided doses.[88]

Nutrition

Antiinflammatory Diet

An antiinflammatory diet is characterized by emphasizing omega-3 fatty acids (found primarily in deep-water fish) and minimizing omega-6 fatty acids, with a focus on unprocessed whole grains, beans, and fruits and vegetables. Fish oil, especially eicosapentaenoic acid (EPA), is often added as a supplementary measure. Significant overlap exists between the antiinflammatory diet and the Mediterranean diet that can reduce risk of cardiovascular disease.[89,90]

Antiinflammatory diets have demonstrated clinical benefits in persons with inflammatory diseases such as rheumatoid arthritis.[89,91] More extensive antiinflammatory dietary measures, such as a gluten-free vegan diet, have been shown to reduce inflammatory markers in patients with rheumatoid arthritis,[92] as well as improve symptoms[93] (see Chapter 86, The Antiinflammatory Diet).

Aerobic and Weight-Bearing Exercise

Moderate aerobic exercise was shown to improve physical function, mood, symptom severity, and self-efficacy in patients with fibromyalgia,[94] as well as enhance energy in patients with unexplained fatigue.[95] Other trials confirmed the benefits of aerobic exercise and muscle strengthening for fibromyalgia.[96–98] Pain, the most characteristic symptom of fibromyalgia, was reduced in persons exercising at low-to-moderate intensity two or three times per week, and positive effects on depressed mood, quality of life, and physical fitness were noted.[99] Aerobic exercise, performed twice weekly over 8 months, can alleviate symptoms as well as demonstrate antiinflammatory effects.[100]

A systematic review confirmed that among myriad treatments proposed for fibromyalgia, exercise, specifically aerobic and weight-bearing exercise of mild to moderate intensity, has consistently shown to be effective in alleviating pain, fatigue, and depression and in improving health-related quality of life in persons with fibromyalgia[101] (see Chapter 88, Writing an Exercise Prescription).

Dosage

Mild aerobic exercise with weight training is performed two to three times weekly for at least 4 weeks.[101] Initiate at 15 minutes and increase to 30 minutes as tolerance grows.

Supplements

Probiotics

Preliminary studies suggested efficacy of the probiotic *Lactobacillus casei* strain Shirota (LcS) in treating anxiety associated with chronic fatigue syndrome.[102] Some protocols for chronic Lyme disease include probiotics.[59]

Dosage

The dose is 24 billion CFUs of *Lactobacillus casei* strain Shirota (LcS) per day. This probiotic is available in a fermented milk commercial product (Yakult).

Omega-3 Fatty Acids

Omega-3 fatty acid intake is inversely associated with major depression,[103,104] a strong comorbidity with chronic fatigue syndrome and fibromyalgia.[105] Further, serum levels of EPA

are significantly lower in patients with chronic fatigue syndrome than in healthy controls.[106] Omega-3 fatty acid supplementation has some evidence of efficacy in treating certain nonspecific symptoms associated with persistent Lyme disease including fatigue, arthralgias,[107] depression,[108] and anxiety.[56]

Dosage

The dose is 2500 mg of omega-3 fatty acids (with 50% or more EPA), consistent with a case series[109] documenting clinically significant pain reduction and improved function associated with various conditions, including fibromyalgia.

Intravenous Micronutrient Therapy

A clinical trial of a popular intravenous formula (the Myers cocktail)[110–112] found both a large treatment effect and a large placebo effect in pain, mood, and global function, with effect sizes comparable to those seen with FDA-approved drugs for fibromyalgia.[111]

Dosage

The Myers cocktail is infused intravenously weekly by slow push (10 minutes). Persons responding to the Myers cocktail should experience significant symptomatic relief within 4 weeks. The Myers cocktail contains the following:

5 mL magnesium chloride hexahydrate (20%)
3 mL calcium gluconate (10%)
1 mL hydroxocobalamin (1000 mcg/mL)
1 mL pyridoxine hydrochloride (100 mg/mL)
1 mL dexpanthenol (250 mg/mL)
1 mL B-complex 100, containing: 100 mg thiamine HCl, 2 mg riboflavin, 2 mg pyridoxine HCl, 2 mg panthenol, 100 mg niacinamide, and 2% benzyl alcohol
5 mL vitamin C (500 mg/mL)
20 mL sterile water

Biomechanical Therapies

Acupuncture

Acupuncture[113] and sham acupuncture[114] have been shown to improve pain symptoms associated with fibromyalgia. Although analgesic effects often do not differ from placebo acupuncture,[115] the therapy has minimal risk,[114] reduces anxiety,[115] and may be effective for fatigue[116] in chronic disease.[117]

Dosage

A 20-minute weekly session is typical.

Massage Therapy

Massage therapy demonstrated short-term beneficial effects in treating fibromyalgia symptoms in randomized trials.[118] Despite the lack of a complete understanding of the mechanisms, massage has clearly been shown to improve osteoarthritis pain.[119–123] Massage therapy has been evaluated and found efficacious as an adjunct treatment for pain secondary to cancer,[124–136] low back pain,[137–139] procedural pain,[140,141] rheumatoid arthritis,[142,143] and fibromyalgia.[144,145] It also has been shown to be beneficial for patients with chronic pain following spinal cord injury.[146] In a randomized, open-label clinical trial, a series of classical Swedish massage therapy sessions was found to be as effective as conventional analgesia for chronic rheumatic pain.[142]

Dosage

Swedish massage or another massage approach (30 to 60 minutes) is recommended once or twice weekly.

Mind-Body Therapy

Psychological trauma is associated with persistent Lyme disease symptoms[147] and fibromyalgia,[148] and chronic stress tends to exacerbate symptoms.[149,150] Mind-body therapies are especially attractive when psychological trauma predates the onset of symptoms because both somatic and psychological benefits are often seen[151] (see Chapter 100, Emotional Awareness for Pain, and Chapter 101, Energy Psychology).

Tai Chi

Wang et al[152] demonstrated significant benefits of tai chi, a Chinese mind-body practice involving meditation, deep breathing, and slow, gentle, graceful movements, for fibromyalgia. Tai chi has also shown promise in improving symptoms of rheumatoid arthritis.[61,153]

Dosage

A group course with an experienced teacher is recommended twice weekly for at least 12 weeks.

Mindfulness Meditation

Several trials have assessed the effects of various regimens of mindfulness meditation, with promising results in outcomes ranging from pain severity, physical function, and tender point threshold[154–157] in persons with fibromyalgia.

Mindfulness-based stress reduction (MBSR) is a standardized protocol of mind-body therapies that involves mindfulness meditation, patient education, and group support.[158–160] MBSR was developed by Kabat-Zinn et al at the Stress Reduction Clinic of the University of Massachusetts Medical Center. Several randomized trials demonstrated the benefit of MBSR for various chronic conditions, with improvements in psychological and somatic measures.[161–170]

Dosage

The standard 8-week course of MBSR consists of an instructor delivering group instruction for 2.5 hours weekly (consisting of meditation practice, group discussions, and mindfulness skill-building activities),[160] a single half-day meditation retreat, and daily practice for 30 to 45 minutes 6 days per week.[158]

Therapies to Consider

If chronic persistent symptoms continue without resolution, and if other conditions are definitively ruled out, a consultation with a Chinese medicine practitioner may be helpful. Some traditional Chinese medicine practitioners report treatments for spirochetal infections and related sequelae. No formal studies have assessed the efficacy and safety of such therapies, and caution should be expressed with using Chinese herbal medicines that may be adulterated with contaminants. Only herbal products employing standard quality control measures (e.g., good manufacturing practices) should be used.

Prevention Prescription

Reduce the risk of tick bites in endemic areas:

- Clear brush and trees, remove leaf litter and woodpiles, and keep grass mowed.
- Wear light-colored clothing that covers the skin to aid in identifying and protecting from tick bites. Tuck pant legs into socks when outdoors in vegetated areas.
- Apply tick and insect repellants containing DEET [*N,N*-diethyl-3-methyltoluamide], although excessive doses have been reported to cause neurologic complications in children.[171]
- Permethrin, a synthetic pyrethroid applied to clothing. is effective in killing ticks. Toxicities have been reported at high doses.[17,172]
- A plant-based insect repellant containing oil of lemon eucalyptus has been shown to protect from mosquitoes, but it has not demonstrated efficacy against ticks.[171]
- The most effective methods shown to reduce the risk of Lyme disease in endemic areas are the use of protective clothing and of tick repellants on the skin and clothing.[173]
- Check skin for ticks after being outdoors in the late spring and summer months in endemic areas. Figure 22-3 illustrates the life cycle of ticks that can transmit Lyme disease.
- Bathe within 2 hours after spending time in vegetation.[174]
- Pesticides are effective, but recommendations are tempered by environmental concerns and the risk of harming children and wildlife.

Reduce the risk of Lyme disease after a tick bite:

- Remove ticks with fine-tipped tweezers. Using a steady motion, grasp the tick as close as possible to the skin. Pull directly away from the skin. Do not use petroleum jelly, nail polish, or heated instruments to remove a tick.
- Monitor for signs and symptoms of Lyme disease after a tick bite.
- Consider antimicrobial prophylaxis (200 mg doxycycline in a single dose for adults or 4 mg/kg up to a maximum dose of 200 mg for children older than 8 years old, and 250 mg of amoxicillin in children younger than 8 years old) if a tick is attached for more than 48 hours in an endemic area,[20] although risk of *Borrelia burgdorferi* infection is low; 1.2% of untreated children in a large cohort developed Lyme disease after a tick bite in a highly endemic area. Treatment subsequent to symptom onset was associated with a complete recovery.[175]

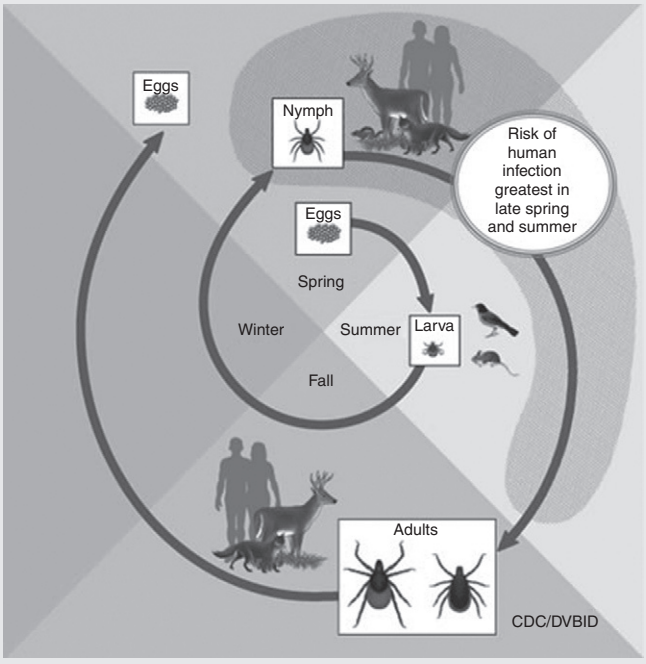

FIGURE 22-3
Life cycle of black-legged ticks that can transmit anaplasmosis, babesiosis, and Lyme disease. (From the Centers for Disease Control and Prevention, Division of Vector-Borne Diseases. *Life Cycle of Hard Ticks That Spread Disease*. <http://www.cdc.gov/ticks/life_cycle_and_hosts.html>; 2011 Accessed 27.07.11.)

Therapeutic Review

Acute Lyme Disease

- Antibiotics for early Lyme disease
  - Doxycycline: 100 mg twice per day for 14 days (range, 10 to 21 days), A2
  - Amoxicillin: 500 mg three times per day for 14 days (range, 14 to 21 days), A2
  - Cefuroxime axetil: 500 mg twice per day for 14 days (range, 14 to 21 days), A2
- Antibiotics for early Lyme disease with neurologic manifestations
  - Doxycycline: 200 mg per day for 14 days A2

Continued

- Ceftriaxone: 2 g once per day intravenously for 14 days (range, 10 to 28 days) 
- Cefotaxime: 2 g intravenously every 8 hours 
- Penicillin G: 18 to 24 million units per day, divided into doses given every 4 hours 

- Supplements
  - Probiotics: *Lactobacillus* GG, *Lactobacillus sporogenes,* or *Saccharomyces boulardii,* 5 to 40 billion colony-forming units (CFUs)/day throughout the duration of antibiotic treatment 

Chronic Persistent Symptoms

- Pharmaceuticals
  - Antiinflammatory treatments: nonsteroidal antiinflammatory drugs, intra-articular steroid injections, disease-modifying antirheumatic drugs; varied as needed 
  - Antibiotics (long-term, intravenous): varied, only when borreliosis is confirmed 
  - Gabapentin: 300 mg/day, titrating up to a maximum tolerated dose within 4 to 12 weeks (average dose, 700 mg) 
- Botanicals
  - *Uncaria tomentosa* (cat's claw): 60 mg daily in three divided doses of an extract free of tetracyclic oxindole alkaloids 
- Nutrition
  - Antiinflammatory diet (see Chapter 86, The Antiinflammatory [Omega-3] Diet) 
  - Aerobic and weight-bearing exercise: 15 to 30 minutes two to three times weekly for at least 4 weeks 
- Supplements
  - Probiotics: *Lactobacillus casei* strain Shirota, 24 billion CFUs; available in a fermented milk product 
  - Omega-3 fatty acids: 2500 mg of omega-3 fatty acids (with 50% or more eicosapentaenoic acid) per day 
  - Intravenous micronutrients therapy: Myers cocktail, 37 mL infused weekly 
- Biomechanical therapies
  - Acupuncture: 20-minute individualized session weekly 
  - Massage therapy: Swedish or other massage approach, 30 to 60 minutes, once or twice weekly, 
- Mind-body therapy
  - Tai chi: group course with an experienced teacher twice weekly for at least 12 weeks 
  - Mindfulness meditation or mindfulness-based stress reduction: group course with a weekly meeting and daily practice 

KEY WEB RESOURCES

Centers for Disease Control and Prevention, Division of Vector-Borne Infectious Diseases. http://www.cdc.gov/lyme

Lyme Disease Tick Map (iTunes app). http://itunes.apple.com/us/app/lyme-disease-tick-map/id369913510?mt=8

University of Rhode Island Tick Encounter Resource Center. http://www.tickencounter.org/

Acknowledgment

The helpful suggestions from Joshua P. Levitt, ND are appreciated.

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Chapter 23

Hypertension

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Hypertension is the most important risk factor for cardiovascular morbidity and mortality in industrialized countries. At least 65 million U.S. residents have blood pressures (BPs) that place them at significantly higher risk of coronary artery disease, heart failure, renal failure, thoracic and abdominal aneurysms, myocardial infarction, and stroke. Hypertension is also associated with cognitive dysfunction, erectile dysfunction, and loss of vision. The higher the pressure is, the greater is the risk of complications.[1]

The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) defined a normal BP as less than 120 mm Hg systolic and less than 80 mm Hg diastolic. The report similarly defined stage 1 hypertension as 140 to 159 mm Hg systolic and 90 to 99 mm Hg diastolic. In between normal and stage 1 values is a category the JNC 7 report termed prehypertension. The intent of using this newer term is to heighten awareness of both risk and opportunities for prevention. The JNC 7 report also noted that for persons with diabetes or renal disease and hypertension, the BP treatment goal is less than 130/80 mm Hg[1] (Table 23–1).

Prehypertension is a condition characterized by systolic blood pressure of 120 to 139 mm Hg and diastolic blood pressure of 80 to 89 mm Hg.

Hypertension has both modifiable and nonmodifiable risk factors. Gender and genetic heritage are certainly nonmodifiable factors. In addition, hypertension is a disease of aging: more than 65% of persons 65 years old or older are hypertensive.[1] Surprisingly, a person who is normotensive at age 55 years still has a 90% lifetime risk of developing hypertension.[2] Although chronologic age is not modifiable, physiologic aging itself may be. Hypertension is certainly also a disease of lifestyle: conventional risk modifications include reducing sodium intake, increasing exercise, moderating alcohol consumption, losing weight, and following the Dietary Approaches to Stop Hypertension (DASH) eating plan. Each of these lifestyle modifications demonstrably reduces BP. Similarly, because smoking, pain, and stress can significantly increase BP, efforts have been made to study the impact of smoking cessation, pain management, and stress management on hypertension.

More than 4 decades of randomized clinical trials have documented that pharmaceutical interventions prevent target organ damage including the number one and number three killers: heart attack and stroke. A reduction of just 5 mm Hg in systolic BP (SBP) is associated with a 7% reduction in all-cause mortality.[3] However, outside of clinical trials, only approximately one third of patients will achieve optimal BP control by using drug therapy.[1] Additionally, lowering of BP itself may not reduce the associated risk of neurocognitive dysfunction.[4] Clearly, an efficacy gap exists between BP reductions achievable in clinical trials and those reductions achievable in clinical practice.

A reduction of systolic blood pressure of 5 mm Hg is associated with a 7% reduction in all-cause mortality.

This efficacy gap in hypertension treatment represents an ideal opportunity to codevelop with a patient a customized action plan that addresses logical options in diet, exercise, supplementation, smoking cessation, and mind-body skills development. Additional insights may also come from both Ayurvedic and traditional East Asian medicine traditions. This chapter addresses how each of these individual interventions can contribute to improved health and well-being. When used in combination, however, these recommendations may be synergistic for other health goals. As an example, for sedentary and overweight or obese persons, the combination of aerobic exercise with the DASH diet and caloric restriction or weight loss not only lowers BP but also improves both insulin sensitivity[5] and neurocognitive function.[6]

TABLE 23-1. Classification and Management of Blood Pressure for Adults*

BP CLASSIFICATION	SBP* (mm Hg)	DBP* (mm Hg)	LIFESTYLE MODIFICATION	*Initial Drug Therapy*	
				WITHOUT COMPELLING INDICATION	WITH COMPELLING INDICATIONS
Normal	Less than 120	And less than 80	Encourage	No antihypertensive drug indicated	Drug(s) for compelling indications‡
Prehypertension	120–139	or 80–89	Yes		
Stage 1 hypertension	140–159	or 90–99	Yes	Thiazide-type diuretics for most; may consider ACEI, ARB, BB, CCB, or combination	Drugs for the compelling indications‡; Other antihypertensive drugs (diuretic, ACEI, ARB, BB, CCB) as needed
Stage 2 hypertension	160 of higher	or 100 of higher	Yes	Two-drug combination for most† (usually thiazide-type diuretic and ACEI or ARB or BB or CCB)	

From U.S. Department of Health and Human Services, National High Blood Pressure Education Program. *The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII)*. NIH publication no. 03–5233. Rockville, MD: National Heart, Lung and Blood Institute, National Institutes of Health; 2003:3.
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta blocker; BP, blood pressure; CCB, calcium channel blocker; DBP, diastolic blood pressure; SBP, systolic blood pressure.
*Treatment determined by highest BP category.
†Initial combined therapy should be used cautiously in those at risk for orthostatic hypotension.
‡Treat patients with chronic kidney disease or diabetes to BP goal of less than 130/80 mm Hg.

Hypertension frequently is asymptomatic; in the absence of symptoms, elevated numbers may not have any significance for a patient. In many cultures of the world, if no pain is felt, no disease is present. Encouraging any intervention to treat an abstract number, particularly a long-term intervention with no immediate benefit, is inherently problematic. For this reason, exploring the meanings, beliefs, and interpretations the patient brings to the experience of hypertension is crucial. The patient's answers should both guide the clinician's approach and foster a working partnership.

Also key is the patient's awareness of whether a BP issue even exists for him or her. Home BP monitoring with records in a diary is one means of raising awareness. Another method is use a 24-hour home BP monitor with a digital record. These approaches help confirm for the patient and the clinician that what is seen in the clinic is also what is happening at home.

To convey the meaning of the results, SBP values can be entered into the National Cholesterol Education Program Risk Assessment Tool for estimating the 10-year risk of either a myocardial infarction or coronary death (see Key Web Resources, later). Patients and clinicians can follow the risk assessment (based on Framingham Study data) for varying values including age, smoking status, and cholesterol status. These data can make concrete the value of normalizing BP and can show the relative value (and additive value) compared with reducing cholesterol now and as one ages.

Because many persons want to avoid pharmaceutical therapies, they seek integrative clinicians who can counsel from an evidence base on the logical options available to them. What follows are nonpharmaceutical approaches that include and go beyond the basic lifestyle modification recommendations found in the JNC 7 report.

Integrative Therapy

Lifestyle Modification

Smoking Cessation

Smoking cessation, of course, should be part of every comprehensive lifestyle modification plan. Cigarette use causes a 4 mm Hg increase in SBP and a 3 mm Hg increase in diastolic blood pressure (DBP) compared with placebo.[7] Persons with hypertension who smoke, however, have an additional increased risk of cardiovascular events compared with those with hypertension who do not smoke. This risk includes both ischemic stroke and hemorrhagic stroke and correlates directly with the number of cigarettes smoked.[8,9]

Diet

Two very well-studied diets for hypertension prevention and control, the Mediterranean and DASH diets, are quite different from the standard American diet because they are high in vegetables, fruits, and low-fat dairy products and are low in saturated fat and refined grains. This means that they are not high in sodium, but are instead are rich in potassium, magnesium, calcium, and fiber. Unlike the standard American diet, these diets incorporate both healthy fats and more complex, less refined carbohydrates.

Mediterranean Diet

The Mediterranean diet's capacity to prevent or treat hypertension was evaluated in 9408 men and women enrolled in a prospective cohort study from 1999 to 2005.[10] The study documented that, after adjustment for major hypertension risk factors and nutritional covariates, the degree of adherence to the Mediterranean diet over 6 years was associated with modest BP reduction. For study participants with high adherence, mean SBP declined by 3.1 mm Hg (95% confidence interval

[CI], −5.4 to −0.8), and mean DBP declined by 1.9 mm Hg (95% CI, −3.6 to −0.1).[10]

Beyond hypertension, a systematic review of 35 different experimental studies demonstrated that the Mediterranean diet has favorable effects on lipoprotein levels, endothelium vasodilation, insulin resistance, metabolic syndrome, antioxidant capacity, myocardial and cardiovascular mortality, and cancer incidence in obese patients and in those with previous myocardial infarction.[11] Additionally, the study by the National Institutes of Health and AARP (formerly the American Association of Retired Persons) of 214,284 men and 166,012 women demonstrated that, over 10 years, adherence to the Mediterranean diet was associated with approximately a 20% reduction in all-cause mortality in both men and women.[12] In comparing high with low conformity adherence in men, cardiovascular and cancer mortality were 0.78 (95% CI, 0.69 to 0.87) and 0.83 (95% CI, 0.76 to 0.91), respectively. Women similarly demonstrated a reduction of 12% for cancer mortality ($P = .04$).[12] From the HALE (Healthy Aging: Longitudinal Study in Europe) study of persons 70 to 90 years old, adherence to the Mediterranean diet and a healthful lifestyle was associated with a more than 50% lower rate of all-cause and cause-specific mortality[13] (see Chapter 86, The Antiinflammatory [Omega-3] Diet).

Olive Oil

One of the main components of the Mediterranean diet is olive oil, which provides both high levels of monounsaturated fatty acids, principally oleic acid, and healthy polyphenols. Oleic acid was shown to have antihypertensive effects in laboratory animals.[14] Phenolic compounds in olive oil prevent lipoperoxidation, induce favorable changes of lipid profile, improve endothelial function, and have antithrombotic properties.[15] In the Prevención con Dieta Mediterránea (PREDIMED) study of 772 asymptomatic persons 55 to 80 years of age who were at high cardiovascular risk, participants allocated to Mediterranean diets supplemented with either nuts or virgin olive oil, compared with participants allocated to a control low-fat diet, demonstrated mean reductions in systolic pressure of 5.9 mm Hg (CI, −8.7 to −3.1 mm Hg) and 7.1 mm Hg (CI, −10.0 to −4.1 mm Hg), respectively.[16]

Olive oil represents a logical substitute for butter and partially hydrogenated vegetable oils. The Food and Drug Administration (FDA) allows manufacturers to state on labels that consuming approximately 2 tablespoons (23 g) of olive oil a day may reduce the risk of heart disease. In general, use virgin olive oil for hot cooking and extra virgin olive oil for cold cooking such as in salad dressing or for dipping.

The consumption of a diet rich in polyphenols, including those found in olive oil and cocoa beans, appears to be important for hypertension prevention and control. Polyphenols can induce nitric oxide–mediated endothelium-dependent relaxation in most arteries including the coronary arteries. They can also induce endothelium-derived hyperpolarizing factor–mediated relaxations in many arteries.[17,18]

Cocoa (*Theobroma cacao*)

In observational studies, regular intake of cocoa-containing foods was linked to lower cardiovascular mortality. In a cohort of 470 Dutch men who were followed up for 15 years, cocoa intake was inversely associated with BP and was positively associated with reduced risk of both cardiovascular and all-cause mortality.[18a]

The first meta-analysis published reviewed five randomized controlled studies of cocoa administration ($N = 173$) with an average intake of 100 g daily (500 mg of polyphenols) for a median duration of 2 weeks.[19] The results demonstrated reductions in the pooled mean SBP and DBP of 4.7 mm Hg (95% CI, −7.6 to −1.8 mm Hg; $P = .002$) and 2.8 mm Hg (95% CI, −4.8 to −0.8 mm Hg; $P = .006$), respectively, compared with controls. Of the five studies cited, only two trials enrolled hypertensive patients.[19]

Following this report, the authors of the meta-analysis enrolled 44 adults with untreated upper-range prehypertension or stage 1 hypertension in a prospective 18-week randomized controlled trial of either 6.3 g (30 kcal) per day of dark chocolate containing 30 mg of polyphenols or matching polyphenol-free white chocolate.[20] Even this low-dose dark chocolate intake reduced the hypertension prevalence from 86% to 68%, with mean SBP decreasing by 2.9 (1.6) mm Hg ($P < .001$) and DBP declining by 1.9 (1.0) mm Hg ($P < .001$). This decrease was accomplished without changes in body weight, plasma levels of lipids, glucose, and 8-isoprostane (a measure of oxidative stress). The BP decrease was also accompanied by a sustained increase of the vasodilative nitric oxide donor *S*-nitrosoglutathione by 0.23 (0.12) nmol/L ($P < .001$). In comparison, the polyphenol-free white chocolate intake caused no changes in BP or plasma biomarkers.[20]

The benefit of flavanol-containing cocoa appears to extend to persons with diabetes as well. A 30-day, thrice-daily regimen of consumption of flavanol-containing cocoa (321 mg flavanols per dose) versus a matched product with 25 mg of flavanols per dose in 41 persons treated for diabetes increased baseline brachial artery flow-mediated dilatation by 30% ($P < .0001$) without evidence of tachyphylaxis or decline in glycemic control.[21]

The most recent pooled meta-analysis included 13 trials (15 treatment arms) and documented the most significant findings for hypertensive or prehypertensive subgroups (SBP: −5.0 ± 3.0 mm Hg; $P = .0009$; DBP: −2.7 ± 2.2 mm Hg; $P = .01$) compared with placebo.[22] BP was not reduced to less than 140 mm Hg systolic or 80 mm Hg diastolic. Daily flavanol dosages ranged from 30 to 1000 mg in the active treatment groups (dark chocolate with 50% to 70% cocoa).[22]

> Consider recommending one fourth of a standard-sized dark chocolate bar consisting of 70% cocoa daily.

Red Wine

Although alcohol consumption can cause multiple organ damage and can raise BP, red wine consumption is inversely associated with mortality from cardiovascular diseases.[23] Some studies have shown this effect even at high intakes, as much as 300 mL of wine per day.[24] Risk reduction is greatest for red wine at low to moderate intake.[25] One possible explanation is that red wine is an extremely rich source of bioactive polyphenols. Noteworthy compounds include the flavonoids quercetin, catechin and epicatechin, proanthocyanidins, and anthocyanins and phenolic acids, including gallic, caftaric, and caffeic acid, as well as the trihydroxystilbene termed *resveratrol*. These substances are not found in white wines because the fermentation process for white wines, unlike that for red wines, does not include the polyphenol-rich grape skins, seeds, and stems.[26]

Each polyphenol may play some role in preventing or treating hypertension. For example, quercetin, catechin, and resveratrol promote nitric oxide production by vascular endothelium. Although animal studies documented many potentially beneficial effects with oral administration of quercetin or resveratrol, they did not document a reduction in BP.[27,28]

DASH Diet

The DASH diet trial enrolled 459 participants and provided each with all his or her food for 11 weeks.[29] For the first 3 weeks, the participants were provided a control diet that was low in fruits, vegetables, and dairy products, with a fat content typical of the average diet in the United States. Participants were then randomly assigned to receive for 8 weeks the control diet, a diet rich in fruits and vegetables, or a "combination" diet rich in fruits, vegetables, and low-fat dairy products and with reduced saturated and total fat. Sodium intake and body weight were maintained at constant levels. For the 326 participants with prehypertension, the DASH diet resulted in reduced SBP and DBP of 3.5 mm Hg ($P < .001$) and 2.1 mm Hg ($P = .003$), respectively. Among the 133 subjects with stage 1 hypertension, the DASH diet reduced SBP and DBP by 11.4 and 5.5 mm Hg, respectively, more than the control diet ($P < .001$ for each).[29] These results have since been replicated in numerous settings (see Chapter 87, The DASH Diet).

Omega-3 Fatty Acids

A diet rich in cold-water fatty fish or grass-fed animals is also rich in omega-3 polyunsaturated fatty acids that may prevent the development of hypertension. Omega-3 fatty acid deficiency contributed to the development of hypertension in animal models.[30] This effect appears to be true for humans as well. A 20-year follow-up of a cohort of 4508 adults 18 to 30 years old who did not have hypertension at baseline documented an inverse association of long-chain omega-3 fatty acid intake with the development of hypertension. For the highest intake quartile compared with the lowest, after adjustment for potential confounders, the hazard ratio was just 0.65 (95% CI, 0.53 to 0.79; P(trend) < .01).[31] A double-blind placebo-controlled intervention of 4 g of omega-3 fatty acids for 8 weeks in patients with chronic kidney disease with an initial mean supine BP of 125.0/72.3 mm Hg demonstrated significant reductions in 24-hour SBP (−3.3 ± 0.7 mm Hg) and DBP (−2.9 ± 0.5 mm Hg), along with a 24% reduction in triglycerides.[32]

> Omega-3 fatty acids may be particularly useful in patients with the metabolic syndrome because of the effect of these fatty acids on improving insulin sensitivity and on reducing blood pressure and triglycerides.

Fiber

A meta-analysis of 25 randomized controlled trials published up to the year 2004 documented that supplemental intake of dietary fiber significantly reduced both SBP and DBP in hypertensive patients.[33] The degree of reduction was significant: SBP, −9.5 mm Hg (95% CI, −9.50 to −2.40); and DBP, −4.20 mm Hg (95% CI, −6.55 to −1.85). The investigators suggested that a period of at least 8 weeks was necessary to achieve the maximal BP reduction.[33] A 2007 study in hypertensive, overweight patients of psyllium powder, at a dose of 3.5 g 20 minutes before each meal, documented significant SBP and DBP reduction compared with controls.[34]

Exercise

Both JNC 7 and the American College of Sports Medicine recommended aerobic endurance exercise for the primary prevention, treatment, and control of hypertension. BP reductions of approximately 5 to 7 mm Hg systolic can follow an isolated exercise session (acute) or exercise training (chronic). This BP reduction can last up to 22 hours following endurance exercise. The higher the initial BP is, the greater is the response.

The American College of Sports Medicine recommended the following exercise prescription for persons with high BP[35]:

Frequency: on most, preferably all, days of the week

Intensity: moderate (40% to less than 60% oxygen consumption reserve [VO_2R])

Time: 30 minutes or more of continuous or accumulated physical activity per day

Type: primarily endurance physical activity supplemented by resistance exercise[35] (see Chapter 88, Writing an Exercise Prescription)

Weight Loss

A 2008 meta-analysis of all weight loss studies demonstrated that dietary interventions to reduce body weight resulted in better BP reduction than did either of the prescription drugs orlistat or sibutramine.[36] Weight loss of 4 kg (10 lb) by diet reduced SBP by approximately 6 mm Hg. Similar weight loss with orlistat reduced SBP by approximately 2.5 mm Hg. Sibutramine treatment reduced body weight but did not lower BP and may have even elevated it. The investigators noted that no prospective studies demonstrated that mortality or other patient-relevant end points could be lowered by weight reduction.[36]

Supplements

Several limitations exist in the literature on interventional nutrition. First, few studies measure and report serum levels at baseline and conclusion. The failure to document the presence or absence of a serum or intracellular deficiency or functional insufficiency means that dosing is blind. If one size does not fit all, then studies are at high risk for false-negative results because of underdosing. Additionally, treatment of a patient population with sufficient levels presumably means that additional dosing will not bring benefit. Without measurement of serum levels, adherence to the intervention protocol cannot be assessed. Second, few studies intervene with a dose based on achievement of a targeted serum level. Most dosing is extrapolated from in vitro studies or epidemiologic studies of intake in a large population. Individual variability in uptake and metabolism does not enter into dosing considerations. Third, differences in the bioavailability and function of the many forms of a dietary supplement may exist. The result is that much of the interventional nutrition research does not answer the very important clinical question, "Does replenishment of a deficiency to a given serum level result in an improved clinical outcome?" Evidence-based patient-centered care requires significantly better clinical studies.

Coenzyme Q10

Coenzyme Q10 (CoQ10, ubiquinone, or ubiquinol) is a crucial cofactor in the electron transport chain and oxidative phosphorylation for production of adenosine triphosphate (ATP). The highest tissue concentration is found in the heart, and the highest cellular concentration is on the inner membrane of the mitochondrion. CoQ10 can be a potent antioxidant. Reduced levels are associated with aging, hyperthyroidism, cardiovascular disease, total parenteral nutrition, aerobic training, and ultraviolet exposure.[37] Statins and some beta blockers, such as propranolol, can reduce endogenous production of CoQ10 by as much as 40%.[38] Supplementation can reduce two significant drivers of hypertension, oxidative stress and hyperinsulinemia.[39]

Statin drugs and some beta blockers (propranolol) can reduce the endogenous production of CoQ10 by as much as 40%.

Low serum levels of CoQ10 were first associated with hypertension in 1975.[40] Since then, several studies have documented that supplementation can significantly reduce both systolic and diastolic hypertension. This action happens without affecting plasma renin activity, aldosterone, or sodium and potassium. In 109 symptomatic hypertensive patients, supplementation with CoQ10 (75 to 360 mg/day) to achieve a serum level higher than 2.0 mcg/mL resulted in substantial reduction in mean SBP (from 159 to 147 mm Hg) and DBP (from 94 to 85 mm Hg), with concomitant improvements in New York Heart Association (NYHA) functional class and medication requirements.[41] After an average of 4.4 months, 37% of patients were able to discontinue 1 antihypertensive drug, 11% discontinued 2 drugs, and 4% discontinued 3 drugs. Only 3% required the addition of 1 antihypertensive drug, and none required the addition of more than 1 antihypertensive drug. Twenty-five percent of all patients were able to control their BP with only CoQ10 supplementation.[41]

A 2007 meta-analysis of 12 clinical trials (N = 352 patients) concluded that CoQ10 supplementation in hypertensive patients could lower SBP by up to 17 mm Hg and DBP by up to 10 mm Hg without significant side effects.[42] In 3 randomized double-blind controlled trials (N = 120), mean SBP in the treatment group decreased by 16.6 mm Hg ($P < .001$) from a mean of 167.7 mg Hg (95% CI, 163.7 to 171.1 mm Hg). The mean DBP decreased by 8.2 mm Hg ($P < .001$) from 103 mm Hg (95% CI, 101 to 105 mm Hg) before treatment. In comparison, the placebo arms of the trials demonstrated minimal and statistically insignificant reductions in SBP and DBP. In the open-label uncontrolled trials included in the analysis, patients were treated at doses of 60 to 120 mg daily for 6 to 12 weeks. Mean SBP declined by 13.5 mm Hg (95% CI, 9.8 to 17.1 mm Hg; $P < .001$), and mean DBP declined by 10.3 mm Hg (95% CI, 8.4 to 12.3 mm Hg; $P < .001$) This meta-analysis noted that in many of the studies included, patients were able to discontinue medication.[42]

Dosage

The dose to achieve a serum level greater than 2.0 mcg/mL is 75 to 350 mg a day taken with meals that contain some fat.

Precautions

Side effects are infrequent and include abdominal discomfort, nausea, vomiting, diarrhea, anorexia, rash, and headache. CoQ10 has an antiplatelet effect, so theoretically it can increase the risk of bleeding with antiplatelet or anticoagulant agents. Excretion is through the bile, and accumulation can occur in patients with hepatic impairment or biliary obstruction.

Vitamin D

Calcitriol, also known as 1,25-dihydroxyvitamin D, is the activated secosteroid hormone form of vitamin D that has receptors on nearly every tissue, including vascular smooth muscle cells[43] and renin-producing juxtaglomerular cells.[44] Calcitriol regulates hundreds of genes including the renin gene and thus the renin-angiotensin system that controls BP.

Observational data from both the Health Professionals Follow-up Study (613 men) and the Nurses' Health Study (1198 women) associated low vitamin D status with significantly increased risk of incident hypertension over 4 to 8 years. For participants with a serum 25-(OH) vitamin D level lower than 15 ng/mL compared with participants with a level higher than 30 ng/mL, the relative risk for men was 6.13 (95% CI, 1.00 to 37.8) and for women was 2.67 (95% CI, 1.05 to 6.79).[45] In 2010, the Intermountain Heart Collaborative Study Group documented that for 41,504 patients, vitamin D deficiency (less than 30 ng/mL) was associated with highly significant ($P < .0001$) increases in the prevalence of hypertension and the associated cardiac risk factors of diabetes, hyperlipidemia, and peripheral vascular disease. Deficiency also correlated strongly ($P < .0001$) with coronary artery disease, myocardial infarction, heart failure, stroke, and incident-related death.[46]

Despite the potential benefits of vitamin D for cardiovascular health, few prospective trials support the hypothesis that vitamin D replenishment to normal levels reduces BP. For 148 older women with a mean 25-(OH) vitamin D serum level of 10 ng/mL (severe deficiency), 800 units of vitamin D_3 supplementation per day for 8 weeks, compared with placebo, raised serum levels by 12 ng/mL and reduced systolic pressure by 7 mm Hg.[46a] In contrast, for 189 men and women with a mean baseline level of 13 ng/mL, a single dose of 100,000 units of vitamin D_3, compared with placebo, raised serum levels to a mean of 20 ng/mL at 5 weeks but did not change BP.[46a]

The largest prospective trial to date enrolled 438 participants with a mean body mass index of 35, a mean 25-(OH) vitamin D level of 23.2 ± 8.5 ng/mL, SBP of 124 ± 15, and DBP of 75.4 ± 9.7 mm Hg and randomized them into 3 treatment groups: placebo, 20,000 units, or 40,000 units of oral cholecalciferol per week.[47] At the end of 1 year, the low-dose group increased their serum 25-(OH) vitamin D levels to a mean of 40 ng/mL, and the high-dose group increased their levels to a mean of 55 ng/mL with no significant change in BP.[47] Because the main objective of this study was to study the effect of vitamin D supplementation on weight change, the study was not designed and powered for detecting effects on BP. Additional prospective studies are now under way. The most important question at this time is whether a threshold serum level is needed to reduce the risk of incident hypertension or to reduce already elevated BPs. Additionally, the length of time of vitamin D sufficiency required for prevention or reduction must be defined.

Dosage
Until more is known, supplement to keep serum 25-hydroxyvitamin D levels between 40 and 80 ng/mL.

Precautions
Some concern exists regarding increased calcification of blood vessels with aggressive calcium and vitamin D supplementation.

Magnesium
Magnesium is a well-understood and frequently used intervention for the hypertension of preeclampsia. JNC 7 guidelines did not recommend oral supplementation of magnesium. In addition to the potentially high magnesium intake with either a Mediterranean diet or the DASH diet, however, several studies documented that low dietary intake of magnesium correlated strongly with high BP. The Women's Health Study followed 28,349 female U.S. health professionals who were at least 45 years old and were without hypertension for nearly 10 years.[48] Magnesium intake, after adjustment for age and randomized treatment, was inversely associated with the risk of incident hypertension. The highest quintile of intake (median, 434 mg/day) had a relative risk just 0.87 (95% CI, 0.81 to 0.93; P (for trend) < .0001) compared with those in the lowest quintile (median, 256 mg/day). Further adjustment for other risk factors attenuated this inverse association slightly.[48] Natural sources of magnesium include pumpkin seeds, nuts, quinoa, spinach, bran cereal, buckwheat, and beans.

Oral clinical intervention studies have not demonstrated a consistent benefit. As noted earlier, several limitations exist in the literature. For magnesium, few studies have measured serum levels, and even fewer have measured intracellular magnesium levels. Serum magnesium levels do not reflect intracellular magnesium.[49]

Additionally, the many forms of magnesium may have different bioavailability and physiologic activity. The result is a "one size fits all" approach to magnesium studies of varying dosing and varying type of magnesium that prevents any meta-analysis of existing randomized trials. Despite these limitations, magnesium appears to be beneficial and nontoxic.

One clinical trial enrolled 48 patients with mild uncomplicated hypertension and randomized them to 12 weeks of 600 mg/day of oral magnesium pidolate and lifestyle recommendations or a control group of lifestyle recommendations. Mean 24-hour SBP declined 5.6 ± 2.7 mm Hg (P < .001), and DBP declined 2.8 ± 1.8 mm Hg (P = .002) compared with controls.[50] In 82 diabetic hypertensive adults with documented hypomagnesemia who were taking captopril but not diuretics, supplementation of 2.5 g of magnesium chloride over 4 months, compared with placebo, dropped SBP 20.4 ± 15.9 mm Hg versus 4.7 ± 12.7 mm Hg (P = .03). The magnesium intervention reduced diastolic pressure 8.7 ± 16.3 mm Hg versus 1.2 ± 12.6 mm Hg in the placebo group. The adjusted odds ratio between serum magnesium and BP was 2.8 (95% CI, 1.4 to 6.9). A threshold serum level for effect was not reported.[51]

Dosage
The dose is 400 to 800 mg of nonoxide forms of magnesium (e.g., citrate, glycinate, taurate), to achieve a normal intracellular and serum level.

Precautions
Magnesium can cause loose bowel movements. Start at a low dose (120 to 200 mg) and slowly increase as tolerated.

Botanicals

Garlic (Allium sativum)
Garlic has been widely promoted for antihyperlipidemic effects, but both animal and human studies have suggested a BP-lowering effect. Two separate meta-analyses published in 2008 demonstrated significant BP-lowering effects in persons with hypertension.[52,53] The first meta-analysis included 11 of 25 studies from the systematic review. These demonstrated a mean decrease in the hypertensive subgroup of 8.4 ± 2.8 mm Hg for SBP (P < .001), and 7.3 ± 1.5 mm Hg for DBP (P < .001).[52] The second meta-analysis included 10 trials in the analysis, of which 3 had patients with elevated BPs. For hypertensive participants, the garlic interventions reduced SBP by 16.3 mm Hg (95% CI, 6.2 to 26.5) and DBP by 9.3 mm Hg (95% CI, 5.3 to 13.3) compared with placebo.[53]

Dosage
The dose for raw garlic cloves is one half to two per day. Supplements can help prevent garlic breath. Consider a standardized dose of 350 mg twice a day (4000 mcg of allicin).

Precautions
Adverse effects include the following: diaphoresis; dizziness; mouth, esophagus, and stomach irritation; nausea; and vomiting. Allergic reactions are rare. Doses greater than for culinary use may increase the risk of bleeding if they are taken with anticoagulants or antiplatelet agents.

Hawthorn (Crataegus monogyna)
Hawthorn as an herbal extract is a cardiovascular tonic popular in Europe that has been in use since at least the first century AD. Hawthorn is a short deciduous tree whose leaves, berries, and flowers contain high concentrations of flavonoids. Extracts are used for their positive inotropic and vasodilatory properties. Two clinical trials for BP demonstrated very mild changes.[54,55] Hawthorn is most often used for early-stage congestive heart failure (see Chapter 24, Heart Failure).

Dosage
The German Commission E Monographs cites the use of standardized extracts containing 30 to 169 mg of proanthocyanidins (18.75%) calculated as epicatechin or 3.5 to 19.8 mg of flavonoids (2.2%) calculated as hyperoside taken in two to three individual doses for a total of 750 to 1500 mg of hawthorn per day.[56]

Precautions
Transient side effects including dizziness, gastrointestinal complaints, headaches, and heart palpitations have been reported.[57] Results from the HERB-CHF trial of *Crataegus* extract WS 1442 documented that participants treated with the extract were 3.9 times more likely to experience progression of heart failure at the start of hawthorn therapy compared with placebo. This increased risk decreased over time.[58]

Herbs to Avoid in the Treatment of Hypertension

Herbs that require close monitoring in the treatment of patients with hypertension include licorice, ephedra, and *Panax ginseng*. These have the capacity to raise blood pressure significantly.

Mind-Body Therapy

Despite numerous historical reports of decreases in BP attributed to mind-body practices,[59–64] a Cochrane Review[65] raised concerns about the impact of these interventions on BP because many studies were conducted in the 1980s and 1990s, and the methodologic quality of these studies was inconsistent. Specifically, not all the studies were randomized controlled trials, the enrollment criteria were not specific to age group, cardiovascular risk factors, or type of hypertension, and the degree of BP reduction varied widely. This important meta-analysis of randomized controlled trials somewhat surprisingly concluded that mind-body practices produced only modest benefits in reducing SBP, even though the investigators reported a roughly 5.5 mm Hg reduction in SBP and a 3.5 mm Hg reduction in DBP.[64] SBP reductions between 2 and 5 mm Hg result in decreased mortality from stroke (14%), coronary heart disease (9%), and total mortality (7%).[66]

Since 1995, additional well-designed randomized controlled trials have demonstrated the efficacy of mind-body interventions, including relaxation response elicitation,[67] biofeedback,[68] transcendental meditation,[69,70] yoga,[71] qi gong,[72,73] and tai chi,[74] on reduction of SBP or DBP. Aggregating these studies, one finds average reductions of roughly 10 mm Hg and 7 mm Hg for SBP and DBP, respectively.

Relaxation Response

One study examined the efficacy of an 8-week relaxation response in hypertensive older adults (mean age, 66.8 years) with elevated SBP and normal DBP who were taking at least 2 antihypertensive medications.[67] Participants were blinded to hypothesis and were randomly assigned to 2 possible interventions to reduce BP: group 1 (relaxation response intervention; $n = 61$) or group 2 (intensive lifestyle modification; $n = 61$). SBP decreased by 9.4 mm Hg and 8.8 mm Hg in the relaxation response and lifestyle modification groups, respectively ($P < .0001$) without group difference. In a second phase of the study, participants who achieved an SBP of less than 140 mm Hg and had at least a 5 mm Hg reduction from baseline entered an antihypertensive medication elimination protocol. Forty-four subjects in the relaxation response group and 36 in the lifestyle modification group qualified for the protocol. Participants in the relaxation response group were more likely to eliminate an antihypertensive medication successfully than were those in the lifestyle modification group (odds ratio, 4.3; 95% CI, 1.2 to 15.9; $P = .03$). The relaxation response intervention not only led to an important decrease in BP comparable to that of intensive lifestyle modification, but also resulted in a significantly greater capacity for participants to eliminate an antihypertensive medication without increasing BP.

Biofeedback

The impact of a biofeedback intervention was tested in unmedicated persons with hypertension (mean age, 50.5 years).[68] Biofeedback ($n = 21$) had a nominal impact on SBP (0.3 mm Hg reduction) and DBP (0.9 mm Hg increase) relative to the control condition ($n = 21$) (0.4 mm Hg reduction in SBP and 3.0 mm Hg reduction in DBP). No differences were shown across groups (see Chapter 94, Enhancing Heart Rate Variability).

Transcendental Meditation

Two studies examined the effect of a 12-week proprietary Transcendental Meditation (TM) intervention on BP in medicated African Americans. In the first study,[69] 111 individuals (mean age, 67 years) were randomized to TM, progressive muscle relaxation (PMR), or health education. Results indicated that TM resulted in a 10.6 mm Hg reduction in SBP and a 6.6 mm Hg reduction in DBP, significantly greater than the 4.0 mm Hg and 2.1 m Hg reduction for PMR and greater than the 1.5 mm Hg reduction in SBP and 0.6 mm Hg increase in DBP for the health education group. In a more recent study enrolling younger subjects (mean age, 48.5 years),[70] the TM intervention ($n = 54$) resulted in a 1.6 mm Hg reduction in SBP and a 4.2 mm Hg reduction in DBP at the end of the 12-week intervention. PMR ($n = 52$) led to a 1.77 mm Hg increase in SBP and a 1.4 mm Hg reduction in DBP, whereas health education ($n = 44$) resulted in a 2.0 mm Hg increase and a 0.5 mm Hg decrease in DBP. In all, the results of these well-controlled trials indicate a significant impact on BP by the TM intervention (see Chapter 98, Recommending Meditation).

Yoga

A study to explore whether a yoga intervention affects BP was conducted in unmedicated persons with hypertension who were 35 to 65 years old.[71] The 33 subjects were equally randomized to yoga intervention, treatment with antihypertensive medications, or a no-treatment control. Yoga resulted in large reductions in SBP (33.3 mm Hg) and DBP (26.3 mm Hg), comparable to the impact of antihypertensive medications on SBP (24.0 mm Hg) and DBP (9.9 mm Hg). Both the active interventions were superior to the smaller reductions exhibited in the no-treatment group (SBP, 4.2; and DBP, 2.0 mm Hg).

Qi Gong

Numerous studies have examined the effect of a qi gong intervention on BP. However, only 2 exist in the English language. In the first study,[72] 58 unmedicated individuals (mean age, 56 years) were randomized to either a 10-week qi gong intervention or a wait list control group. Qi gong led to a significant reduction on SBP and DBP (approximately 10 mm Hg and approximately 3 mm Hg, respectively) compared with increases in SBP and DBP (approximately 3 mm Hg and approximately 1 mm Hg, respectively) in the wait list control group. In the second study,[73] 36 unmedicated participants were equally divided randomly to a 8-week qi gong intervention or a wait list control. Qi gong had a significant reduction on SBP and DBP (approximately 12 mm Hg and approximately 10 mm Hg, respectively) compared with increases in SBP and DBP (approximately 2 mm Hg and approximately 2 mm Hg, respectively) in the wait list control group. Because both studies included a wait list control group, placebo-controlled studies are now needed. Nevertheless, especially if one considers the numerous studies published in Chinese,[74] some support exists for considering a qi gong intervention for hypertension.

Tai Chi

The impact of a tai chi intervention was tested in a group of 76 people with stage 1 hypertension or high-normal BP and no medications (mean age, 51.6 years).[75] The 12-week intervention had a large impact on SBP (15.6 mm Hg reduction) and DBP (8.8 mm Hg decrease) relative to the sedentary control condition (n = 37) (6.4 mm Hg increase in SBP and 3.4 mm Hg increase in DBP). Tai chi resulted in significant reductions in BP relative to a sedentary control.

Despite important methodologic concerns raised in meta-analyses from earlier studies, more recent evidence examining the impact of various mind-body approaches on BP supported clinically relevant and persistent reductions. Although it is true that several of the more recent studies also were limited by small sample sizes, the overall consistency of positive results indicates that, as a whole, mind-body interventions do positively affect both SBP and DBP. Many mind-body studies now address the mechanistic and biologic underpinnings of the way in which these approaches reduce BP.[71–73,76] Understanding the mechanisms of how these therapies decrease BP will increase appropriate use of these therapies in clinical contexts.

Therapies to Consider

Ayurveda and traditional Chinese and East Asian medicine are complete paradigms from outside the Western scientific understanding that requires measurement of BP. For this reason, no "traditional" approach exists in either Eastern tradition to the management of the Western diagnosis of hypertension. For Ayurvedic and traditional East Asian medicine practitioners, contemporary approaches to hypertension are extrapolated from ancient texts and modern experience. Their concomitant use may lead patients to a more health-conscious lifestyle.

Ayurveda

Practitioners may use diet, lifestyle adjustments, herbs, breathing exercises, massage, and yoga to balance doshas pertinent to the experience of hypertension such as a state of excess pitta (fire and heat). For many persons with hypertension, a pitta-pacifying diet of cooling foods may be beneficial. Foods that may lead to imbalanced pitta states include coffee, alcohol, and hot, spicy, and oily foods, which can include many nuts, in addition to fermented and pickled foods. These foods may be especially challenging in hot summer months. Patients may also benefit from yoga for hypertension. A study of 57 prehypertensive or stage 1 hypertensive participants randomized to Iyengar yoga or enhanced usual care demonstrated significant reductions after 12 weeks of 6 mm Hg SBP (P = .05) and 5 mm Hg DBP (P < .01) in the yoga group compared with baseline.[77]

Traditional Chinese and East Asian Medicine

Practitioners may identify persons with the Western diagnosis of hypertension as having one or more Eastern diagnoses such as yin deficiency of liver and kidney, ascendant liver yang, phlegm stagnation, or blood stagnation. Persons with a Western diagnosis of hypertension may be treated for an Asian pattern with acupuncture, moxibustion, or herbs to tonify, expel phlegm and wind, clear heat, resolve blood stasis, or clear dampness. Commonly used herbs in multiple-herb formulas include Gouteng (*Uncaria* species), Niu Xi (*Cyathala* species), Tianma (*Gastrodia* species), Chuanxiong *(Ligusticum sinense),* Fuling (*Poria cocus* Wolf), Zexie (*Alismatis* species) and Juhua (chrysanthemum). The Chinese herb termed Danshen *(Salvia miltiorrhiza),* commonly used for cardiovascular issues, should not be used concurrently with warfarin.[78] Use of any herbal medicines with Western cardiovascular pharmaceuticals warrants close monitoring. Acupuncture may provide positive effects with enhanced regulation of the autonomic nervous system and achievement of a balanced constitutional state. Currently, insufficient evidence exists to support the use of acupuncture,[79,80] moxibustion,[81] or ancient multiple-herb formulas for treating the Western diagnosis of hypertension.

Prevention Prescription

Michael Pollan advises this: "Eat food. Not too much. Mostly plants." These three guidelines will minimize intake of unhealthy fats including hydrogenated vegetable oils, limit intake of unhealthy sugars including high-fructose corn syrup, and significantly increase soluble fiber intake.

- Exercise at least 30 minutes a day at least 4 days per week.
- Limit alcohol consumption.
- Do not smoke.
- Breathe: incorporate mind-body practices into your daily routine.

Therapeutic Review

Dietary

- Follow the DASH diet eating plan with its emphasis on foods rich in potassium, magnesium, and calcium. A1
- Reduce dietary sodium to less than 2.4 g per day (1 teaspoon). A1
- Limit alcohol to two drinks or less per day for men and one drink or less per day for women. A1
- Consider 10 to 30 g per day of 70% cacao dark chocolate (one fourth of a regular-sized chocolate bar).

Exercise

- Aim for 30 minutes a day of aerobic exercise. A1

Weight Loss

- Aim for a weight loss of at least 10 lb (4.5 kg) if overweight. A1

Continued

Supplements

- Maintain serum 25-(OH) vitamin D level greater than 40 ng/mL. C 1
- Ensure 1000 mg a day of eicosapentaenoic acid and docosahexaenoic acid by fish or krill oil. A 2
- Consider coenzyme Q10 to achieve a serum level higher than 2.0 mcg/mL. B 2
- Consider magnesium at 6 mg/kg. B 2

Botanicals

- Consider a trial of garlic at 350 mg (4000 mcg allicin) twice daily. B 2
- Consider the tonifying effect of hawthorn at 750 to 1500 mg per day. B 2

Mind-Body Therapy

- Attempt to practice any of these approaches for approximately 20 minutes daily.
  - Practices to stimulate the relaxation response A 1
  - Biofeedback C 1
  - Transcendental meditation A 1
  - Yoga B 1
  - Qi gong B 1
  - Tai chi A 1

Pharmaceuticals

- Follow the seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) guidelines, which emphasize thiazide diuretics as first-line agents. A 2
- Stage 1 hypertension (140 to 159/90 to 99 mm Hg)
  - Start with single-drug treatment (diuretic, angiotensin-converting enzyme inhibitor [ACEI], angiotensin receptor blocker [ARB], or calcium channel blocker)
- Stage 2 hypertension (higher than 160/100 mm Hg)
  - Use two-drug regimen (diuretic, ACE or ARB, beta blocker, calcium channel blocker)

Other Therapies

- Consider Ayurvedic assessment for dietary and other means of balancing one's dosha (constitutional state). C 1
- Consider traditional East Asian medicine including acupuncture for balancing one's constitutional state. C 1

Note: With use of all therapies, including pharmaceuticals, an organized system of regular follow-up and review with self-monitoring and appointment reminders appears to be an effective adjunct for blood pressure control.[82] B 1

KEY WEB RESOURCES

Risk Assessment Tool for Estimating 10-year Risk of Developing Hard Coronary Heart Disease (Myocardial Infarction and Coronary Death): http://hp2010.nhlbihin.net/atpiii/calculator.asp?usertype=prof.	Systolic blood pressure values can be entered into this National Cholesterol Education Program risk assessment tool.
Your Guide to Lowering High Blood Pressure: Healthy Eating: http://www.nhlbi.nih.gov/hbp/prevent/h_eating/h_eating.htm.	This National Heart, Lung and Blood Institute Web site contains DASH diet instructions.
The DASH Diet Eating Plan. http://dashdiet.org/default.asp.	This Web site is a companion to Marla Heller's *The DASH Diet Action Plan*. Northbrook, Ill: Amidon Press; 2007.
HeartDecision calculator. https://www.heartdecision.org/index/tool#.	This calculator is used to assess cardiovascular risk and was created by physicians in the Division of Cardiology of the University of Wisconsin School of Medicine and Public Health in Madison, Wisconsin. It also includes helpful patient handouts.
The Eighth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8): http://www.nhlbi.nih.gov/guidelines/hypertension/jnc8/index.htm.	This National Heart, Lung and Blood Institute Web site contains information on the forthcoming eighth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) (expected availability for public review and comment: 2012; expected release date: 2012).

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Chapter 24

Heart Failure

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Much has changed within a relatively short time span with respect to the management of chronic heart failure. Sadly, much remains largely unchanged. Pharmacologic and technologic advances for the treatment of heart failure helped set the stage for updated treatment guidelines developed jointly by the American Heart Association (AHA) and the American College of Cardiology (ACC) in 2005. The guidelines have undergone gentle refinements since then, and the results of more recent investigations offer great promise for people with chronic heart failure. The reality, however, is that morbidity, mortality, and the escalating financial burden to society associated with heart failure remain unacceptably high. The statistics are sobering. At 40 years of age, the lifetime risk of developing heart failure for both men and women is 20%. Almost 6 million U.S. residents (2.6% of the population) are believed to have had heart failure in 2006, with an incidence approaching 10 per 1000 population after age 65 years. Heart failure is the most frequent Medicare diagnosis-related group,[1] and a conservative estimate of the direct and indirect cost of heart failure in the United States for 2010 is $39.2 billion.[2] The 1-year mortality rate for heart failure is high; 1 in 5 will die, and in 2006, 1 in 8.6 death certificates (282,754 deaths) in the United States mentioned heart failure.[3,4] Most cardiologists and epidemiologists believe that the incidence of left ventricular systolic dysfunction will continue to grow as the population ages and as more people survive heart attacks. These same experts believe that the statistics show that the attention and energy applied by the health care system to the war on heart failure should be equal to those applied to the war on cancer.

Few, if any, medical problems so burden our health care system as heart failure and offer so true a picture of both the need and potential benefit of an integrative approach to care. The single best way to treat heart failure is to prevent its development, because once established, heart failure follows an inexorable progression toward greater infirmity and death within a few years. Prevention, prevention, prevention must be our mantra with respect to heart failure management. Lifestyle and dietary measures that promote heart health should be established early in life, and improved access to preventive medical care across socioeconomic strata should be mandated. Careful surveillance for early signs of hypertension, diabetes, obesity, and coronary artery disease is essential, as well as aggressive treatment of these same maladies, with means both safe and effective drawn from the spectrum of available interventions.

Integrative treatment of heart failure focuses primarily on prevention.

For people who have already developed symptomatic heart failure, the emphasis rests squarely on conventional medical therapy, with physiologic goals of lowering both preload and afterload, maintaining stable left ventricular function, limiting activation of the renin-angiotensin-aldosterone system, and inhibiting release of neurohormonal factors. Complementary medical therapies with promise of efficacy and evidence of safety can be employed as adjuncts, to the benefit of most patients.

Heart failure exists in various different forms, including acute and chronic, congestive, right and left sided, and systolic and diastolic. This chapter focuses exclusively on chronic systolic heart failure, a disorder marked by impaired left ventricular systolic dysfunction (ejection fraction less than 45%), in which cardiac output is inadequate to meet metabolic demands.

Heart failure most commonly develops as a consequence of long-standing cardiovascular disease, especially hypertension or coronary artery disease, leading to ischemic cardiomyopathy. Once held to be solely a manifestation of the mechanical inability of the heart to pump blood adequately throughout the body, the pathophysiology of heart failure is now recognized to be complex and multifactorial. Initially positive neurohormonal compensatory mechanisms, believed to involve angiotensin II, norepinephrine, aldosterone, natriuretic peptides, vasopressin, and endothelin,[5]

TABLE 24-1. Pathophysiologic Features

- Increased calcium entry into myocytes
- Myocyte hypertrophy and loss with interstitial fibrosis, with resulting ventricular hypertrophy and dilation (structural remodeling)
- Reduced wall motion
- Increased myocardial energy expenditure
- Systemic vasoconstriction
- Sodium retention and circulatory congestion
- Increase in circulating catecholamines
- RAAS activation
- Increased levels of tumor necrosis factor-alpha and atrial and B-type natriuretic peptides

Data from references 6–9.
RAAS, renin-angiotensin-aldosterone system.

TABLE 24-2. New York Heart Association Functional Classification System

NYHA CLASS	DESCRIPTION
I	Physical activity not limited by symptoms such as shortness of breath, fatigue, or palpitations
II	Physical exertion mildly limited, with symptoms of shortness of breath, fatigue, or palpitations developing with typical daily activities
III	Physical activity severely curtailed; symptoms of shortness of breath, fatigue, or palpitations developing with any kind of activity
IV	Symptoms and physical discomfort present even at rest

NYHA, New York Heart Association.

among other compounds, ultimately become maladaptive and contribute to clinical deterioration (Table 24-1).[6–9] In the most severe form of heart failure, pulmonary edema, backward pressure is so high within congested capillaries that fluid leaks into lung tissue and compromises gas exchange, thus creating a life-threatening situation. Death most often results from progressive cardiac decompensation and respiratory failure or cardiac dysrhythmia (sudden cardiac death).

Classification systems have been proposed, owing in part to the myriad clinical presentations possible with heart failure. The New York Heart Association (NYHA) system (Table 24-2) defines level of illness according to functional capability and symptoms and is useful, but it does not always help inform therapeutic decision making because symptoms can fluctuate without concomitant change in left ventricular systolic dysfunction. In response to the increasingly complicated nature of caring for people with heart failure, symptomatic and otherwise, the ACC/AHA jointly developed an updated classification system emphasizing the progressive nature of the disease. These guidelines focus on early treatment of risk factors to prevent heart failure, as well as specific interventions recommended at each stage of heart failure development to minimize morbidity and mortality.[10]

TABLE 24-3. 2005 ACA/AHA Stages of Heart Failure

ACC/AHA STAGE	DESCRIPTION
A	At risk for HF but without structural heart disease or HF symptoms
B	Structural heart disease but without signs or symptoms of HF
C	Structural heart disease with prior or current symptoms of HF
D	Refractory heart failure requiring specialized intervention

Modified from Hunt SA, Abraham WT, Chin MH, et al. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult—summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). *J Am Coll Cardiol.* 2005:46:1116–1143.
ACC, American College of Cardiology; AHA, American Heart Association; HF, heart failure.

The ACC/AHA guidelines do not replace the NYHA system but offer greater utility with regard to cumulative diagnostic and therapeutic intervention (Table 24-3).

Integrative Therapy

The critical message regarding heart failure management cannot be overemphasized—do everything to prevent the disease from ever developing in the first place. Integrative means to help prevent or at least aggressively treat disorders that contribute to development of heart failure (including hypertension, coronary artery disease, diabetes, and dyslipidemia) can be found under appropriate chapter headings in this text. The aims of treatment for established heart failure are straightforward: prevent progressive cardiovascular deterioration, minimize symptoms and enhance the quality of life, and increase survival rates. Figure 24-1 is a flow chart comparing Western, integrative, complementary, and shared approaches to the treatment of heart failure. Figure 24-2 is a treatment algorithm for heart failure by stage of the disease.

Herbs and Supplements

Be sure to advise patients that the agents discussed in the following paragraphs do not act quickly, that 4 to 6 weeks may pass before clinical benefit is evident, and that these agents offer the greatest promise of clinical benefit in people with less severe disease (ACC/AHA stages A to C and NYHA classes I to III). Thus, the use of these agents is not appropriate for acutely worsening heart failure.

Botanicals

*Hawthorn (*Crataegus oxycantha *or* Crataegus monogyna*)*

Long a favored herbal remedy in Europe, hawthorn is a slow-acting cardiac tonic whose active constituents are considered to be flavonoids, such as vitexin and rutin, and oligomeric

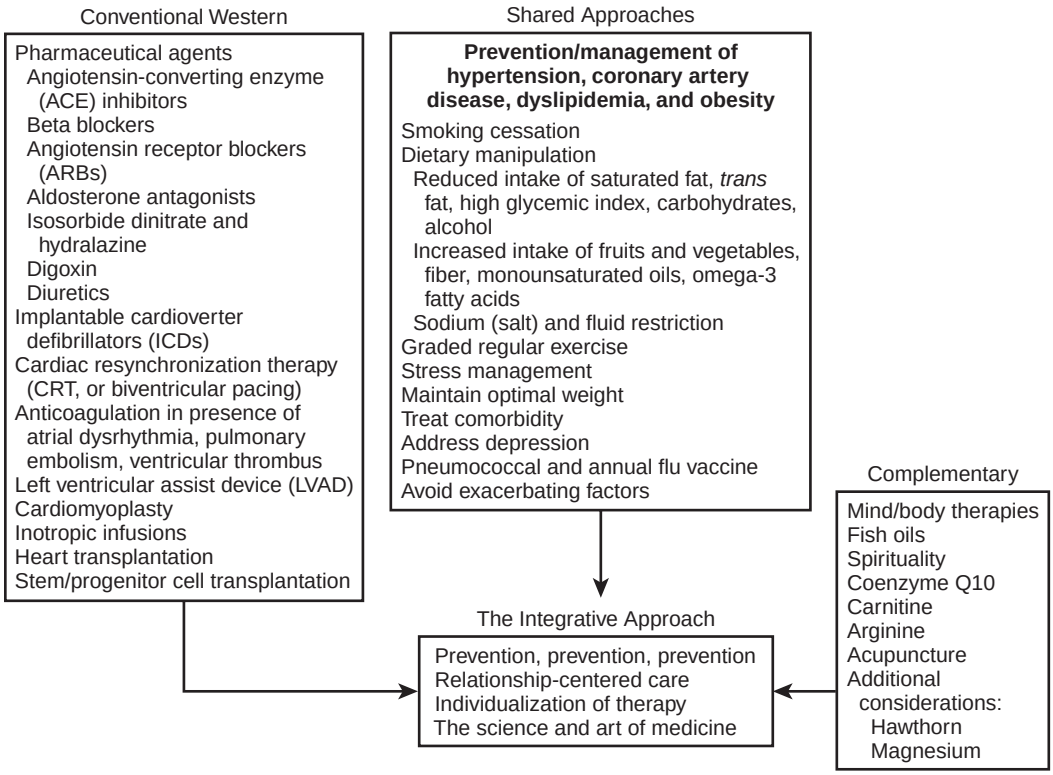

FIGURE 24-1
Heart failure: therapeutic options.

proanthocyanidins. The German Commission E specifically recommended hawthorn leaf and flower as the plant parts to be used therapeutically.

Numerous beneficial effects have been ascribed to hawthorn based on both animal and human studies,[11–13] including the following:

- Increased coronary artery blood flow
- Enhanced pumping efficiency of the heart (improved contractility)
- Antioxidant activity
- Phosphodiesterase inhibition
- Angiotensin-converting enzyme (ACE) inhibition
- Antidysrhythmic effects (lengthens the effective refractory period, unlike many cardiac drugs)
- Mild reduction in systemic vascular resistance (lowered blood pressure)

Reviews of placebo-controlled trials have reported both subjective and objective improvement in patients with mild forms of heart failure (NYHA classes I and II).[12,14,15] In one study, hawthorn was pitted against the ACE inhibitor captopril in comparable groups of people with heart failure. At trial's end, both groups had improved exercise capacity compared with baseline measurements, with no statistically significant differences between the two treatment arms of the trial. However, the investigators employed a relatively low dosage of captopril.[16] Other studies of hawthorn in people with heart failure revealed improvement in clinical symptoms, pressure-rate product, left ventricular ejection fraction, and patients' subjective sense of well-being.[17–21] A 2008 systematic review suggested significant improvements in symptoms and physiologic outcomes associated with the use of standardized extracts of hawthorn for people with heart failure.[22] Most of the studies with positive results, however, did not include treatment with drugs now accepted as standard medical therapy, such as ACE inhibitors and beta blockers. Later studies employing hawthorn in the setting of chronic heart failure in combination with current standard medical therapy reported less successful outcomes. In one trial, the standardized hawthorn extract WS 1442 was added to conventional medical therapy for heart failure that included ACE inhibition and beta blockade over 6 months. The results for hawthorn showed no significant benefit to patients with respect to a 6-minute walk test, the primary end point, or to secondary end points including indices of quality of life and NYHA classification. A modest improvement in left ventricular ejection fraction was identified.[23] Results of SPICE, a large randomized clinical trial of hawthorn for people with NYHA heart failure classes II and III and left ventricular dysfunction performed over 24 months suggested no statistically significant benefit on the composite end point of cardiac death, nonfatal myocardial infarction, and hospitalization for worsening disease. The trend was toward reduced cardiac mortality in the treatment group, most notably for those with significantly impaired left ventricular function.[24] Perhaps most concerning are the results of a retrospective safety analysis of the use of hawthorn in NYHA class II to III heart failure over 6 months.[25] This analysis revealed that hawthorn use not only failed to impede progression of disease but also appeared in some patients to increase the risk of early heart failure progression. Hospitalization rates were higher, and death rates were slightly higher, compared with those patients who received placebo.[25] In light of a previously good safety record, these findings are both puzzling and concerning.

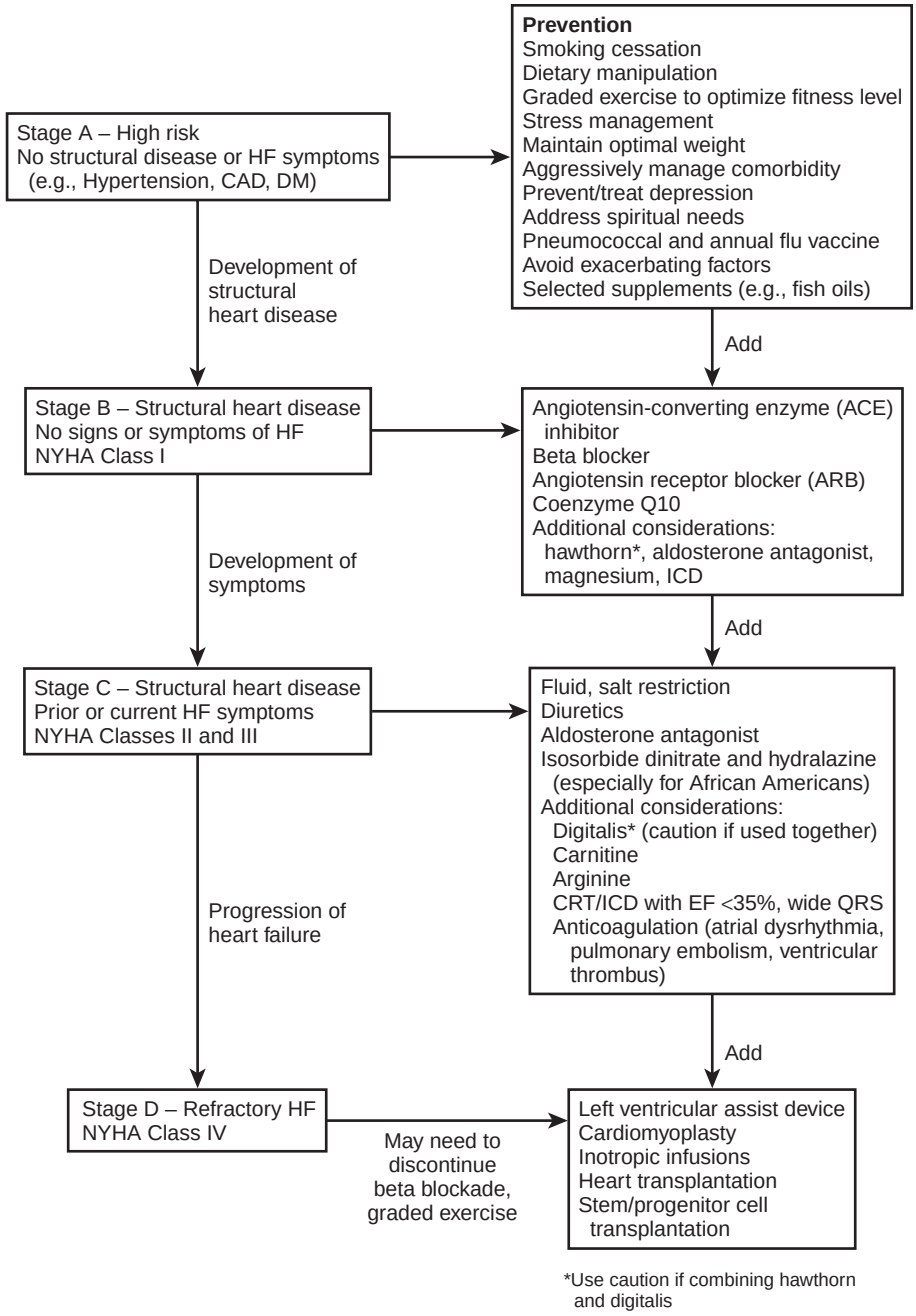

FIGURE 24-2
Clinical pathway: management of heart failure (HF). CAD, coronary artery disease; CRT, cardiac resynchronization therapy; DM, diabetes mellitus; EF, ejection fraction; HF, heart failure; ICD, implantable cardioverter defibrillator; NYHA, New York Heart Association. (Modified from Hunt SA, Abraham WT, Chin MH, et al. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult—summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure]. *J Am Coll Cardiol*. 2005;46:1116–1143.)

Dosage

Hawthorn is usually standardized to its content of flavonoids (2.2%) or oligomeric proanthocyanidins (18.75%). The recommended daily dose, as reflected in the literature, ranges from 160 to 1800 mg, but most practitioners believe that therapeutic efficacy is greater with higher doses (600 to 1800 mg/day). Again, no noticeable improvement may occur for 6 to 12 weeks.

Precautions

With the exception of the one study referenced earlier, few side effects have been associated with the use of hawthorn. Practitioners should remember that hawthorn possesses a mild hypotensive effect. One significant concern regarding a potential herb-drug interaction has largely been allayed. It was previously suggested that hawthorn could enhance the activity of digitalis glycosides, thus increasing the risk of side effects even though the plant does not contain digitalis-like substances itself. Research suggested no significant interaction between the agents,[26] but the investigators noted that they should still be combined with caution until such a conclusion becomes definitive. Most conventional medical practitioners reflexively state that hawthorn should not be given to people taking digitalis for heart failure. A far more integrative perspective would be one considering the possibility of lowering the therapeutically effective dosage of digitalis and thereby minimizing the side effects associated with its use, by combining it with hawthorn. Similarly, because the purported beneficial actions of hawthorn overlap some of those inherent to medications such as ACE inhibitors and

beta blockers, combination therapy possibly would permit the use of lower doses with no diminution of therapeutic effectiveness. Further research is needed. Short of this, the indications for hawthorn in the setting of chronic heart failure have contracted significantly.

Hawthorn, a long-favored herbal remedy for mild forms of chronic heart failure, possesses actions largely supplanted by conventional medications and in one study was associated with untoward risk.

Supplements

Coenzyme Q10

Coenzyme Q10 (sometimes abbreviated CoQ10) has long been used as a nutritional supplement for cardiovascular disease and at one time was one of the top six pharmaceuticals consumed in Japan under the name ubidecarenone.[27] In more recent years, coenzyme Q10 has become increasingly known in the United States, and significant attention has been paid to published research examining the potential role of this agent in disease management. A naturally occurring substance that behaves like a vitamin, coenzyme Q10 is present in small amounts in most diets. Coenzyme Q10 is also synthesized within the body from tyrosine, partially through a common pathway shared with cholesterol synthesis. It is found in highest concentrations within the mitochondrial membranes of organs that have significant energy requirements, especially the heart, where it acts as a carrier of both electrons and protons, and interacts with enzymes intricately involved with energy production.[28–31] Coenzyme Q10 exerts antioxidant[32] and membrane-stabilizing[33] effects as well.

The concentration of coenzyme Q10 within the plasma and myocardium is lower in subjects experiencing cardiac failure when compared with controls, regardless of the cause of the heart failure.[34–36] The more severe the degree of heart failure as reflected by the NYHA functional classification system, the greater is the deficiency of coenzyme Q10.[37–40] Whether a decreased coenzyme Q10 concentration is causal, as could be the case with idiopathic dilated cardiomyopathy, or secondary, as is likely with ischemic cardiomyopathy, is unclear. Regardless, a demonstrated myocardial deficiency of coenzyme Q10, the knowledge that exogenous administration can correct the deficiency,[36,41] and an appreciation of its necessity for adequate myocardial energy provision together formed the initial rationale for coenzyme Q10 administration in the broad setting of heart failure.

The first clinical application of coenzyme Q10 in cardiovascular disease was reported in 1967.[42] Since that time, numerous studies evaluating coenzyme Q10 use for chronic heart failure have been published. Unfortunately, the studies are of highly variable quality: some were uncontrolled or of short duration (weeks to a few months); they examined only a small number of subjects; they were performed before the widespread use of ACE inhibitors, beta blockers, and aldosterone antagonists; or they measured only functional parameters. Nonetheless, most of the published data suggest a supportive role for coenzyme Q10, with beneficial effects on ejection fraction,[43–45] end-diastolic volume index,[44,46] development of pulmonary edema and hospitalization rate,[47] and symptoms.[45,48,49] Research has shown that withdrawal of coenzyme Q10 supplementation results in worsening cardiac function and symptoms,[50] and two studies suggested a survival benefit when coenzyme Q10 was added to a conventional therapeutic regimen.[51,52] Two more recent studies, however, failed to show clinical efficacy.[53,54] More recently, the authors of a 12-week observational trial combining coenzyme Q10 with a proprietary maritime pine bark extract in a small number of patients with NYHA class II to III heart failure reported improvements in ejection fraction and treadmill walking distances.[55] Large multicenter trials to determine the true efficacy of coenzyme Q10 are needed.

Dosage

The optimum dosage of coenzyme Q10 in the setting of heart failure is as yet undetermined. Studies have used doses ranging from 30 to 600 mg/day, but most practitioners initially prescribe 100 to 200 mg daily. Softgel capsules of coenzyme Q10 appear to provide superior bioavailability.[56]

Precautions

Coenzyme Q10 has been found to be remarkably free of significant side effects. The most common adverse reaction is gastrointestinal upset (epigastric discomfort, loss of appetite, nausea, and diarrhea), occurring in fewer than 1% of all subjects.[57] Caution is advised for people taking anticoagulation therapy, given that case reports exist of possible procoagulant activity in patients taking warfarin, perhaps because of the compound's structural similarity to menaquinone.[58–60] Patients taking 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) may benefit from supplementation with coenzyme Q10. As alluded to earlier, cholesterol and coenzyme Q10 partially share the mevalonate pathway, the same biosynthetic pathway disrupted by statin drugs. Cholesterol production and the endogenous pathways for coenzyme Q10 production are thus both compromised by HMG-CoA reductase inhibition.[61–65]

Carnitine

Carnitine, another vitamin-like substance, acts as a specific carrier of the fatty acids required for energy production and moves them from the cytoplasm into the mitochondria. Carnitine is synthesized from the amino acid lysine, but it is also available in small amounts in foods such as red meat. Unfortunately, the organs in which carnitine is most highly concentrated (those with high levels of fatty acid metabolism, including the heart and skeletal muscle) are incapable of synthesizing carnitine themselves.[66] Myocardial carnitine is most highly concentrated within the left ventricle.[67,68] Levels of carnitine have been found to be low in patients with heart failure,[69,70] and depletion of myocardial L-carnitine appears to affect cell membrane function adversely, thus translating into impaired myocardial contractility.[71–73]

Only the L-form of carnitine should be used therapeutically. Investigators have suggested that propionyl L-carnitine (PLC; created through the esterification of L-carnitine) is most effective in the setting of heart disease because of its highly lipophilic nature.[74] PLC has been shown to improve muscle metabolism,[75] to stimulate the Krebs cycle,[76] and to

improve heart contractility[77,78] in animal models. Studies using L-carnitine in humans with ischemic heart disease or peripheral vascular disease revealed enhanced cardiac performance and increased exercise tolerance.[79–81]

Human trials using PLC in the setting of heart failure provided promising results.[82] Long-term administration of PLC was shown to improve ventricular function, reduce systemic vascular resistance, and increase exercise tolerance.[83,84] Administration acutely lowered pulmonary artery and capillary wedge pressure in one study.[85] Another reported a statistically significant reduced 3-year mortality rate in patients taking PLC.[86] In a well-done study that reported no significant benefit of PLC use in heart failure, the trend was toward beneficial effects for those people with somewhat preserved heart function (ejection fraction between 30% and 40%), and the safety of the agent was confirmed.[87]

Dosage

The dosage of PLC used in most studies is 2 g/day, divided into doses given two to three times daily (range, 1 to 3 g/day).

Precautions

The existing literature strongly suggests that the use of PLC is safe for patients with heart failure. L-Carnitine has been reported to cause an unpleasant body odor in extremely high doses. Most studies that used PLC, however, revealed no side effects, and no major toxicity was reported,[66] although an effect on peripheral thyroid hormone action was posited.[88]

L-Arginine

L-Arginine is an essential amino acid possessing vasodilatory effects that may enhance coronary artery blood flow and lessen the work of the heart by decreasing vascular resistance. Whereas further research is indicated, existing data are promising, albeit inconsistent. Use of L-arginine has been associated with improved hemodynamics and decreased endothelial dysfunction,[89–93] improved exercise tolerance,[89,94,95] improved kidney function,[96] and enhanced quality of life.[97]

Dosage

The typical dose used in heart failure is 2 to 6 g three times daily.

Precautions

L-Arginine increases potassium levels when it is used with other potassium-sparing drugs,[98] and it may increase the incidence of recurrent herpetic lesions. One trial cast doubt on the utility of arginine therapy after myocardial infarction and even raised the suggestion that such an intervention may increase mortality in older patients.[99]

Pharmaceuticals

Angiotensin-Converting Enzyme Inhibitors

Simply put, early institution of maximal therapy with ACE inhibitors saves lives. Numerous studies have shown that treatment with ACE inhibitors slows progression of heart failure and can improve quality of life, as well as long-term prognosis.[100–102] The biggest problem surrounding use of this class of agents is that many patients are not receiving maximal beneficial dosages. Such undertreatment stymies anticipated therapeutic benefits.

Dosage

Initial and target dosages for commonly used agents are as follows[103]:

Captopril: 6.25 to 100 mg three times daily
Enalapril: 2.5 to 20 mg twice daily
Lisinopril: 2.5 to 20 mg daily
Fosinopril: 5.0 to 40 mg daily
Ramipril: 1.25 to 10 mg daily
Quinapril: 5 to 40 mg daily
Trandolapril: 1 to 4 mg daily

Precautions

Many physicians are still wary of potential side effects, such as hypotension, kidney problems (increasing creatinine level), and electrolyte disorders (hyperkalemia). A safe and effective approach is to start with a low dosage, increase that dosage slowly, and periodically check electrolyte levels. Anyone who receives a verified diagnosis of heart failure and can tolerate ACE inhibitors should be taking them, and the dosage should be appropriately maximized. Some people develop a chronic, dry cough with ACE inhibitors that may limit the drug's utility. In this instance, angiotensin receptor blockade and vasodilator therapy are appropriate considerations. However, efforts should first be made to ensure that the cough is not secondary to the development of congestive heart failure.

Angiotensin Receptor Blockers

Angiotensin II subtype I receptor blockers provide more complete blockade of the renin-angiotensin system than do ACE inhibitors, they decrease morbidity and mortality to a degree similar but not superior to that of ACE inhibitors, they have fewer side effects than ACE inhibitors, and they may be of added benefit when combined with ACE inhibitors as part of the standard therapeutic regimen.[104–108] More recent data brought this last point into question, however, by suggesting that the combination of ACE inhibitors with angiotensin receptor blockers (ARBs) should be used with caution; some studies pointed to increased morbidity and mortality, or no significant all-cause mortality benefit, with combined therapy.[107,108] ARBs are a reasonable alternative for patients who cannot tolerate ACE inhibitor therapy.[107,109]

Dosage

Initial and target dosages for commonly used agents are as follows[103]:

Losartan: 12.5 to 100 mg daily
Candesartan: 4 to 32 mg daily
Valsartan: 40 to 160 mg twice daily

Precautions

ARBs are typically well tolerated.

Aldosterone Antagonists

Aldosterone mediates sodium retention, cardiac remodeling, myocardial fibrosis, and baroreceptor dysfunction.[110] Studies addressing the use of spironolactone, a diuretic and nonselective aldosterone antagonist, revealed that the agent reduces

both the need for hospitalization and the risk of sudden death when it was added to standard conventional Western medical therapy.[111–114] Eplerenone is a more selective aldosterone antagonist that has also been shown to reduce morbidity and mortality in heart failure. Although the benefits of aldosterone antagonism in heart failure are well established, this form of therapy remains woefully underused by physicians, perhaps because of the fear of hyperkalemia.[115] Data suggest the possibility of an important role for spironolactone even for people with NYHA class I to II heart failure.[116] All patients with advanced heart failure should be considered for aldosterone antagonist therapy.[117,118]

Dosage

Initial and target dosages for commonly used agents are as follows[103]:
Spironolactone: 12.5 to 50 mg daily
Eplerenone: 25 to 50 mg daily

Precautions

Spironolactone and eplerenone are known to promote potassium and magnesium retention. Be sure to document adequate kidney function before starting patients on either of these agents, and monitor electrolyte levels frequently.

Beta Blockers

Once contraindicated in the setting of heart failure, beta blockade has clearly been shown to benefit all but the most severe functional classes of heart failure when it is added to a regimen of ACE inhibitors or ARBs, by enhancing left ventricular systolic function, decreasing the rate of hospitalization, and lessening the incidence of sudden cardiac death.[119–125] Beta blockers not only affect the mechanical pump of the heart (improving ventricular function) and provide autonomic balance but also counteract specific neurohormonal processes that contribute to progressively worsening heart function through cardiac remodeling.[126–128] Beta blockade combined with ACE inhibition is now considered a cornerstone of systolic heart failure management.

Three beta blocking agents have been shown most beneficial in the clinical setting, although which agent is most beneficial in specific instances is unclear, as is the existence of a consistent place for beta blocker therapy in stages A or D heart failure. Treatment should be initiated at low doses and gradually titrated upward.[129]

Dosage

Initial and target dosages for commonly used agents are as follows[103]:
Carvedilol: 3.125 to 50 mg twice daily
Metoprolol succinate extended release: 12.5 to 200 mg daily
Bisoprolol: 1.25 to 5 mg daily

Precautions

Side effects include hypotension and bradycardia.

> Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta blockers, and aldosterone antagonists all have a positive impact on mortality related to heart failure.

Cardiac Glycosides (Digoxin)

Digoxin has been a mainstay of the conventional Western medical armamentarium since the days of William Withering, who first explored the benefit derived from the use of leaves of the common foxglove plant *(Digitalis purpurea)* more than 100 years ago. Digoxin is most commonly employed in the treatment of supraventricular dysrhythmias (atrial fibrillation) and heart failure, especially when the heart failure is associated with hypertension, cardiac valvular disease, or coronary artery disease.

Digoxin has long been known to be a positive inotrope (increase the pumping efficiency of the heart), but more recent work showed it to possess beneficial neurohormonal activity as well. Although the administration of digoxin does not appear to affect overall mortality, when it is added to the standard regimen of ACE inhibitors and diuretics, digoxin has been shown to improve symptoms, enhance exercise capacity, improve patients' quality of life and clinical status, and reduce hospitalization rates.[130–134]

Dosage

The initial and target dose is as follows[103]:
Digoxin: 0.125 to 0.25 mg daily in most patients

Precautions

Although digoxin is a useful drug, it has a very narrow therapeutic range, and toxicity is not uncommon. Some physicians initiate digoxin therapy early in the course of illness, and others prescribe it only in moderate to severe heart failure. Digoxin can be used both in the setting of acute cardiac decompensation and for chronic maintenance therapy. Do not prescribe digoxin as monotherapy—people with heart failure should almost always be taking an ACE inhibitor and using other interventions, as described previously. A lowered dosage of digoxin is often necessary for patients with significant renal insufficiency.

Isosorbide Dinitrate and Hydralazine

Few therapies underscore the notion that no two people are alike as clearly as the combination of nitrates and hydralazine. The combination of hydralazine and isosorbide dinitrate was the first treatment shown to improve survival in heart failure, but it was subsequently shown to be less effective than ACE inhibition in direct comparisons.[129] African Americans with heart failure, however, do not appear to respond as favorably to ACE inhibitors or beta blockers as do non-African Americans and have a less active nitric oxide system than do non-African Americans. Reevaluation of the Veterans Administration Cooperative Study on Vasodilator Therapy of Heart Failure (V-HeFT trial)[135] showed a significant reduction in mortality for African Americans who were taking nitrates and hydralazine. Subsequently, the African-American Heart Failure Trial (A-HeFT) was performed using the same fixed combination of isosorbide dinitrate and hydralazine in addition to standard therapy.[136] The study was stopped early because the reduction in mortality using the drug combination was so striking—43%. Besides the known vasodilatory effects, isosorbide dinitrate is a nitric oxide donor, whereas hydralazine inhibits breakdown of nitric oxide, and together the drugs act to increase nitric oxide levels. In 2005, the U.S. Food and Drug Administration approved the use of BiDil (a fixed-dose

combination of isosorbide dinitrate and hydralazine) for the treatment of heart failure in African Americans. More recent data suggest a possible role for the drug combination as add-on therapy for patients of any race who have advanced heart failure.[137]

Dosage

Initial and target dosages for commonly used agents are as follows[103]:

Hydralazine/isosorbide dinitrate (BiDil): 37.5 mg hydralazine/20 mg isosorbide dinitrate to 75 mg hydralazine/40 mg isosorbide dinitrate three times daily

Precautions

Headaches and dizziness have been reported, as has the potential for hypotension.

Diuretics

Diuretics help lessen cardiac workload by decreasing preload, yet until 2006, few data showed that these agents prolonged survival.[138,139] The most commonly used diuretics in the setting of heart failure are the so-called loop diuretics, such as furosemide, which are especially beneficial once congestion has developed.

Dosage

Initial and maximal dosages for commonly used agents are as follows[103]:

Furosemide: 20 to 600 mg daily
Bumetanide: 0.5 to 10 mg daily
Torsemide: 10 to 200 mg daily
Ethacrynic acid: 25 to 200 mg daily

Precautions

Periodic blood tests are necessary to evaluate electrolyte balance, especially potassium and sodium levels. One challenge is that diuretics may actually increase renin and aldosterone levels and thereby worsen the neurohormonal milieu. Benefits of therapy usually outweigh risks, however, as noted in a review finding that diuretic therapy not only improved symptoms of heart failure but also reduced morbidity and mortality.[138]

Biomechanical Therapy

The risk of sudden cardiac death in patients with heart failure is markedly increased, likely because of the increased incidence of ventricular dysrhythmias. With an eye toward preventing sudden cardiac death, treatment of heart failure is becoming increasingly mechanized. Evidence supporting the use of cardiac resynchronization therapy (CRT, a form of biventricular pacing) to correct dyssynchronous ventricular contraction and associated incomplete ventricular filling, and implantable cardioverter defibrillators (ICDs) either separately or combined, is compelling, with data strongly suggesting improved quality of life and reduced mortality, especially for those patients with stage C disease.[140–150] The use of CRT combined with an ICD in asymptomatic or mildly symptomatic patients with heart disease, reduced ejection fraction, and a wide QRS complex was associated with a 34% reduction in the risk of death or heart failure events as compared with the use of ICD alone.[150] Guidelines recommended CRT in patients with a left ventricular ejection fraction of less than 35%, NYHA class III to IV symptoms, and a QRS complex duration of more than 0.12 seconds.[1,129] The utility of this approach may be expanding because evidence points to potential health benefits across the spectrum of heart failure presentations, even for patients with mild disease.[151] Drugs remain the mainstay of treatment for people with heart failure and left ventricular dysfunction, but mechanical device therapy is now offering significant benefits to a major subset of patients. Placement of left ventricular assist devices, cardiomyoplasty, revascularization for ischemic heart failure, and heart transplantation represent the most drastic surgical considerations for the treatment of heart failure.

The most significant recent change in the conventional medical treatment of chronic heart failure is the increased reliance on device therapy (cardiac resynchronization therapy and implantable cardioverter defibrillators).

Bioenergetics

Acupuncture

Investigators have posited that acupuncture may ameliorate conditions that worsen the prognosis for people with heart failure, specifically high sympathetic activity.[152,153] A pilot study of acupuncture offered to 17 subjects with stable NYHA class II to III heart failure and who were receiving appropriate medical therapy reported no benefit with respect to ejection fraction but a marked improvement in 6-minute walk test results for the active group.[154] These results are intriguing, and more research is needed to evaluate the use of acupuncture before it can be recommended for treatment of heart failure.

Mind-Body Therapy

Depression is an independent risk factor for heart failure and is extremely prevalent among patients with established disease.[155,156] Depression-specific activation of inflammatory cytokines occurs in people with heart failure and may lead to worsening morbidity and mortality rates.[157,158] Numerous reports showed that providing adequate means of stress reduction can help relieve depression and anxiety, lessen the risk of developing cardiovascular disease, and improve the health and well-being of people with established heart disease.[159–165] Some of the benefits of mind-body therapies may be related to impacts on the autonomic nervous system.[166] Little research has been performed on the treatment of depression specific to people with heart failure, but this situation has been improving of late.[167] One older study of biofeedback for patients with advanced heart failure reported increased cardiac output and reduced systemic vascular resistance compared with controls.[168] A more recent small trial examining the effects of transcendental meditation compared with health education in African Americans with heart failure found improvements in 6-minute walk scores, depression scores, and measures of quality of life after 6 months, as well as a reduced rate of hospitalization.[169]

Health benefits were also identified in the results of the SEARCH (Study of the Effectiveness of Additional

Reductions in Cholesterol and Homocysteine) trial, which examined the effects of training in mindfulness meditation and coping skills in association with support group discussion for more than 200 adults with reduced ejection fraction or congestive heart failure.[170] Although medical management was not maximized in a small percentage of subjects, measures of anxiety and depression were significantly lower in the active group. The study found no impact on hospitalization or death rates, but symptom improvement persisted at 12 month follow-up. A small study of older patients with heart failure who were receiving maximal medical therapy showed improvements in neurotransmitter levels and quality of life measures after subjects listened to 30-minute meditation tapes twice daily at home for 12 weeks.[166]

Additional studies supporting the benefits of mind-body approaches for patients with heart failure include those focusing on Freeze-Frame stress management,[171] behavior modification,[172] relaxation response training,[173,174] and tai chi.[175,176]

Lifestyle

Community education regarding the adverse effects of smoking, excessive alcohol intake, and obesity must continue and expand. Assistance with tobacco and alcohol cessation, as well as weight management planning, should be made readily available across socioeconomic lines.

Having heart failure is not a contraindication to participating in exercise. Several trials showed that appropriate, graded exercise programming can improve function and quality of life for people with heart failure.[177–180] Lack of improvement after fitness training is associated with a poor prognosis.[181] Results of the HF-Action trial[182] were disappointing, showing at best a modest impact on hospitalization and mortality rate with regular exercise; however, the results reinforced the safety of regular exercise and cardiac rehabilitation for people with heart failure. The combination of physical exertion and a healthy diet can help patients maintain optimal body weight and thereby lessen strain on the heart. Sufficient rest is also important, and asking people to aim for at least 7 to 8 hours of sleep each night is prudent.

Regular participation in spiritual or religious practices may also help fend off heart disease.[183–186] Once heart failure is established, studies reveal that many patients struggle with their spirituality, a struggle that adds to an already stressful situation and perhaps leads to morbidity.[187,188] The burden of symptoms, mood disorders, and spiritual challenges associated with heart failure has been equated with those experienced by people with cancer.[189] Attention to spiritual needs can help people adjust to their new circumstances, address specific regrets with regard to prior lifestyle choices, and search for present meaning and future hope.[190,191]

Nutrition

Adhering to an antiinflammatory diet (see Chapter 86, The Antiinflammatory Diet) may both help prevent development of heart failure and slow progression of established disease. People who have stage C heart failure typically require additional means to keep the illness in check. Fluid and sodium (salt) restriction has been shown to affect cardiac function and symptoms positively in patients with heart failure. In the early stages of heart failure, the degree of restriction need not be severe, and avoiding added salt should be sufficient. With worsening heart function, patients may need to limit sodium intake to 2 g/day and daily ingestion of water to 1.5 to 2 L (see Chapter 87, The DASH Diet).

Supplementation with B vitamins, especially thiamine, should be considered,[192–194] as well as micronutrient supplementation, including magnesium.[195–198] Questions persist about the safety of high-dose vitamin E in patients with established cardiovascular disease.[199]

Future Therapy

Table 24-4 provides a list of future considerations for the therapy of heart failure.[200,201]

TABLE 24-4. Future Considerations

- Calcium sensitizers
- Continuous-flow left ventricular assist devices
- Cytokine inhibitors
- Endothelin receptor blockers
- Erythropoiesis-stimulating proteins
- Fish oils
- Free fatty acid oxidation inhibitors
- Gene expression (miRNA)
- Matrix metalloproteinase inhibitors
- Modified natriuretic peptides
- Nitric oxide–enhancing therapy
- Phosphodiesterase III inhibitors
- Ribose
- Statin therapy
- Stem and progenitor cell transplantation
- Taurine
- Vasopressin antagonists

Data from Jackevicius CA, Page RL 2nd, Chow S, et al. High-impact articles related to the management of heart failure: 2008 update. *Pharmacotherapy.* 2009;29:82-120; and Tang WH, Francis GS. The year in heart failure. *J Am Coll Cardiol.* 2010;55:688–696.

Prevention Prescription

- Do not smoke. If you do smoke, get help to quit.
- Follow an antiinflammatory or Mediterranean-style diet.
- Participate in regular physical fitness activities.
- Manage stress in healthy ways.
- Maintain a healthy weight for height.
- Work with your doctor to manage medical conditions that may lead to heart failure, especially high blood pressure, coronary artery disease, high cholesterol levels, and diabetes.
- Speak with your doctor about ways to prevent and if necessary, treat depression.
- Attend to your spiritual side.
- Have the pneumococcal vaccination and your annual flu vaccination.
- Avoid overuse of nonsteroidal antiinflammatory medications (NSAIDs).

Therapeutic Review

All patients with heart failure should be started on some combination of angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), or beta blocker, and aggressive management of comorbidity should be undertaken.

Removal of Potential Exacerbating Factors

- Try to discontinue nonsteroidal antiinflammatory drugs and first-generation calcium channel blockers.

Stress Management and Mind-Body Therapy

- Promote proper attention to mood and stress management, and offer instruction in and access to tools such as meditation, relaxation response, and tai chi. B1

Graded Exercise

- Enroll patients in a certified cardiac rehabilitation program. A1

Nutrition

- Encourage an antiinflammatory diet or Mediterranean-style diet. A1
- Urge fluid and salt restriction. A2

Spirituality

- Inquire about and address needs in an open fashion, and use pastoral care services as appropriate. B1

Bioenergetics

- Acupuncture B1

Supplements

- Coenzyme Q10: 100 to 200 mg daily A2
- Propionyl-L-carnitine: 1 to 3 g daily B1
- Arginine: 2-6 g three times daily B3

Botanicals

- Hawthorn: 600 to 1800 mg daily (exercise caution when using with digoxin) A3

Pharmaceuticals

- ACE inhibitors A2
- ARBs A2
- Beta blockers A2
- Aldosterone antagonists A2
- Isosorbide dinitrate in combination with hydralazine A2
- Diuretics A2
- Digitalis A2

Surgery

- Cardiac resynchronization therapy or implantable cardioverter defibrillator A2
- Left ventricular assist device A2
- Cardiomyoplasty A3
- Inotropic infusions B3
- Heart transplantation A3
- Stem or progenitor cell transplantation B2

KEY WEB RESOURCES

American Heart Association. http://www.heart.org/HEARTORG/Conditions/HeartFailure/Heart-Failure_UCM_002019_SubHomePage.jsp.	Heart failure management resource
Heart Failure Society of America. http://www.heartfailureguideline.org/	Guidelines
Agency for Healthcare Research and Quality. http://www.guideline.gov/content.aspx?id=10587	Heart failure management guidelines
Natural Medicines Comprehensive Database. http://naturaldatabase.therapeuticresearch.com/home.aspx?cs=&s=ND	Evidence-based assessment of vitamins, supplements, and herbs (subscription required)

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Chapter 25

Coronary Artery Disease

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Despite the many advances, cardiovascular disease is responsible for more than 2000 deaths every day in the United States.[1] Investigators estimate that 1 of 3 U.S. residents is destined to die of cardiovascular cause. Clearly, we have work to do. The causes of cardiovascular disease are diverse but, in large part, are related to lifestyle and environment. Rates of stress, obesity, and diabetes continue to soar. The Centers for Disease Control and Prevention estimates that 1 out of 3 children born in the year 2000 will go on to develop diabetes during his or her lifetime.[2] Consequently, for the first time in history, it is possible that children will have a shorter life expectancy than their parents.[3]

An integrative approach acknowledges the great value and potentially lifesaving benefits of modern pharmacology and procedures while at the same time recognizing the limitations of these approaches when they are used in isolation. An integrative approach is ideally suited for prevention and treatment of coronary disease because it addresses many of the root causes, especially those influenced by lifestyle. The goal of this chapter is to gain perspective into the power of a broader spectrum of therapies beyond those that typically constitute conventional cardiovascular care.

Pathophysiology

What triggers a cardiovascular catastrophe? For many years, investigators believed that a cardiovascular event occurred after many years of progressive narrowing of a coronary artery. This view held that with each passing year, layer on layer of cholesterol-laden deposits accumulated on the surface of a coronary artery. This theory held that, over time, cholesterol deposits accumulated and ultimately stopped blood flow, thus leading to myocardial infarction. In more recent years, this paradigm has been largely upended and replaced by a more complex, and less intuitive, picture.

Angiographic studies have revealed, quite surprisingly, that acute coronary events often arise from "mild" coronary lesions that are far less than 50% obstructive.[4] The explanation for this paradoxical finding is that vulnerable plaques, those most likely to rupture and evolve into a complete thrombotic occlusion, are those with large lipid cores and thin fibrous caps.[5] Most of the plaques with the largest lipid cores are not severely stenotic (the lipid-laden deposits enlarge the artery and do not always reduce the area of blood flow). Conversely, some of the most severely stenotic plaques are not necessarily the ones with the largest lipid cores and therefore may not be the most "vulnerable."

A useful way of thinking about this concept and of conveying it to patients is that a mild coronary lesion can be considered a "fault line" that, in a quiescent phase, appears quite passive and harmless. However, similar to any fault line, these seemingly harmless plaques may erupt at any moment and cause a potentially lethal cardiac event.

This situation has implications for both detection and treatment of coronary artery disease. With regard to detection, a mildly stenotic coronary lesion is not flow limiting and therefore would not be expected to result in chest pain or provoke abnormal findings on a cardiac stress test. This is the explanation for the anecdote familiar to most clinicians and patients about the individual who sailed through a stress test with "normal" results only to suffer a cardiac catastrophe a short time later.

The finding that a coronary event can rapidly develop from what angiographically appears to be a "mild" coronary lesion emphasizes the need to prevent coronary lesions from developing, rather than to focus on reducing the severity of severe stenoses with interventional procedures.

The triggers of coronary artery disease are both genetic and environmental. Genetic tendencies include inherited metabolic disorders including dyslipidemia and diabetes. Environmental and lifestyle factors include nutritional imbalance, sedentary lifestyle, stress and depression, smoking, and air pollution. These topics are explored in detail in this chapter.

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Integrative Therapy

Nutrition

Nutrition is perhaps the most powerful therapy available for prevention and treatment of coronary disease.

Mediterranean Diet

The power of nutritional therapy is highlighted by the striking results of the Lyon Diet Heart study.[6] In this study of individuals who survived myocardial infarction, patients were divided into two groups distinguished only by dietary intervention. The control group was advised to consume a "prudent" diet consisting of reduced cholesterol and total fat. The intervention group, conversely, was advised to eat a Mediterranean-style diet. Patients in this group were counseled to eat more vegetables and fruit and more nuts and fish, to use olive oil and canola-based margarine as their predominant cooking oils, and to reduce their intake of red meat and refined carbohydrates.

The study was intended to last 5 years but was stopped short at 27 months because of a strikingly beneficial effect in the Mediterranean diet group. At that point, a 73% reduction in cardiovascular events, including myocardial infarction and cardiac death, was observed in the Mediterranean-style diet group. A longer-term follow-up study published 5 years later demonstrated a durable benefit of the Mediterranean-style diet with a 72% reduction in cardiovascular events after 5 years.[7]

The substantial benefits of the Mediterranean diet are not surprising, given the proven benefits of its component parts. High consumption of vegetables and fruit is the cornerstone of the Mediterranean-style diet. Daily consumption of vegetables in the Lyon study averaged 427 g (approximately five servings).[8] Increased intake of vegetables, especially dark green leafy vegetables, has been associated with a substantially reduced risk of coronary heart disease. Each daily serving of dark green leafy vegetables, for example, has been linked to a 23% reduction in coronary heart risk.[9] Fruit intake in the Lyon study averaged 271 g (approximately two servings) (see Chapter 86, The Antiinflammatory Diet).

The results of the Lyon Mediterranean diet study underlie my personal recommendation for daily consumption of five servings of vegetables per day and two servings of fruit.

Whole Grains

Other key constituents of the Mediterranean diet are avoidance of refined grains and an emphasis on consumption of whole grains. Refined grains, typically void of fiber, are deleterious in several ways. As compared with their whole grain counterparts, refined grains result in a more exuberant release of glucose into the circulation, thus triggering higher insulin levels and a greater tendency toward atherosclerosis. Higher sugar intake is associated with reduced levels of high-density lipoprotein (HDL) and increased levels of the riskier, more atherogenic small dense low-density lipoprotein (LDL)[10] (see Chapter 85, The Glycemic Index/Load).

The manner in which grains are prepared also has important health implications. Boiled whole grains (e.g., oat, quinoa, barley) are typically a healthier choice than bread made from the flour of whole grains.

Examples of whole grains include barley, buckwheat, quinoa, polenta, and brown rice. A meta-analysis demonstrated a 21% lower risk of cardiovascular events when 2.5 servings per day of whole grains were consumed compared with the absence of whole grain foods in the diet.[11] The manner in which grains are prepared also has important health implications. Consuming pulverized grains, even whole grains, results in a higher blood glucose level than when the intact grain is eaten.[12] Therefore, boiled whole grains are typically a healthier choice than is bread made from the flour of whole grains.

Fish

Fish is another integral component of a heart healthy diet, with benefits in both primary and secondary prevention of heart disease. In the Chicago Western Electric Study, more than 35 g of fish intake/week (approximately three servings) led to a 38% reduced risk of cardiac death.[13] The Diet and Reinfarction Trial (DART) similarly demonstrated a 29% reduction in all-cause mortality in men instructed to eat fish compared with those who did not after only 2 years.[14] Accordingly, substituting chicken or fish for red meat has been shown to reduce the risk of coronary heart disease.[15]

Nuts

Nuts, a part of the Mediterranean-style diet, have potent benefits for reduction of coronary heart disease. Four servings of nuts per week (30 g/serving, or approximately one large handful/serving) have been shown to reduce the risk of coronary heart disease by 37%.[16] Increasing consumption of nuts to two handfuls per day reduces LDL cholesterol (LDL-C) by as much as 10% in those with baseline values of greater than 160 mg/dL.[17]

The success of nutritional interventions is greatly enhanced when the patient perceives that nutrition is a priority of the health care practitioner. At every clinical encounter with a patient, I recommend making a point to inquire about the number of servings of vegetables and fruit consumed every day, the type of grains, the quantity of fish, and the servings of nuts consumed on a weekly basis. Emphasizing the importance of diet during each visit allows obstacles to be identified and progress celebrated.

Exercise

Patients often inquire about "natural" methods for prevention and treatment of heart disease. In concert with dietary changes, no other therapy is more potent than the addition of regular exercise. Surprisingly, intensity of exercise appears to be less important than frequency and consistency. In the Health Professionals Follow-Up Study, walking for 30 minutes per day was associated with an 18% reduction in the occurrence of cardiovascular disease.[18] In the Women's Health Initiative observational study, exercise of as little as 4.2 metabolic equivalent of task (MET)-hour/week resulted in a 27% reduction in heart disease risk. The benefits of exercise were even greater when a higher level of exercise, 32.8 MET-hour/week, were performed.

Although aerobic exercise is generally emphasized for cardiovascular health, resistance training also adds considerable benefit. Resistance training for at least 30 minutes per week resulted in a 23% lower risk of heart disease compared with men who did no resistance training.[18]

Therefore, a reasonable prescription for exercise could start at 30 minutes of brisk walking every day, in addition to two to three sessions per week of light resistance training interspersed with stretching. More vigorous workouts of longer duration are likely to be of even greater benefit. Of course, individual prescriptions must take into account the patient's general health history and cardiovascular status. Stress testing before beginning a program may be appropriate for patients with a history of heart disease or for those with multiple cardiovascular risk factors, especially those who have been previously sedentary.

Pharmaceuticals

In addition to the nutrition and exercise "foundations" of heart health, patients with symptomatic coronary artery disease should receive treatment informed by American Heart Association/American College of Cardiology (AHA/ACC) guidelines. Proven medical therapy for symptomatic coronary disease includes aspirin, nitrates, beta blockers, and calcium channel blockers. Angiotensin-converting enzyme inhibitors are also potent antihypertensives and may provide additional cardiovascular prevention above and beyond antihypertensive properties. Statin therapy should also be considered an essential component of therapy in patients with established vascular disease, as well as in those at high risk for vascular disease both for lipid lowering and for the many "pleotropic" or nonlipid beneficial metabolic effects. A detailed discussion of these therapies is beyond the scope of this chapter but can be found in the AHA/ACC guideline statements (see Key Web Resources, later). Tables 25-1 and 25-2 provide information on interactions of pharmaceuticals and supplements.

Antiplatelet and Anticoagulant Therapies

Aspirin is the most widely prescribed over-the-counter therapy in cardiology and arguably one of the most potent. Aspirin is a mainstay of therapy for patients with established cardiovascular disease and is also frequently recommended for individuals at high risk of disease. Dosing remains a challenge because higher doses have greater antiplatelet action, as well as a higher risk of gastrointestinal bleeding. Balancing the risks and benefits was addressed in a meta-analysis that recommended 160 mg/day, although individual patient factors must be incorporated in all treatment decisions.[19]

Patients who take warfarin may approach integrative practitioners for recommendations regarding alternative options, including patients with atrial fibrillation who would like to discontinue taking warfarin. Patients frequently inquire about the possibility of replacing warfarin or the antiplatelet agent clopidogrel with over-the-counter products, including nattokinase, fish oil, and vitamin E, among others. Unfortunately, to date, no studies support the use of botanicals or herbs in place of warfarin in clinical situations of high thrombotic risk.[20]

TABLE 25-1. Important Herbal and Supplement Interactions With Antiplatelet Drugs and Warfarin

AGENTS	HERB OR SUPPLEMENT	EFFECTS OF INTERACTION
Antiplatelet drugs (aspirin, ticlopidine, NSAIDs, clopidogrel)	Caffeine	Antiplatelet effect
	Cordyceps fungus	Platelet antagonism
	Curcumin	Antiplatelet effects
	Dong quai	Platelet antagonism
	Feverfew	Inhibition of platelet aggregation
	Fish oil	Platelet antagonism
	Garlic	Inhibition of platelet aggregation
	Ginger	Prolongation of bleeding time
	Ginkgo	Antiplatelet activity, hemorrhage
	Green tea	Antiplatelet effects
	Guggul	Antiplatelet activity
	Horse chestnut	Antiplatelet activity
	Policosanol	Antiplatelet activity
	Resveratrol	Inhibition of platelet aggregation
	Vitamin E	Antiplatelet activity
Warfarin	Coenzyme Q10	Decrease in INR
	Dong quai	Elevation of PT and INR
	Fenugreek	Possible increase in INR
	Fish oil	Elevation of INR
	Garlic	Elevation of INR
	Ginkgo	CNS hemorrhage
	Ginseng	Decrease in INR
	Green tea	Decrease in INR
	L-Carnitine	Potential increase in INR
	St. John's wort	Decrease in INR

From Burleson K. Coronary artery disease. In: Rakel D, ed. *Integrative Medicine*, 2nd ed. Philadelphia: Saunders; 2007:302.
CNS, central nervous system; INR, international normalized ratio; NSAIDs, nonsteroidal antiinflammatory drugs; PT, prothrombin time.

Angioplasty and Stents

Angioplasty and stents are commonly regarded as the most potent interventions available in cardiology. In the past, investigators logically assumed that mechanically opening a severely stenotic coronary artery would reduce the likelihood

TABLE 25-2. Important Herbal and Supplement Interactions With Other Cardiovascular Drugs

CARDIOVASCULAR DRUG	HERB OR SUPPLEMENT	EFFECTS
Digitalis	Hawthorn	Potentially increased serum levels
	Herbal laxatives	Decreased absorption
	Psyllium	Hypokalemia
	St. John's wort	Decreased serum levels
Amiodarone	—	See precautions for digoxin, warfarin, statins, or herbs with hepatic effects
Propranolol	Guggul	Decreased bioavailability
Clonidine	Yohimbine	Both alpha$_2$-antagonists
Calcium channel blockers	Guggul	Decreased bioavailability
Cyclosporine	St. John's wort	Decreased serum levels
Statins	Red rice yeast	Magnified side effects

From Burleson K. Coronary artery disease. In: Rakel D, ed. *Integrative Medicine*, 2nd ed. Philadelphia: Saunders; 2007:303.

of progression to coronary occlusion and myocardial infarction. Surprisingly, however, angioplasties and stents have not been shown to reduce the risk of myocardial infarction and do not prolong life in most patients who receive these therapies—patients who are asymptomatic or those with stable coronary disease. Survival benefit from angioplasties and stents appears confined to patients who are having an acute myocardial infarction or an episode of unstable angina. In the more chronic setting, the benefit is restricted to improvement of chest pain.

This counterintuitive finding was observed in several studies and summarized in a meta-analysis of 11 trials including nearly 3000 patients.[21] More recently, the COURAGE trial confirmed the lack of survival benefit from adding catheter-based coronary intervention to medical therapy alone.[22] The explanation for the lack of expected outcomes benefit from angioplasty and stents in the stable patient is uncertain, but it likely relates to the finding that mechanical interventions are generally directed at one or two of the possibly hundreds of "vulnerable" plaques that exist in an individual's coronary tree.

Despite the evidence, stating that the absence of expected outcomes benefits from catheter-based intervention in stable patients with coronary disease has dramatically altered physicians' practice would be misleading. Numerous reasons exist for this, including patients' (and physicians') emotional discomfort about not intervening on a severe stenosis identified on angiography and fear of medical and legal implications. These concerns are clearly separate from the scientific findings, however.

Lipid Management

Lifestyle changes are the foundation of a solid prevention program, and the role of lipid management is subordinate to optimizing lifestyle measures. Nevertheless, lipid management is an extremely important consideration for both primary and secondary prevention. Among the lipid parameters, the priorities for prevention are as follows, in order of importance: LDL, HDL, and triglycerides. Total cholesterol is not the most useful end point because it is a summated term that may either underestimate or overestimate risk. One third of heart attacks occur in individuals with a total cholesterol value lower than 200 mg/dL[23] (see Chapter 39, Dyslipidemias).

Low-density Lipoprotein

Among all lipid parameters, control of LDL is of primary importance because it is most closely related to cardiovascular risk. Nevertheless, the optimal measurement to describe the risk imparted by LDL is somewhat controversial. LDL is an apolipoprotein that carries the bulk of circulating cholesterol. Traditional measurement of LDL-C, the basis for most treatment decisions, assesses only the cholesterol content of this complex molecule.

Mounting evidence suggests that the cholesterol content of LDL may not be the best reflection of risk, however. Instead, quantification of the number of LDL particles appears to correlate more closely with cardiovascular risk than does the conventional measurement of LDL-C.

To understand more clearly how to relate cholesterol concentration to LDL particle number, consider the following example: imagine filling 2 bathtubs with cholesterol to the same level designated by the LDL-C value. For the purpose of this example, we will designate an LDL-C of 125 mg/dL as corresponding to filling the bathtub halfway with cholesterol balls. In the first tub, 100 large balls are used to fill the tub halfway. In the second, tub, 2000 small marbles are used to fill the tub to the exact same halfway mark. At first glance, both tubs, filled halfway to the same level of 125 mg/dL, would appear to represent equal cardiovascular risk. However, the person with 2000 smaller particles has a much higher risk of cardiovascular disease than the other individual with an identical LDL-C but with many fewer particles. In other words, risk is much more closely linked to the number of LDL particles than to the concentration of cholesterol.[24]

Several tests are available that quantify the number of atherogenic particles (most of which are LDL particles). The most readily available method for estimating the number of atherogenic particles is non–HDL-C, a simple value that is calculated by subtracting HDL-C from the total cholesterol. Calculation of non–HDL-C is especially helpful when triglycerides exceed 200 mg/dL, an environment in which formation of small, dense LDL is more likely. Non-HDL goals are 30 mg/dL higher than LDL-C goals.[25]

A more accurate reflection of the number of atherogenic particles, however, is apolipoprotein B (ApoB). ApoB takes advantage of the fact that each atherogenic particle contains exactly one molecule of ApoB.[26] Therefore, ApoB has been shown to relate more closely than LDL-C to cardiovascular risk. Another option to measure the number of atherogenic particles is LDL particle number, a proprietary test, that

was shown in the Framingham Offspring Study to predict cardiovascular risk more closely than LDL-C.[24] Treatment goals for ApoB and LDL particle number have not been well established but are commonly set at percentile rankings in the population (i.e., lower than the fifth percentile for a very high-risk patient).[27]

The most potent agents available for reduction of LDL-C, ApoB, and LDL particle number are prescription 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors, or statins. These medications are capable of lowering LDL-C by more than 50% and have been proven to reduce the likelihood of a cardiovascular event by approximately one third in both primary and secondary prevention studies. Some studies with statins have shown overall mortality benefit, but total mortality benefit is not a consistent finding.[28]

Statin-Related Myalgias

Despite the proven benefits of statins in high-risk individuals, treatment is not without risk. Myalgias are a particularly frequent adverse reaction that may be more common than described in the package insert for these medications. An observational study of statins in clinical practice reveals that muscle-related adverse reactions occur in as many as 11% of patients.[29] The potential for adverse muscle-related symptoms increases as the dose is raised.

A survey of patients taking statins who reported muscle-related symptoms to their physicians revealed a sobering finding: in only 29% of cases did physicians endorse the possibility of a link between the patients' complaint of muscle pain and the use of statins.[30] In 47% of cases, the physicians dismissed the possibility of such a link. Patients' belief that their symptoms are not acknowledged by their physicians may explain why more than 50% of patients stop taking statins after only 1 year.[31]

Alternatives to the use of prescription statins can play an important role when prescription statins cannot be tolerated because of adverse reactions and in patients philosophically opposed to the use of prescription statins.

Options for treatment of patients with intolerance to prescription statins include (1) reducing the dose of the prescription statin, (2) changing to a different prescription statin, or (3) using nonprescription lipid-lowering therapy.

Surprisingly, reducing the dose of a statin by half is expected to reduce the LDL-C–lowering impact by only 7%.[32] Nevertheless, adverse reactions, particularly myalgias, are often improved or eliminated by lowering the dose.[29] Therefore, for patients with mild myalgias related to statin use, dosage modification may eliminate the adverse reaction without sacrificing appreciable lipid control.

Another option is to prolong the dosing frequency of the prescription statin. Rosuvastatin, with the longest half-life of any of the available statins, was shown to retain potent LDL-C reductions when it was given as infrequently as once or twice per week.[33,34] In one study, a mean rosuvastatin dose of 10 mg given once a week resulted in a mean 23% reduction in LDL-C.[34]

Another option for the patient intolerant to a prescription statin is to switch to a different statin. Reactions can be idiosyncratic, and one brand may be well tolerated when others are not. Rosuvastatin and pravastatin may be better tolerated in some individuals, possibly related to the hydrophilic nature of these drugs. Fluvastatin can also be considered because it has a metabolic pathway unique among all statins (mostly by 2C9) that may explain the finding that, in a large survey, it had the lowest risk of myalgias among all the statins.[29]

Water-soluble statins such as rosuvastatin and pravastatin may cause fewer myalgias in some patients. Fluvastatin may also cause fewer muscle symptoms because of its unique metabolism.

High-Density Lipoprotein

HDL is protective against atherosclerotic disease because of its role in removing LDL from plaque (reverse cholesterol transport) and its antioxidant function. Average HDL-C for men is 40 to 45 mg/dL and for women is 50-55 mg/dL. Low HDL levels are associated with significantly increased cardiovascular risk even in individuals with low LDL concentrations.[35]

Lifestyle measures are the primary strategies for raising HDL and include weight loss, exercise, and smoking cessation.[36] Reducing intake of added sugar and food with high glycemic load will also raise HDL.[10]

Alcohol is effective at raising HDL levels, and this effect may explain the lower risk of cardiovascular events associated with moderate alcohol intake (one serving/day).[37] All forms of alcohol, including white and red wine, beer, and hard liquor, are capable of raising HDL. The cardiovascular benefits need to be balanced by the potential for accidents and abuse, as well as the increased risk of breast cancer associated with alcohol intake in women.

The most potent pharmacologic agent available for boosting HDL-C is niacin. The HDL-raising effect of niacin is dose related, with an increase of 20% to 30% observed at the highest doses, generally approximately 2000 mg/day.[38,39] Limited data suggest a very potent, additive, and possibly synergistic benefit when niacin is added to a statin. In the HDL-Atherosclerosis Treatment Study, patients with low baseline HDL who were treated with both a statin and niacin had an unprecedented 90% reduction in cardiovascular events compared with patients treated with placebo.[40] In another study, patients receiving a baseline statin who also received niacin had significantly more regression of carotid intimal/medial thickness compared with patients receiving a statin and ezetimibe.[41] These results were surprising because, with treatment, LDL-C was lower in the ezetimibe group.

Supplements

When none of the dosing options for prescription statins is tolerated (or the patient refuses to consider a prescription statin), nonprescription therapies may be particularly useful.

In order of efficacy, the following nonprescription therapies are useful for control of LDL-C: fiber, stanols or sterols, niacin, and red yeast rice.

In contrast, herbal and botanical preparations often used for cholesterol management that have been shown to have modest benefit or no benefit include policosanol,[42] garlic,[43] and guggulipids.[44]

Fiber

The water-soluble fraction of fiber, soluble fiber, reduces the absorption of cholesterol in the intestinal tract. Therefore, additional fiber, either in food or in supplements, can aid in cholesterol management. Each gram of dietary fiber decreases LDL-C by approximately 2 mg/dL.[45]

Dosage

Supplementation with psyllium, totaling 10 g per day, can reduce LDL-C by 7%.[46]

Stanols and Sterols

Plants do not contain cholesterol but are rich in phytosterols and stanols. Sterols and stanols reduce cholesterol by competing with dietary and biliary cholesterol for intestinal absorption. These agents are capable of reducing LDL-C by up to 14% when they are used either as monotherapy or as an adjunct to statin therapy.[47]

Dosage

The usual dose of stanols or sterols is 1.8 g/day as a single dose (added in certain margarines or in pill form).

Precautions

These agents are generally well tolerated, but they can cause gastrointestinal distress.

Niacin

Niacin, a B vitamin, shifts all lipids in a favorable direction. At higher dosages, niacin can reduce LDL-C by 15% to 20%, shift LDL particle size to the more favorable, larger form, raise HDL, and lower lipoprotein (a). "No flush" or "flush-free" niacin (inositol hexaniacinate) should be avoided because these products do not contain the active form of niacin and consequently have no significant lipid-altering properties for most individuals.[48] Care should also be taken to avoid niacinamide and nicotinamide, products with names resembles niacin but with no lipid-altering properties.

Dosage

The usual starting dose is 500 mg per day, titrated upward by 500 mg increments every 6 to 8 weeks as needed, to maximal daily dose of 2000 mg per day. Check liver function tests after each dose adjustment.

Precautions

Although niacin has ideal lipid-altering properties, its use is encumbered by frequent adverse reactions, which are typically annoying but harmless. The most common adverse reaction is flushing, which can occur in up to 50% of individuals and is especially likely when initiating therapy or increasing the dosage. The best strategy to reduce the risk of flushing involves taking niacin with food, typically dinner, and to use aspirin or nonsteroidal antiinflammatory agents just before taking niacin. Additional relief from flushing may be possible by taking niacin with applesauce as an after-dinner snack. The reason that applesauce may be beneficial in reducing flushing is unknown but it may relate to quercetin, an antioxidant found in high concentration in apples and applesauce and shown to reduce niacin-induced flushing in an experimental animal study.[49]

Strategies to reduce niacin flush:
Take niacin with dinner, or after dinner with apple sauce.
Take aspirin or a nonsteroidal antiinflammatory drug with niacin.
Avoid "no flush" niacin because it is usually ineffective.

Red Yeast Rice

Red yeast rice is the most effective over-the-counter therapy for treatment of elevated LDL-C, with reductions of 20% to 30%.[50,51] The combination of red yeast rice, fish oil, and therapeutic lifestyle changes has been proven to lower LDL-C by 42%, a reduction comparable to simvastatin 40 mg. This supplement, taken in pill form, is the fermentation product resulting from growing the yeast *Monascus purpureus* on rice. Red yeast rice contains a family of cholesterol lowering molecules known as monacolins, the most prevalent of which is monacolin K, better known by the chemical name lovastatin.

The concentration of monacolins varies widely among different preparations of red yeast rice.[52] In addition, some brands have been shown to contain citrinin, a potentially nephrotoxic fermentation byproduct.[52] Therefore, practitioners should become familiar with a particular brand of red yeast rice and advise patients to continue taking the same brand to increase the likelihood of a consistent result.

Red yeast rice may be a useful option for patients who have not been able to tolerate prescription statins, typically because of myalgias. In a study of patients unable to take a prescription statin because of the development of myalgias, 93% of those taking red yeast rice were free of significant muscle symptoms and had an average LDL-C reduction of 21%.[53]

Outcomes data have also been reported with red yeast rice. A Chinese study of 4870 patients who suffered myocardial infarction were followed up for nearly 5 years, and these patients had a proven significant reduction in cardiovascular events, as well as a 33% reduction in total mortality compared with placebo[54] (Table 25-3).

Dosage

The usual (and maximal) dose is 1200 mg twice daily. Patients may use a lower starting dose of 600 mg twice daily if they have a history of significant statin intolerance.

Precautions

The amount of active ingredient varies by brand. In addition, a few brands have been shown to contain citrinin, a potential nephrotoxin. Obtain baseline liver and renal function tests

TABLE 25-3. Nonprescription Therapies for Reduction of Low-Density Lipoprotein Cholesterol

PRODUCT	PERCENTAGE OF REDUCTION
Psyllium (10 g/day)	7%[46]
Sterol and stanol (1.8 g/day)	14%[47]
Niacin (up to 2 g/day)	15%–20%
Red yeast rice (2400 mg/day)	20%–30%

and repeat laboratory studies 2 months after initiating therapy and twice a year thereafter. Consumerlabs.com has analyzed red yeast rice brands for potency and the presence of citrinin (see Key Web Resources, later).

Fish Oil

High triglyceride values are associated with increased risk in both men and women, but the risk is higher in women.[55] The mechanism of increased risk is not well understood, although it is likely related to the association between high triglycerides and the predominance of the riskier small, dense LDL particles.

Beyond lifestyle changes, the most effective pharmacologic treatment for elevated triglycerides includes fibrates (gemfibrozil and fenofibrates) and fish oil. Fish oil has been shown to reduce triglyceride levels by 50% when baseline levels exceed 500 mg/dL.

Dosage

For prevention, a dose of approximately 1000 mg of combined eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) is recommended. For treatment of elevated triglycerides, doses of 1000 to 4000 mg combined EPA and DHA are required. This can be achieved with either over-the-counter fish oil or prescription Lovaza. Care should be taken to dose fish oil in terms of combined EPA and DHA content, rather than "total" fish oil labeled on the front of over-the-counter products. For example, if the label lists EPA 300 mg and DHA 200 mg and the serving size is two capsules, then to obtain 1000 mg of EPA and DHA, the dose would be four capsules daily.

Precautions

Fish oil can have a mild anticoagulant effect and should be used with caution in patients taking warfarin. It can also cause mild gastrointestinal upset, which may be relieved by storing fish oil in a freezer before use.

Fish oil dosing:
- Dosage should specify eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) content, rather than total fish oil.
- Advise patients to check the nutrition label of products to confirm the EPA and DHA content.
- The typical dosage for prevention is approximately 1000 mg combined EPA and DHA.
- The typical dosage for treatment of hypertriglyceridemia is 1000 to 4000 mg combined EPA and DHA.

Coenzyme Q10

Not controversial: Coenzyme Q10 (CoQ10) is a mitochondrial membrane–bound compound involved in electron transport and energy production. Therapy with statins lowers the level of circulating CoQ10.

Controversial: Supplementing patients who take statins with CoQ10 reduces the risk of statin-related adverse side effects.

Two randomized studies evaluated treatment with CoQ10 to improve statin-related myalgias, and the results were conflicting. One study of 44 patients with a history of statin-related myalgias showed no improvement when CoQ10 at 200 mg/day was added.[56] In contrast, another study of 32 patients demonstrated a significant reduction in myalgias with CoQ10 at 100 mg/day.[57]

Analysis of the possible role of CoQ10 deficiency on statin-related myalgias is difficult. Although blood levels of CoQ10 typically drop with statin therapy, tissue levels are not consistently affected.[58] The majority of circulating CoQ10 is found in LDL, and, therefore, any intervention that lowers LDL also lowers CoQ10.[58] Therefore, despite strongly polarized opinions regarding the need for CoQ10, the role of CoQ10 in patients treated with statins is uncertain. What does appear clear is that no significant adverse reactions have been reported with CoQ10, even when it is used at doses much higher than 200 mg/day.[59]

Given the high safety margin and evidence of improvement in some patients, many clinicians find it reasonable to attempt a trial of Coenzyme Q10, 100 mg/day, in patients with a history of suspected statin-related muscle symptoms.

Dosage

A dose of 100 mg/day may reduce the development of myalgias in patients taking statins. CoQ10 has no intrinsic lipid-altering properties and has not been reported to reduce the likelihood of developing coronary artery disease. Evidence indicates, however, that CoQ10 at doses up to 200 mg/day may improve systolic function for patients in congestive heart failure.[60]

Vitamin D

Receptors for vitamin D have been identified in heart muscle cells, as well as within arterial walls. Activation of these receptors has many beneficial functions that relate to blood pressure regulation and normal arterial function.[61]

Accordingly, deficiency of vitamin D has been associated with increased cardiovascular risk. The Framingham Offspring Study evaluated individuals without known cardiovascular disease and found that a vitamin D level lower than 15 ng/mL was associated with a 62% increase cardiovascular risk. The link between vitamin D deficiency and cardiovascular risk was especially prominent in persons with hypertension.[62]

Vitamin D deficiency also appears to play a role in statin intolerance. The development of myalgias appears to be more prevalent among vitamin D–deficient patients. In one study, the average vitamin D level in patients with statin-related myalgias was 21 ng/mL, as compared with patients without myalgias, who had an average vitamin D level of 30 ng/mL.[63]

This finding was extended by the observation that patients with statin-related myalgias who are vitamin D deficient (mean vitamin D level, 29 ng/mL) may experience resolution of their symptoms with vitamin D replacement.[64]

Dosage

Although much needs to be learned about the relationship between vitamin D and cardiovascular disease, available data suggest that levels higher than 30 ng/mL are desirable. For patients who are vitamin D deficient, replacement can be achieved with daily dosing of over-the-counter vitamin D_3 (doses of 1000 to 5000 units per day, depending on the severity of the baseline deficiency).

Precautions

Excess vitamin D can cause hypercalcemia Thus, levels should be rechecked to assess adequacy of treatment to reduce toxicity.

Folic Acid

Folic acid and other B vitamins have been proposed as useful supplements in patients with coronary artery disease because these substances lower the circulating levels of homocysteine. Elevated homocysteine levels were previously linked to an increased risk of both coronary heart disease and stroke.[65]

Unexpectedly, randomized trials of folic acid, vitamin B_6, and vitamin B_{12} failed to show benefit for secondary prevention despite the achievement of reduced homocysteine levels: the Norwegian Vitamin (NORVIT) trial (3749 individuals following myocardial infarction who were given regimens containing folic acid at 800 mcg per day) and the Heart Outcomes Prevention Evaluation-2 (HOPE-2) trial (5522 patients with vascular disease or diabetes who were taking folic acid at 2500 mcg per day).[66,67] In the NORVIT trial, the trend was toward harm in the group given a combination of folic acid, vitamin B_6, and vitamin B_{12}.

The reason that folic acid has failed to reduce the occurrence of cardiovascular events is unclear. One explanation is that folic acid is simply a marker, as opposed to a target, of increased risk. An alternative explanation is that folic acid causes harm by some unknown mechanism that offsets the benefits of homocysteine reduction.

Although folic acid supplementation has not proven useful, foods rich in folate, particularly dark green leafy vegetables, are strongly associated with cardiovascular benefit. One study demonstrated a 23% reduction in the development of coronary heart disease with each daily serving of green leafy vegetables.[9] Therefore, consumption of foods rich in folate should be encouraged.

> Folic acid supplementation has not proven useful for prevention of cardiovascular events, but foods rich in folate, especially dark green leafy vegetables, are associated with significant benefit.

Vitamin E

Vitamin E was postulated to reduce the risk of coronary disease because of its potent antioxidant properties. An early study, the Cambridge Heart Antioxidant Study (CHAOS), showed benefit in reducing nonfatal myocardial infarction with a median follow-up of approximately 1.5 years.[68] Subsequent studies of longer duration (3.5 to 8 years) and larger sample size (9541 to 14,641 patients) failed to confirm a beneficial effect, with no reduction in cardiovascular events with vitamin E supplementation.[69–71] These trials used 400 to 800 units of alpha-tocopherol per day, mostly from synthetic sources.

Vitamin E exists in eight isomers: four tocopherols and four tocotrienols. One of the concerns of vitamin E studies was the use of the isolated alpha-tocopherol fraction of vitamin E. Some experimental data suggest that gamma- and delta-tocopherol may be more beneficial than the alpha isomer used in clinical trials.[72,73]

> The evidence to date does not support the use of the synthetic alpha-tocopherol isomer of vitamin E for prevention of cardiac disease. Additional research is needed to evaluate the effect of mixed tocopherols and tocotrienols on cardiovascular events.

Mind-Body Therapy

One of the areas in which an integrative approach stands to contribute most to the field of cardiology is in appreciation of the role of the mind-body connection in heart health. Although many people are intuitively aware that thoughts and emotions can influence the body, most conventional medical encounters do not include assessment of the patient's emotional state, let alone offer therapies directed at mind-body interventions.

The emotional states most commonly linked to heart disease are stress, anxiety, and depression. Of equal importance is the known association between happiness and heart health. The link between stress and anxiety with heart disease is strong and far-reaching, so much so that anxiety disorders diagnosed early in life, by age 20 years, independently predict a doubling of heart disease risk more than 30 years later.[74]

The mechanism by which stress affects cardiac function is unclear, but knowledge is increasing rapidly in this area. Stress clearly leads to an increase in catecholamine levels, which are known to increase blood pressure and heart rate, thereby increasing cardiac work.[75] In a fascinating experiment, psychological stress provoked by mental arithmetic produced severely reduced coronary blood flow, identical to that typically observed with strenuous exercise.[75]

A particularly extreme manifestation of stress on heart health is Takotsubo cardiomyopathy. In this fascinating but potentially lethal condition, psychological stress has been shown to lead to a marked increase in circulating catecholamine levels. The jump in catecholamine triggers acute heart failure typically requiring maximal cardiac support. Antecedent psychological stressors documented to trigger "stress cardiomyopathy" include the death of a parent, a surprise birthday party, fear of a medical procedure, and public speaking.[76] Following the acute phase of Takotsubo cardiomyopathy, cardiac function often recovers completely.

Perhaps less well recognized is the influence of stress on lipids. Both acute stress and chronic stress have been linked to unfavorable lipid responses. Within hours of acute psychological stress, total cholesterol has been shown to

increase by 7 mg/dL and LDL-C by 5 mg/dL.[77] Furthermore, the acute lipid response to stress was shown to identify those individuals with hypercholesterolemia measured 3 years later, a finding suggesting that stress may be a contributor to chronic dyslipidemia.[77]

Just as emotional factors may contribute to the development of heart disease, they can also be harnessed to promote heart health. Meditation practiced for 5 years in individuals with coronary disease was demonstrated to reduce the combined risk of a cardiovascular event and death by 43%.[78] The mechanism of risk reduction by meditation likely includes a decrease in cardiovascular workload, as demonstrated by the ability of meditation to blunt the expected increase in heart rate associated with infusion of isoproterenol[75] (see Chapter 98, Recommending Meditation). Another study showed that patients assessed as "optimists" had a 55% reduced risk of cardiovascular death, adjusted for traditional risk factors, compared with their less upbeat peers.[79]

A wide range of therapies is available to assist patients with cardiac disease to manage their stress and anxiety more effectively. In addition to the conventional treatments with psychoactive medication or referral for cognitive-behavioral therapy, the palette available to the integrative practitioner includes meditation, yoga, biofeedback, healing touch, Reiki, massage, and acupuncture.

No one resource is generically superior to another. Instead, referral should be made based on an individualized assessment including the patient's prior knowledge or history with a particular approach, the patient's philosophical inclination, local expertise, and cost. This "matching" process is truly one of the arts of integrative medicine.

Other Therapies

Enhanced External Counterpulsation

Enhanced external counterpulsation is a noninvasive method of improving blood flow to the heart and reducing anginal symptoms. This treatment involves repetitive leg compressions with a pneumatic device that drives blood backward into the aorta and increases coronary blood flow. A study of 1097 patients with coronary disease showed that 73% had improvement in the severity of angina at the completion of treatment, with sustained benefit after 2 years.[80] Another study examined 363 patients with severe angina and depressed left ventricular function.[81] After treatment, 72% patients had a reduction in severity of angina from severe to mild or none, with benefit continued after 2 years.[81]

Protocols generally involve 35 1-hour sessions of treatment spread out over 5 weeks. Patients referred for this treatment historically have been those with refractory angina who have exhausted medical therapy and mechanical revascularization options.

Chelation Therapy

Chelation therapy has been proposed as a treatment for atherosclerotic vascular disease. The hypothesized mechanisms of benefit include the binding of calcium in atherosclerotic plaque, as well as reduction of oxidative stress leading to improved vascular function. Reviews of the limited available data suggest no overall benefit of chelation therapy for the treatment of vascular disease.[82,83] More information will be available when the results of a $30 million National Institutes of Health study, the Trial to Assess Chelation Therapy (TACT), is completed. This study is testing the impact of ethylenediaminetetraacetic acid (EDTA) chelation on approximately 2000 individuals following myocardial infarction.[84]

Prevention Prescription

- Nutrition (Mediterranean diet)
- Weight management
- Smoking cessation if needed
- Exercise (aerobics and resistance training)
- Tools for management of stress and anxiety
- Lipid management

Therapeutic Review

Nutrition

- Mediterranean-style diet — A1
  - Five servings vegetables/day
  - Two servings fruit/day
  - Whole grains, elimination of refined carbohydrates
  - Two servings fish/week
  - Reduction of red meat consumption
  - Frequent nut consumption

Exercise

- 30 minutes/day walking or more intensive aerobics for a minimum of 30 minutes three times/week — A1
- Resistance training at least 30 minutes/week — B1

Smoking Cessation — A1

Lipid Management

- For low-density lipoprotein cholesterol
  - Fiber supplements (e.g., psyllium, 10 g/day) — B1
  - Stanols and sterols: 1.8 g/day — B1
  - Niacin: 500 to 2000 mg/day — A2
  - Prescription statins: dose varies — A2

Continued

- Red yeast rice: 1200 to 2400 mg/day divided twice daily
- For high-density lipoprotein cholesterol
  - Exercise
  - Weight loss
  - Reduced intake of carbohydrates
  - Niacin: 500 to 2000 mg/day
- For triglycerides:
  - Exercise
  - Weight loss
  - Reduced intake of carbohydrates
  - Fish oil: 1000 to 4000 mg eicosapentaenoic acid and docosahexaenoic acid per day
  - Fibrates: fenofibrate, 45 to 150 mg/day
- To reduce statin-related myalgias
  - Consider coenzyme Q10: 100 mg/day
  - Replete vitamin D deficiency: goal is level greater than 30 ng/mL

Stress and Anxiety Reduction

- Breathing exercises
- Biofeedback
- Meditation
- Yoga
- Acupuncture
- Cognitive-behavioral therapy
- Anxiolytics

Antianginal Therapy

- Acetylsalicylic acid: 81 to 325 mg daily
- Beta blockers (e.g., metoprolol succinate: usual dose 50 to 200 mg daily)
- Nitrates (e.g., isosorbide mononitrate: usual dose 30 to 120 mg daily)
- Calcium channel blockers (e.g., amlodipine: 2.5 to 10 mg daily)
- Angioplasty and stents (for angina)
- Enhanced external counterpulsation

KEY WEB RESOURCES

American Heart Association practice guidelines. http://my.americanheart.org/professional/StatementsGuidelines/Statements-Guidelines_UCM_316885_SubHomePage.jsp	This Web site from the American Heart Association (AHA) and American Stroke Association (ASA) publishes medical scientific statements on topics related to cardiovascular disease and stroke. Volunteer scientists and health care professionals from AHA and ASA write the statements, which are supported by scientific studies in recognized journals. These statements generally review available data on a topic, evaluate its relationship to the science surrounding cardiovascular disease, and often conclude with an AHA/ASA position on the topic.
Natural Medicines Database. www.naturaldatabase.com.	This site is an excellent resource for detailed information about supplements including the scientific basis (or lack thereof), adverse reactions, and interactions with drugs and supplements.
ConsumerLab. http://www.consumerlab.com.	This site summarizes testing information regarding the content and purity of commonly recommended supplements.

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Chapter 26

Peripheral Vascular Disease

Danna Park, MD

Pathophysiology

Peripheral vascular disease (PVD) is a term applicable to several vessel occlusive diseases, whether they stem from the venous system or the arterial system. For the purpose of this chapter, discussion is limited to peripheral atherosclerotic vascular disease, also known as peripheral vascular occlusive disease or peripheral artery disease (PAD), because this entity correlates with coronary artery disease, hypertension, and diabetes. However, PVD can arise from numerous vasculitides and from other venous problems such as chronic venous insufficiency. These conditions would require different assessments and treatment strategies, depending on the underlying cause.

The American Heart Association divides PVD into two categories: functional and organic. Functional PVD is not related to structural problems in blood vessel walls; instead, this type of PVD can stem from vessel spasm or compression. Organic PVD is associated with vessel blockage resulting from fatty infiltrates, inflammation, or tissue damage. PAD is a subset of organic PVD.[1]

Most commonly diagnosed when a patient experiences intermittent claudication, PAD is a peripheral sequela of atherosclerosis in the body, which can affect other systems as well and can result in coronary artery disease, stroke, and renal disease. Other diseases and risk factors that place patients at risk for PAD include diabetes, hypertension, tobacco use, and hyperlipidemia. Estimates indicate that 8 million to 10 million U.S. residents are affected by PAD; concurrent with the diagnosis of PAD is an increased risk of cardiovascular mortality (four to six times greater risk than healthy individuals of the same age).[2] Symptoms of PAD may be variable depending on the vessel involved and range from no symptoms, intermittent claudication (reported in only 11% to 40% of patients), impotence, a feeling of weakness in the hip or thigh, or variable pain in the buttocks, thighs, or feet.[3] Signs on physician examination may also be variable and include the following: ulcerations or nonhealing wounds; loss of hair; skin redness; skin coolness to touch; decreased or absent pulses; impaired capillary refill; and dry, scaly, or shiny skin. The best way to diagnose PAD is noninvasive and can be done in the office setting by using the ankle-brachial index (ABI), a comparison of the systolic blood pressure (SBP) in the dorsalis pedis and posterior tibial arteries in the ankle with the brachial artery of the arm (Fig. 26-1). In comparison with confirmed PAD by angiogram, this simple technique is 95% sensitive and almost 100% specific.[4] A normal measurement is greater than 0.9, whereas any value less than 0.9 indicates the presence of PAD. A patient within the range from 0.9 to 0.7 may be asymptomatic or have very mild intermittent claudication symptoms, whereas patients with an ABI of 0.7 to 0.4 have mild to moderate claudication. Patients with an ABI less than 0.4 have advanced PAD with a high likelihood of rest pain and ulceration complications. In addition to ABI, treadmill testing can be a useful adjunct to determine how fast claudication pain develops, the time to maximal pain, and the effect of exercise on ABI, and it can also be used as a screening tool for atherosclerotic heart disease.[5] Standard of care now emphasizes that all patients with PAD have aggressive treatment and risk reduction therapies regardless of the level of symptom severity, because many patients with PAD are asymptomatic.

Performance measures for PAD were established in 2010 by the American College of Cardiology and the American Heart Association in conjunction with other national associations. The measures include periodic measurement of ABI in at-risk patients, treatment with a statin drug to lower low-density lipoprotein cholesterol (LDL-C) to less than 100 mg/dL (or less than 70 mg/dL in patients with PAD with a very high risk of ischemic events), tobacco cessation treatment, antiplatelet therapy with aspirin or clopidogrel, a supervised claudication exercise program, and serial monitoring of patients with asymptomatic abdominal aortic aneurysms or those who have lower extremity vein bypass grafts.[6]

An ABI less than 0.9 suggests PAD. An SBP value of the posterior tibial artery of 100 mm Hg divided by a systolic brachial artery pressure of 140 mm Hg would give an abnormal ABI of 0.71.

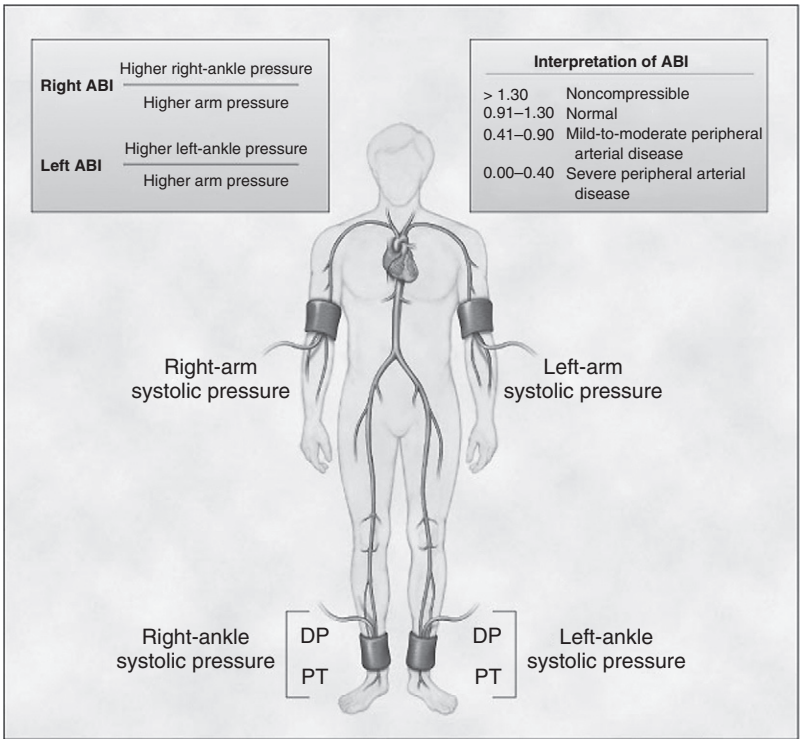

FIGURE 26-1
Diagnosis of peripheral vascular disease using the ankle-brachial index (ABI). DP, dorsalis pedis [artery]; PT, posterior tibial [artery]. (From Hiatt WR. Medical treatment of peripheral arterial disease and claudication. *N Engl J Med.* 2001;344:1608–1621.)

Integrative Therapy

Biomarkers and Genetics

Low-grade inflammation has been implicated as one of the independent risk factors for PAD, but obtaining a significant laboratory panel assessment specific and diagnostic for PAD alone has been elusive. Homocysteine, C-reactive protein (CRP), fibrinogen, lipid levels, and hypercoagulability markers are all associated with coronary artery disease and atherosclerosis, and they can be elevated in other vascular disorders. Although ABI is a very low-cost, reasonable tool with high sensitivity and specificity, it has not yet been universally accepted as a screening tool because it is considered to be technically difficult to perform accurately. Researchers have turned to identification of possible biomarkers specific for PAD that could be assessed by a simple blood test. Beta$_2$-microglobulin, cystatin C, high-sensitivity CRP and glucose were shown to be associated with PAD independent of other "traditional" risk factors.[7]

Genetic variants continue to be investigated, because family studies indicate that PAD is heritable. Assessing the impact of genetic susceptibility is difficult, however, given the many nonheritable risk factors, such as tobacco use, diabetes, and hyperlipidemia. Difficulties include the need to screen thousands of patients for adequate study power, the need to look at more than one single nucleotide polymorphism (SNP) genotype, and the possibility of genotyping errors. Genome-wide association studies may be more useful for investigating multiple SNPs and relationships with PAD versus no PAD.[8]

Risk Factor Reduction

Because PAD is an indicator of systemic atherosclerosis even when the patient is asymptomatic, investigators agree that risk reduction on various levels must be undertaken, especially in the areas of diabetes control, hypertension, hyperlipidemia, exercise, and tobacco cessation.

Diabetes increases risk of PAD by fourfold to fivefold, although the often concomitant problems of tobacco use, high lipid levels, and hypertension seem to play more important roles in atherosclerosis than does the level of glucose control. However, advising aggressive glucose control for risk reduction in overall cardiovascular events seems prudent; a hemoglobin A1c value of 7.0% or less is recommended.[9] Hypertension is associated with a twofold to threefold increased risk of PAD.[9] In the Framingham Heart Study, risk profiles for intermittent claudication showed a twofold increase in risk with stage II or greater hypertension (SBP more than 160 mm Hg or diastolic blood pressure [DBP] more than 100 mm Hg), and a 1.5-fold risk increase with stage I hypertension (SBP more than 140 to less than 160 mm Hg or DBP more than 90 to less than 100 mm Hg). In addition, hypertension is a major risk factor for nonsymptomatic PAD found by noninvasive testing (e.g., ABI) as well as for symptomatic PAD.[10] Risk reduction in this area is of particular importance for overall cardiovascular mortality and morbidity—coronary artery disease is associated with a nearly triple risk for intermittent claudication.[10] Angiotensin-converting enzyme (ACE) inhibitors are particularly well suited for hypertension and PAD because of their positive effects on endothelial remodeling, function, and slowing of atherosclerotic lesion progression.[3]

Hyperlipidemia plays a significant role in overall cardiovascular morbidity and mortality, as well as in PAD—recommended target goals for LDL and triglyceride levels are less than 100 mg/dL (less than 70 mg/dL if many ischemic risk factors are present) and less than 150 mg/dL, respectively. The evidence for the benefits of statin drugs in PAD regardless of the patient's coronary artery disease status is significant, so this therapy should be standard of care

for all patients with PAD. A 2005 Cochrane Review had a small number of eligible studies to examine (seven in all) with regard to lipid lowering for lower extremity PAD; however, results showed a reduction in overall mortality, and one study showed a 28% increase in the ABI (an indication of improvement in vessel disease) and improvement in walking distance overall.[11] Subsequent studies have continued to show that statins increase walking time, improve ABI and claudication symptoms, and decrease all-cause mortality, cardiovascular death, and renal failure.[12] In addition to statin therapy, a low-fat diet should be recommended, and lipid-lowering supplements may be considered in addition to drug therapy (see Chapter 39, Dyslipidemias).

High homocysteine levels have been associated with increased risk of coronary artery disease in addition to being an independent risk factor for PAD. Although checking and treating high homocysteine levels were recommended in the past, some more recent studies and meta-analyses evaluating the effectiveness of treatment with folate (with or without other B vitamins) did not show a decrease in myocardial infarction, stroke, sudden death, or vascular disease despite statistically significant decreases in plasma homocysteine levels. Homocysteine may serve as a marker of coronary and vascular disease, rather than a causal factor. Until more evidence is available, current data are insufficient to support screening or treatment of hyperhomocysteinemia.[13,14]

Lifestyle Interventions

Exercise

Studies indicate that exercise helps relieve intermittent claudication, although it must be prescribed in a graduated fashion as the patient tolerates, by increasing the amount of exercise time as claudication symptoms improve. Potential mechanisms by which exercise is thought to improve claudication symptoms include stimulation of angiogenesis, thus causing formation of collateral vessels and increasing blood flow. Improved endothelial vasodilation with exercise was shown in animal models, whereas an increase in the oxygen extraction capacity of exercised leg muscles was demonstrated in patients with claudication.[15] Given that exercise is also indicated for the medical conditions that are most commonly associated with PAD such as heart disease, diabetes, high cholesterol levels, and hypertension, exercise is one of the primary lifestyle interventions. Because patients with PVD are also at high risk for cardiovascular disease, cardiac testing must be undertaken before establishing and individualizing an exercise program. Overall, exercise has been proven to decrease atherosclerotic risk factors such as hypertension, insulin resistance, obesity, and lipid abnormalities such as high triglycerides and low high-density lipoprotein (HDL).[16] One meta-analysis showed that with exercise rehabilitation, walking distance to onset of claudication pain increased by 179%, whereas distance to maximal claudication pain increased by 122%. Greatest improvement occurred with a walking-based exercise program longer than 6 months of at least 30 minutes of walking three or more times per week with intermittent walking to near-maximal claudication pain as the end point.[17] Lower extremity resistance training was shown to increase functional performance in treadmill walking time, quality of life measures, and stair-climbing ability when compared with a control group, so a combination of aerobic and resistance exercise may be optimal.[18]

An exercise prescription should include the foregoing recommendations and should emphasize periods of walking to the point of high to moderate claudication pain interspersed with rest in the 30-minute period. For those patients who do not have access to a supervised exercise program, a self-motivated walking program is also efficacious. One small observational study showed less annual decline in functional walking distance when walking was incorporated as self-directed exercise three or more times per week.[19] Current evidence continues to support the use of cilostazol in conjunction with exercise as the best way to maximize the greatest change in ABI and walking distance to claudication pain; this combination was better for outcomes than conventional medical management, exercise, or drug therapy alone[5] (see Chapter 88, Writing an Exercise Prescription).

A graduated walking program over 6 months for at least 30 minutes, three or more times per week, can significantly improve claudication pain and exercise endurance.

Tobacco Cessation

That smoking is an enormous risk factor for PAD is universally accepted. The population-attributable risk ranges from 14% to 53%, indicating a huge potential for prevention of PAD if smoking is eliminated.[10] A dose-response relationship has also been established, with an increased prevalence (2.3 times higher) of symptomatic PAD in smokers.[20] Smokers with intermittent claudication have a higher incidence of rest pain, myocardial infarction, and cardiac death; the 10-year survival rate for smokers and nonsmokers with intermittent claudication of 46% and 82%, respectively.[21] Studies show that smoking cessation can cause a 10-fold decrease in the 5-year risk of amputation in patients with PAD, and this finding provides another reason to pursue smoking cessation treatments aggressively in these patients.[22] Surprisingly, radiologic data of patients who continue to smoke heavily after percutaneous transluminal angioplasty (PTA) or stent placement in lower extremity arteries show a reduced restenosis rate. Elevated levels of carbon monoxide resulting from smoking are thought to play antiinflammatory and antiproliferative roles as vascular smooth muscle cell proliferation is inhibited.[23] Obviously, the benefit is far outweighed by the foregoing costs, and smoking cessation should be highly recommended and supported. Options for smoking cessation include nicotine replacement products, counseling, medications such as bupropion and buspirone, hypnosis, acupuncture, and cognitive-behavioral therapy—all these treatments vary in degree of success rates.

Nutrition

Nutrition and weight management are fundamental components of any cardiovascular treatment plan. Dietary recommendations for PVD are in essence the same as for other atherosclerotic conditions, modified by existing risk factors such as insulin resistance or hyperlipidemia as described earlier.[24] Studies looking at dietary factors important in the prevention and management of PVD have focused on dietary fiber and omega-3 fatty acid intake.

Omega-3 Fatty Acids

Omega-3 fatty acids may benefit patients with PVD through lipid-lowering properties, as well as changes in LDL susceptibility to oxidation.[25] A Cochrane Review assessed the benefits as noted in four placebo-controlled randomized trials that used omega-3 enriched foods (e.g., eggs), omega-3–rich fish oils, and supplements.[26] The reviewers concluded that omega-3 fatty acids do have positive effects in this population, as assessed by reductions in triglyceride levels and DBP. However, the effects on clinically relevant outcomes such as pain-free walking distance or ABIs were inconsistent. A study of 60 men with intermittent claudication observed increases in pain-free walking distance and ABI values in those men taking a fortified dairy product that included omega-3 fatty acids, oleic acid, folic acid, vitamin B_6, and vitamin E over a 12-month period.[27] To ascertain the significance of each nutrient is difficult, given the multitude included in the supplement.

Dosage

Recommend foods abundant in omega-3 fatty acids, such as cold-water fish (salmon, mackerel and sardines), omega-3–enriched eggs, flaxseed products, and fish oil supplements (500-mg capsules, 2 to 4 g/day total dose). Be aware that human enzymatic conversion of plant sources of omega-3 fatty acids, such as flaxseed (an alpha-linolenic acid [ALA] source) into useable eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) is very low: in a study of young men, approximately 8% of dietary ALA was converted to EPA and 0% to 4% was converted to DHA.[28] Therefore, the prudent course is not to use flaxseed or other plant sources as the sole sources of omega-3 supplementation in the diet (see Chapter 86, The Antiinflammatory Diet).

Precautions

Fish oil in higher doses may inhibit platelet aggregation and increase bleeding risk.

Fiber

Dietary fiber, which includes all plant food parts that the body is unable to digest or absorb, is often divided into those types that do not dissolve in water (insoluble fiber) and those that do (soluble fiber). Soluble fiber is found in oat bran, psyllium, barley, nuts, seeds, beans, lentils, peas, and some fruits and vegetables. Foods high in insoluble fiber include whole wheat breads, wheat cereals, wheat bran, rye, cabbage, beets, carrots, Brussels sprouts, cauliflower, and apple skin.

Several epidemiologic studies examined the relative merits of soluble and insoluble fiber in patients with PVD. A prospective analysis of the relationship between dietary fiber and PAD risk was conducted using sequential food frequency questionnaires among more than 46,000 men with no baseline cardiovascular disease or diabetes. During 12 years of follow-up, 308 cases of PAD were diagnosed. After adjusting for confounding variables, intake of cereal fiber, but not fruit and vegetable fiber, was inversely correlated with PAD risk.[29,30] Other research on fiber in cardiovascular risk identified differential effects: whole grain (cereal) fiber was linked to lower body mass index, blood pressure, and homocysteine; fruit fiber was associated with lower blood pressure and waist-to-hip ratios; vegetable fiber was associated with lower blood pressure and homocysteine; and fiber from nuts, seeds, and dried fruit was associated with less abdominal obesity, insulin resistance, and lower apolipoprotein B levels.

Given the numerous benefits of all dietary sources, recommending adequate fiber intake from various dietary sources as whole foods rather than as supplements is wise. The recommended goal is a total of 25 to 30 g of fiber per day. Specific instructions to help patients achieve this goal may include the following:

- Eat at least 4½ cups of fruits and vegetables daily.
- Replace white bread with whole grain breads and cereals.
- Add ¼ cup of wheat bran to foods such as cooked cereal, applesauce, or meat loaf.
- Eat cooked beans each week.

Caution patients to add fiber to the diet gradually, to avoid excessive abdominal bloating and discomfort (see Chapter 86, The Antiinflammatory [Omega-3] Diet).

Mind-Body Therapy

Biofeedback

Autogenic training, or biofeedback, may be a useful adjunct for the treatment of PAD. Biofeedback training teaches the patient how to control the sympathetic nervous system and leads to relaxation, stress reduction, and decreased nervous system tone. Thermal biofeedback uses temperature sensors to teach how to increase blood flow to the extremities. As muscles relax, peripheral perfusion improves. Two case studies[31] using thermal biofeedback in patients with diabetic intermittent claudication showed improved distal extremity temperatures, ABIs, and walking distance.[32]

Treatment of Depression

Evaluation and treatment for depression should also be considered for patients with PAD because of the correlation between depression and lower extremity arterial disease. One study showed twice the risk of depressed mood in patients with PAD than in controls, with shorter walking distances significantly correlating with the likelihood of depression.[33] A second study in 2003 reinforced these findings and showed a relationship between depression and the prevalence of leg pain at rest and with exertion, shorter walking distance, and slower walking velocity.[34]

If anger proneness is an issue, counseling should be considered. Anger proneness, depression, and lack of social support systems have been shown to be independent risk factors for coronary artery disease. The Atherosclerosis Risk in Communities Study showed a similar association between anger proneness and incident PAD, with relative risk of PAD of approximately 1.4 in the high-anger group. Moderate and high levels of depressive symptoms also increased the risk of PAD, with relative risks of 1.2 and 1.4, respectively.[35]

Pharmacotherapy

All the antiplatelet agents have potentially serious interactions with most of, if not all, the botanical supplements indicated for peripheral artery disease. Using antiplatelet agents in combination with these supplements is not advised.

Antiplatelet agents have known risk reduction and health benefit in patients with PAD. These agents have shown a preventive benefit of limb loss risk and need for revascularization procedures,[22] as well as overall decreased risk (25% reduction) for cardiovascular events such as vascular death, nonfatal myocardial infarction, and nonfatal stroke.[36] Improvement in the ABI and decreased progression of peripheral disease by angiography have also been demonstrated.[37] Because of these findings, standard medical care for PAD now includes an antiplatelet agent.

Aspirin

Aspirin is probably the most cost-effective therapy and is most commonly used in a dose of 160 to 325 mg/day. Evidence indicates that clopidogrel (Plavix), which blocks platelet activation by adenosine diphosphate, has an advantage over aspirin in decreasing the risk of ischemic stroke, myocardial infarction, and vascular death. The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study showed a 24% risk reduction of the foregoing events in the subgroup of patients with PAD who received clopidogrel (75 mg daily) versus aspirin (325 mg daily).[38] However, the cost difference is substantial: a month's supply of aspirin costs approximately $1.90, and a month's supply of clopidogrel costs $249.00.[39] The low risk of hematologic adverse effects makes clopidogrel the preferred agent over ticlopidine (Ticlid) for aspirin-intolerant or aspirin-allergic patients, because ticlopidine has been associated with serious adverse effects including thrombocytopenia, thrombotic thrombocytopenic purpura, and neutropenia.[40]

Clinical trials evaluating aspirin for PAD have been statistically underpowered, and noncompliance rates in one study (the Aspirin for Asymptomatic Atherosclerosis trial) approached 40%. Despite these limitations, reductions of vascular events were still evident in some trials. Although more studies are needed, evidence favors the use of antiplatelet therapy.[41]

Dosage

The dose for aspirin is 160 to 325 mg/day.

Precautions

Large doses of aspirin have hypoglycemic effects—use caution in diabetic patients. This agent may cause changes in thyroid function tests. Concurrent administration with other antiplatelet or anticoagulant medications increases the risk of bleeding. Do not use aspirin in patients with bleeding disorders, liver disease, vitamin K deficiency, or gastrointestinal bleeding. Use caution in patients with asthma, nasal polyps, or allergic rhinitis. This drug is pregnancy category D.

Adverse Effects

Adverse effects may include gastrointestinal bleeding, dyspepsia, vomiting, diarrhea, hepatotoxicity, tinnitus, vertigo, hematologic dysfunction, urticaria, angioedema, asthma, rash, confusion, and dizziness.

Clopidogrel (Plavix)

Dosage

The dose is 75 mg daily.

Precautions

Clopidogrel is contraindicated if the patient has any active bleeding. Rare reports have noted thrombotic thrombocytopenic purpura even with short exposure (less than 2 weeks). This drug prolongs bleeding time; do not use it in patients with bleeding disorders, gastrointestinal ulcers, or gastrointestinal bleeding, and use it with caution in patients with liver disease and renal disease. Do not use clopidogrel in conjunction with nonsteroidal antiinflammatory drugs. Use with caution in conjunction with aspirin. Clopidogrel inhibits cytochrome P-450 at high concentrations, so use with caution if the patient is taking other drugs that are metabolized using this system.

Drug therapy for intermittent claudication previously included pentoxifylline (Trental) or cilostazol (Pletal). However, as a result of findings from a comparative 24-week study of cilostazol versus pentoxifylline versus placebo for effects on mean and pain-free walking distance in patients with intermittent claudication, cilostazol is now considered more effective. Cilostazol-treated patients had higher increases in pain-free and mean walking distance, and the drug was more effective than placebo or pentoxifylline.[42] In smaller drug withdrawal studies, patients receiving long-term pentoxifylline courses were able to be weaned off their medication without worsening of claudication symptoms. However, one subset of patients does seem to benefit from the drug (approximately 20%)[22] as compared with an estimated benefit of approximately 50% for patients receiving cilostazol.[42]

Cilostazol (Pletal)

Dosage

Give 100 mg twice daily.

Precautions

This drug is contraindicated in congestive heart failure of any severity as a result of phosphodiesterase III inhibition, in patients with active bleeding, or in patients with bleeding disorders. Use caution in patients with renal disease or liver disease. This drug has not been studied in dialysis recipients; reduce the dose if the patient is taking other drugs that inhibit cytochrome P-450, CYP3A4, or CYP2C19; avoid concomitant use with other antiplatelet or anticoagulant medications.

Botanicals

Ginkgo (Ginkgo biloba)

One of the top-selling herbs in the United States, ginkgo has been used medicinally in various cultures for millennia. Strong evidence exists for its use in PVD, evidence attributed to both its inhibition of platelet activating factor and its vascular relaxation by stimulation of endothelium-derived relaxing factor and prostacyclin release and its inhibition of nitric oxide.[43,44] Numerous double-blind randomized trials suggested that *Ginkgo biloba* extract causes small improvements in pain-free walking distance, maximum walking distance, and plethysmography recordings compared with placebo.[45–50] These results were confirmed as statistically significant in four published meta-analyses.[51–54] With pooled data, however, the increase in pain-free walking was a modest 34 m. Later randomized double-blind controlled studies

varied from not showing any difference in supervised exercise training with 240 mg/day of standardized ginkgo compared with placebo[55] to showing modest but not statistically significant increase in maximal treadmill walking time with 300 mg standardized ginkgo extract daily.[56] Additional evidence is needed.

Dosage

A dose of 120 to 240 mg of standardized leaf extract is taken daily in two or three divided doses. Products used in published clinical trials (available as tablets or capsules) include EGb 761, standardized to contain 24% ginkgo flavone glycosides and 6% terpenoids, and LI 1370, which contains 25% ginkgo flavone glycosides and 6% terpenoids. These formulas are available under many brand names. Three to 6 mL of 40 mg/mL ginkgo leaf liquid extract may also be taken to achieve the same dose.

Precautions

Although ginkgo leaf extract has been generally well tolerated and safe in clinical trials up to 1 year, caution needs to be taken in patients prone to bleeding or bruising. Several case reports have noted spontaneous hemorrhage such as subdural hematoma, subarachnoid hemorrhage, and anterior ocular chamber hemorrhage.[57] Combination with products known to increase bleeding, including herbs (e.g., garlic, ginseng, ginger) and pharmaceuticals (e.g., nonsteroidal antiinflammatory drugs, heparin, and warfarin) should be done with extreme caution or avoided. Although no cases of bleeding have been reported with ginkgo used in conjunction with low-dose aspirin (75 to 325 mg daily), similar concerns apply. Some experts advise stopping ginkgo ingestion 3 to 7 days before surgery to avoid perioperative complications.[58] At high doses, ginkgo theoretically can interact with antidepressants through its inhibition of serotonin and dopamine uptake; concomitant use should thus be closely monitored. Isolated reports of seizure in patients taking ginkgo are of unclear significance.

Economic data from 2000 showed that a 120-mg daily dose of ginkgo extract in the United States ranged from $0.41 to $0.84 retail. In contrast, costs of the conventional drug pentoxifylline (1200 mg) ranged from $1.83 to $1.93 and for cilostazol (200 mg) from $2.90 to $4.23.[52]

Policosanol

Policosanol is a mixture of alcohols isolated and purified from the outer wax of sugar cane *(Saccharum officinarum)*. It consists of 66% octacosanol, 12% triacontanol, and 7% hexacosanol and smaller amounts of other alcohols. These substances can also be found in wheat germ oil, alfalfa, and some animal products. Research showed that policosanol may lower serum LDL cholesterol, raise HDL cholesterol levels, and reduce platelet aggregation.[59,60] Policosanol is primarily manufactured in Cuba. A single research group in South America has conducted much of the published clinical data in PVD on a uniform population, a situation that casts some concerns about validity and generalizability. Two randomized, controlled trials found improved walking distance by more than 50% at doses of 10 to 20 mg/day taken for 6-month and 2-year durations.[61,62] In addition, small trials by the same researchers found policosanol more effective than the drug lovastatin for treating intermittent claudication and found that policosanol lowered LDL-C, increased HDL, increased the ankle-arm pressure ratio, and also increased walking distance compared with ticlopidine.[63,64]

Dosage

Typical doses of policosanol for PAD range from 10 to 20 mg daily. Consumerlab.com testing of seven policosanol supplements found that four contained only 23% to 78% of the stated ingredient.

Some "policosanol" products on the market use beeswax as the source. Beeswax contains substances similar to policosanol derived from sugar cane, but in different proportions. The relative efficacy of the beeswax products remains unclear.

Precautions

Policosanol appears to be safe at the recommended dose, with only mild short-term side effects reported in the aforementioned trials. In a study that followed 27,879 participants for up to 4 years, only 0.31% reported adverse effects, primarily weight loss, increased urination, and insomnia.[65] Like ginkgo, however, policosanol inhibits platelet aggregation and should be used cautiously, if at all, with herbs and drugs with anticoagulant effects (see earlier). It should be stopped 7 days before and after any surgery, invasive procedures, or dental procedures.

Padma 28

Padma 28 is a complex Tibetan plant preparation composed of 20 different herbs. Its proposed mechanisms of action include lipid lowering, inhibition of platelet aggregation, and antioxidant effects. A meta-analysis of six randomized, controlled trials examining patients with intermittent claudication taking Padma 28 or placebo found an improvement in maximal walking distance of more than 100 m in pooled data in approximately one out of five patients, with good tolerability of the herbal product.[66] Larger studies are needed to clarify long-term safety and efficacy.

Dosage

The dose is 403 mg, two capsules, twice a day. Padma 28 is produced by Padma AG of Zollikon, Switzerland. A related formula, Padma Basic, is available in the United States.

Precautions

Adverse effects reported in studies include mild gastrointestinal disturbances, fatigue, rash, and progression of symptoms.[67]

Supplements

L-Arginine

Arginine is a semiessential amino acid; with the exception of certain conditions and stresses, the body usually synthesizes adequate amounts. Among its many roles, L-arginine is used as a precursor in the formation of nitric oxide, a substance that relaxes the blood vessels. This property led to the postulate that arginine may benefit patients with cardiovascular diseases, including intermittent claudication.[68] A small number of shorter-term studies had found increases

in pain-free walking distance. In the most recent and longest randomized clinical trial, the Nitric Oxide in Peripheral Arterial Insufficiency (NO-PAIN) study, 133 patients with PAD were randomized to placebo versus 3 g L-arginine for 6 months, with the primary end point being the change in absolute claudication distance using the Skinner-Gardner treadmill protocol at 6 months. Although plasma arginine levels increased in the study group, nitric oxide availability measures did not. Absolute claudication distance increased in both groups, with the placebo group improving more (28.3%) than the arginine group (11.5%).[69] Arginine does not appear to be useful in PAD for long-term use, perhaps as a result of arginine tolerance and the body's adaptation to higher doses over time.

Dosage

No firmly established dose recommendation exists for arginine. Studies in coronary artery disease and claudication employed 2 to 3 g orally three times a day, for 3 to 6 months. Dietary sources of arginine include nuts, dairy products, poultry, and fish.

Precautions

At moderate doses, oral arginine appears to be safe, with minimal side effects. High-dose arginine is not recommended because it can stimulate the body's production of gastrin, with the potential for gastric ulcers or interaction with other irritants. Arginine may also affect growth hormone, glucagon, and insulin activity and should be used cautiously in diabetic patients. Arginine has the potential to promote low blood pressure and electrolyte and chemical disturbances (e.g., high potassium, low sodium, and high blood urea nitrogen levels). This is a particular concern for individuals who take drugs that also alter potassium balance (e.g., potassium-sparing diuretics and ACE inhibitors), as well as those with severe kidney or liver disease. Arginine can also increase bleeding risk when it is taken with herbs and drugs with anticoagulant or antiplatelet effects (see the earlier discussion of ginkgo). Arginine should be used with caution in combination with nitrates or sildenafil because of potentiating vasodilation and additive hypotensive effects.

Antioxidants

The role of antioxidants, such as vitamin E (alpha-tocopherol), vitamin C, and beta-carotene, in the prevention or treatment of many conditions is an area of active controversy. Initial studies showing benefit were countered by others that demonstrated harmful effects such as increased all-cause mortality.[70] Oxidative stress plays a key role in the initiation and progression of the atherosclerotic process; in theory, antioxidants could act as a defense.[71]

Epidemiologic data support the importance of antioxidants in the diet: the Rotterdam Study performed a cross-sectional analysis of the association of dietary beta-carotene, vitamin C, and vitamin E with prevalence of PVD. Of 4367 subjects with no baseline cardiovascular disease, PVD (diagnosed by ankle-arm SBP index) was found in 204 men and 370 women. Based on analysis of food frequency questionnaires, vitamin C intake was significantly inversely associated with PAD in women, and vitamin E intake was inversely associated with PAD in men.[72] However, the data regarding antioxidant in supplement form are less convincing. A Cochrane Review identified five trials of vitamin E in PVD that met the eligibility criteria.[73] Each trial reported positive effects on clinical outcomes, yet all were judged to be flawed and of overall poor quality. A double-blind placebo-controlled trial of 1484 individuals with intermittent claudication compared vitamin E (50 mg daily), beta-carotene (20 mg daily), or a combination of the two versus placebo and found no benefit in any of the treatment groups.[74]

> The data for antioxidant use in peripheral vascular disease are currently insufficient to recommend the use of these agents, especially in light of potential safety issues.

L-Carnitine

L-Carnitine plays an important role in energy production by chaperoning activated fatty acids into the mitochondrial matrix for metabolism and chaperoning toxic metabolites out of the intracellular space.[75] L-Carnitine also works indirectly to stimulate the enzyme pyruvate dehydrogenase and increase pyruvate oxidation. By counteracting high levels of free fatty acids, which occur in ischemia, and by enhancing carbohydrate metabolism, L-carnitine may attenuate injury from ischemia.[76]

Clinically, L-carnitine may be of some benefit in intermittent claudication.[77,78] Hemodynamic studies suggest that L-carnitine may increase walking distance by improving energy use in the muscles, rather than by affecting peripheral blood flow.[79]

Several multicenter double-blind placebo-controlled trials in Europe examined the potential utility of a special form of carnitine called propionyl-L-carnitine.[80–82] In a study involving 495 patients, a 44% improvement in walking distance was noted in patients with moderate to severe PVD (initial maximal walking distance of less than 250 m) as compared with placebo.[80] However, patients with milder degrees of PVD did not benefit from supplementation. Another study of 155 patients with disabling claudication in the United States and Russia found significantly improved walking distance and speed (by the Walking Impairment Questionnaire), enhanced physical functioning, and reduced body pain in the treatment group.[85] Many, although not all, other published studies on both L-carnitine and propionyl-L-carnitine also posted positive results. In 2008, a phase IV multicenter clinical double-blind randomized controlled trial of cilostazol and L-carnitine (levocarnitine tartrate) commenced to evaluate peak walking times for cilostazol versus cilostazol plus levocarnitine tartrate. Claudication onset time and quality of life measures were secondary outcome measures. The study, Evaluation of Cilostazol in Combination with L-Carnitine (ECLECTIC), was completed in December 2010.

Dosage

Acetyl-L-carnitine or propionyl-L-carnitine is taken at 500 to 2000 mg daily in divided doses. Dietary sources rich in carnitine include meat, poultry, fish, and dairy products.

Precautions

At recommended doses, carnitine and its derivatives are well tolerated. Possible mild side effects include transient gastrointestinal symptoms and body odor.

Inositol Hexaniacinate

Inositol hexaniacinate, a form of vitamin B_3, is believed to perform the same functions in the body as niacin. Activities include free fatty acid mobilization, a decrease in very low-density lipoprotein and cholesterol synthesis, an increase in HDL levels by decreasing its catabolism, and fibrinolysis. The benefits noted in patients with intermittent claudication have been attributed to the resulting reduction in fibrinogen, improvement in blood viscosity, and improved oxygen delivery. Double-blind studies found that inositol hexaniacinate, typically given at doses of 2 g twice daily, can improve walking distance in people with intermittent claudication.[84,85]

Dosage

Recommended doses range from 1500 mg to 4 g daily, in two to four divided doses.

Precautions

Although niacin has been associated with many acute and chronic toxic reactions, no adverse effects have been reported from the use of inositol hexaniacinate with intake of up to 4 g daily.[86] Given the strong association of niacin with hepatotoxicity, however, a prudent approach would be to avoid inositol in patients with known liver disease and monitor liver function tests during the initial 3 to 6 months of treatment in other patients. Given its fibrinolytic effect, inositol should be used with caution with other blood thinners.

Mesoglycan

Mesoglycan is a sulfated polysaccharide compound found in many tissues in the body, including the joints, intestine, and the lining of blood vessels. It was shown to have antithrombotic and fibrinolytic activity in laboratory and animal research. A 20-week double-blind placebo-controlled trial that enrolled 242 patients with intermittent claudication (absolute walking distance between 100 and 300 m) evaluated the effects of mesoglycan (100 mg a day orally, after a 3 week course of injected treatment). Half of the mesoglycan-treated group achieved clinical response (defined as greater than 50% improvement in walking distance) compared with 26% of the participants from the placebo group.[87] A double-blind comparative trial between heparin sulfate and mesoglycan demonstrated a 34% improvement in pain-free walking distance.[88] In contrast, a small study comparing defibrotide with mesoglycan (24 mg twice daily for 6 months) showed no improvement in pain-free walking distance or posterior tibial pressure after exercise testing.[89] Further, higher-quality research is needed to clarify the potential role of mesoglycan before it can be recommended for PVD.

Dosage

The dose often used in studies of mesoglycan is 100 mg orally daily. In some regimens, an injected or intravenous dose is given initially.

Precautions

Mesoglycan was well tolerated in studies, with isolated complaints of headache and diarrhea. However, mesoglycan does act as an anticoagulant and was found to cause a doubling of activated partial thromboplastin time values in more than 80% of patients.[90] Mesoglycan should not be used in conjunction with any drugs or supplements that affect blood clotting.

Interventional Options

Surgery

Surgical intervention is usually reserved for severe disease, as would be expected. Functional outcome and patient satisfaction seem to be greatest when disease is limited to the primary lesion only, the age of the patient is younger than 70 years, the patient is not diabetic, and the ABI normalizes after the procedure.[91] After revascularization, patients commonly are receiving some type of antithrombotic therapy, although the choice of drug (oral anticoagulant versus antiplatelet agent) depends on the type of procedure performed and whether a prosthetic graft was used. Obviously, this situation will affect the integrative practitioner in that it will limit which other integrative approaches, such as botanicals and supplements, may be used.

Angioplasty and Stenting

Percutaneous interventional procedures such as PTA are more commonly being used to attempt limb salvage before more invasive operative approaches or when a patient is not a candidate for surgery. Indications for PTA include claudication symptoms that are functionally limiting, pain at rest, or tissue loss; however, limitations for angioplasty or stenting include the location of the lesion (e.g., stents are not recommended for femoropopliteal lesions because of the high restenosis rate), the length of the lesion, the presence of multiple areas of stenosis, or calcification of the lesion.[92] Other techniques incorporated into PTA for prevention of restenosis include brachytherapy (endovascular radiation therapy) and photodynamic therapy, in which a photosensitive drug is given, followed by endovascular light activation.

Stem Cell Therapy

Bone marrow–derived stem and progenitor cell therapy for revascularization of ischemic limbs is one of the most important areas of research to date in PAD. These cells are thought to help in the normal process of arteriogenesis and capillary growth in the collateral circulation as blood vessel narrowing becomes progressively severe in PAD progression. Animal model studies of ischemic extremities showed incorporation of injected endothelial progenitor cells into capillaries and arteries, improved blood flow, and a higher percentage of limb salvage compared with controls. One small human study in patients with limb ischemia not amenable to revascularization showed that injections of bone marrow–derived mononuclear cells into the lower extremity of the ischemic limb were superior to placebo and peripheral blood mononuclear cells injections, with increases in ABI, transcutaneous oxygen pressure, rest pain, and pain-free walking distance.[93] Nineteen other small human studies showed benefits similar to the foregoing, and at least four studies are currently in progress. Questions that remain to be definitively answered include the cell type to be used, the best cell separation technique, the appropriate dosage of cells, the use of colony-stimulating factors, and safety issues.

Chelation

Intravenous chelation therapy (usually a combination of ethylenediaminetetraacetic acid [EDTA], trace elements, and vitamins) was hypothesized to improve PAD because of the mineral-binding effect of EDTA. Some of the theories of mechanism of action for chelation in atherosclerotic disease are that EDTA is thought to chelate calcium from plaques directly, to

chelate other metals involved in free radical formation and the inflammatory response, or to inhibit platelet aggregation.[94] Although few randomized controlled trials of chelation in PAD have been conducted, two systematic reviews, one in 1997[95] and another in 2005, supported the conclusion that chelation is not superior to placebo in the treatment of PAD. The 2005 review from the Cochrane Peripheral Vascular Diseases Group included four studies in which EDTA was compared with placebo. Three of the four studies showed no difference in a variety of PAD outcomes, the first including digital subtraction angiograms,[96] the second including walking distance/subjective walking distance or ABI,[97] and the third including pain-free plus maximal treadmill walking distance and ABI.[98]

Therapies to Consider

Osteopathic Manipulative Treatment

Osteopathic medicine was founded in 1874 by Andrew Taylor Still. This system of medicine uses a holistic view of body systems that focuses on the musculoskeletal system, with manual techniques to affect muscles, bones, joints, and tendons, in addition to other more familiar conventional medical treatments and therapies. The goal of osteopathic manipulative treatment (OMT) is to effect a balance between the parasympathetic and sympathetic nervous systems and thus improve somatic function. Vascular flow improvements have been shown in various manual medicine therapies, probably mediated in part by nitric oxide release. One small case-control study of OMT in 30 patients with PAD used an intervention of 30 minutes of several OMT interventions at the practitioner's discretion to treat any somatic dysfunction findings. Treatments were given every 2 weeks for 2 months, 1 month with no treatment, and then every 3 weeks for 3 months. Techniques included strain-counterstrain, myofascial release, muscle energy, soft tissue, and other osteopathic manual medicine therapies. Assessments included brachial artery flow-mediated vasodilation, ABI, time to onset of claudication pain, and quality of life measures using the Short Form 36 Health Survey (SF-36). At 6 months, the OMT group had statistically significant increases in ABI, time to claudication pain, and quality of life scores. In addition, blood levels of serum interleukin-6, soluble intercellular adhesion molecule-1, and soluble vascular cell adhesion molecule-1 also decreased significantly.[99] Although the study was small, these improvements suggest that OMT may be a useful adjunct for some patients.

Hydrotherapy

Hydrotherapy, or balneotherapy, is an ancient method used for the treatment of disease and injury by many cultures, including those of ancient Rome, China, and Japan. It is now most often employed by naturopaths and in European therapeutic spas. Naturopaths believe that, beyond the vasodilatory effects, hydrotherapy functions by affecting the quality of the blood through detoxification. The technique often recommended involves alternating immersion in hot and cold containers of water. In some cases, minerals are added to the baths.[100] Limited evidence, primarily from German studies in the 1950s, suggests that hydrotherapy may be a helpful adjuvant therapy.

Carbon Dioxide Therapies

European naturopaths may employ subcutaneous carbon dioxide (CO_2) insufflations, during which CO_2 is infiltrated into the subcutaneous tissue through a small-gauge needle. Proponents claim that it works by a vasodilatory effect on nearby capillaries. A systematic review found mixed results from three randomized controlled trials.[101]

Other research looked at the efficacy of CO_2-containing baths (1000 to 1200 mg CO_2/kg water) and CO_2-enriched air. Studies in patients with arterial insufficiency (Fontaine stages II to IV) demonstrated increases in parasympathetic activity, vasodilation, and oxygen use.[102–104] Whether these physiologic effects translate into clinical benefits remains to be seen; only one small study was found reporting an increase in pain-free walking distance after a course of 20 CO_2 bath treatments.[105] These therapies should thus be considered experimental at present.

Traditional Chinese Medicine

Various modalities from traditional Chinese medicine may be beneficial in the management of PVD. Minimal data are available regarding the use of acupuncture for PVD. One study examined lower extremity perfusion after needle stimulation at point N8 for 20 minutes; the results were positive, but whether the difference was statistically significant is not clear.[106] A review of studies looking at peripheral ulcer healing in response to acupuncture concluded that although beneficial effects were reported, the studies were uncontrolled, retrospective, and often without assessment by validated techniques.[107] Other traditional Chinese medicine practices such as qi gong and tai chi may also be considered in the treatment plan.

Prevention Prescription

- Promote risk factor reduction in the following areas: diabetes, hypertension, and hyperlipidemia.
- Strongly support tobacco cessation.
- Provide an exercise prescription (see Chapter 88, Writing an Exercise Prescription).
- Provide a comprehensive nutritional plan, incorporating the previously mentioned medical issues as needed.
- Add dietary fiber and omega-3 fatty acids (see Chapter 86, The Antiinflammatory [Omega-3] Diet).
- Recommend a total of 25 to 30 g/day of fiber. Specific instructions to help patients achieve this goal may include the following:
  - Eat at least 4½ cups of fruits and vegetables daily; replace white bread with whole grain breads and cereals; add ¼ cup of wheat bran to foods (e.g., cooked cereal, applesauce, or meat loaf); eat cooked beans each week. Caution patients to add fiber to the diet gradually, to avoid excessive abdominal bloating and discomfort.
  - Recommend foods abundant in omega-3 fatty acids (e.g., cold-water fish such as salmon, mackerel, and sardines), but limit fish intake to two 6-oz portions per week. Include omega-3–enriched eggs, flaxseed products, or fish oil supplements (500-mg capsules, 2 to 4 g/day total dose).
- Evaluate for depression and anger proneness.
- Consider autogenic or biofeedback training.

Therapeutic Review

Risk Factor Reduction

- Address diabetes control, hypertension, hyperlipidemia, and tobacco cessation.

Nutrition Recommendations and Weight Loss, If Needed

- Include recommendations for dietary fiber, dietary antioxidants (not supplements), and omega-3 fatty acid intake.

Exercise

- Prescribe a supervised claudication exercise program of 30 to 45 minutes at least three times a week for a minimum of 12 weeks.

Autogenic/Biofeedback Training

Antiplatelet Agent (Standard of Care)

- Aspirin: 160 to 325 mg daily
- Alternatives include the following:
  - Clopidogrel (Plavix): 75 mg daily (preferred)
  - Cilostazol (Pletal): 100 mg twice daily
- Precautions: All antiplatelet agents have potentially serious interactions with most of, if not all, the botanical supplements indicated for peripheral artery disease (PAD). Using antiplatelet agents in combination with these supplements is not advised. Statin therapy is indicated to lower low-density lipoprotein cholesterol to less than 100 mg/dL (or less than 70 mg/dL in patients with PAD with a very high risk of ischemic events). Angiotensin-converting enzyme therapy should be highly considered.

Botanicals

- Ginkgo (*Ginkgo biloba*): 120 to 240 mg of standardized leaf extract taken daily in two to three divided doses
- Policosanol (sugar cane derived): 10 to 20 mg daily
- Padma 28 (Padma Basic in United States): 403 mg, two capsules, twice daily
- Acetyl-L-carnitine: 500 to 2000 mg daily in divided doses
- Inositol hexaniacinate: 2 g twice daily (Avoid inositol in patients with known liver disease; monitor liver function tests during the initial 3 to 6 months of treatment in other patients.)
- Mesoglycan: 100 mg by mouth daily (Mesoglycan has an anticoagulant function; do not use in conjunction with any drugs or supplements that affect blood clotting.)

Percutaneous Interventional Procedures

- These procedures are indicated for claudication symptoms that are functionally limiting, pain at rest, or tissue loss, for attempted salvage before a more invasive approach, and for patients who are not surgical candidates.

Surgical Intervention

May include revascularization, angioplasty, or stenting.

KEY WEB RESOURCES

Natural Medicines Comprehensive Database: www.naturaldatabase.therapeuticresearch.com	This peer-reviewed, nonbiased database is regularly updated with information on integrative approaches to medical conditions, as well as information on herbs and supplements. It includes an easy-to-use format for checking drug-herb-supplement interactions.
American Heart Association: www.americanheart.org	This comprehensive site provides general patient information and conventional treatment options for PVD.
National Heart, Lung and Blood Institute: www.nhlbi.nih.gov	This comprehensive site provides information about current research and trials, as well as patient materials (multilingual available) for PVD and heart disease.

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Chapter 27

Arrhythmias

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Cardiac arrhythmias are slow (brady), fast (tachy), or irregular heart rhythm disturbances (ectopy, atrial fibrillation, and others). Arrhythmias may be a normal phenomenon related to change in autonomic tone; examples include sinus arrhythmia, sinus bradycardia, and sinus tachycardia. Arrhythmias should be evaluated and treated for interrelated reasons: (1) to eliminate symptoms, (2) to prevent imminent death and hemodynamic collapse, and (3) to offset long-term risk of serious symptoms and death. This chapter focuses on an approach to evaluate and treat arrhythmias by using an integrative approach.

Common arrhythmias encountered in an office-based setting include atrial premature beats, ventricular premature beats, bradycardias, supraventricular tachycardia, nonsustained ventricular tachycardia, atrial fibrillation, and follow-up of already treated sustained ventricular tachycardia or ventricular fibrillation. Potentially symptomatic and dangerous (potentially life-threatening) arrhythmias that require evaluation for possible acute and chronic therapy include (1) sustained ventricular tachycardia in the setting of heart disease, (2) ventricular fibrillation (cardiac arrest), (3) atrial fibrillation, (4) supraventricular tachycardia, (5) sinus bradycardia (and pauses), and (6) atrioventricular (AV) block. Junctional rhythm, AV dissociation, and ectopic beats are common, may cause concern, and may require special attention, further evaluation, and therapy. These latter arrhythmias are generally not serious enough to require long-term aggressive treatment unless they are associated with severe symptoms.

Pathophysiology

Types and Mechanisms

Heart rhythm disturbances have multiple potential mechanisms and causes. The heart rhythm is a mechanical response to electrical activation of specialized fibers and atrial and ventricular myocardium. Electrical activation is generally initiated in the sinus node and then leads to activation through various atrial conductive pathways to the AV node, the His-Purkinje system, and the ventricles. The sinus node may be activated slowly as a result of damage to this structure or because of autonomic effects. Increased vagal tone, for example, slows the sinus node rate. Abnormalities in conduction disturbances throughout the normal pathways can also lead to heart block and bradyarrhythmia.

The autonomic nervous system can influence the sinus node either to slow it or to speed it. The autonomic nervous system can also influence other tissue in the heart to make it more automatic, accelerate faster, and overtake normal sinus node activation. This influence can lead to activation resulting from an ectopic focus.

Tachyarrhythmia

Common rhythm disturbances causing an increase in heart rate are known as tachycardias. Tachycardias include sinus tachycardia. This arrhythmia can be a normal response to stress and exercise, or it can be an inappropriate acceleration for no apparent reason. Supraventricular tachycardias are less common but are tachycardias that require tissue above the His bundle to propagate. Supraventricular tachycardias occur in various forms: atrial flutter, atrial fibrillation, those resulting from abnormal areas in the atria, those secondary to rhythm disturbances in the vicinity of the AV node, and those caused by rhythm disturbances related to extra pathways that connect the atria to the ventricles. These tachycardias are in part related to the underlying mechanisms for arrhythmias that include reentry, triggered automaticity, and normal and abnormal automaticity.

Tachyarrhythmias can result from abnormally fast ventricular activation independent of atrial activation. This arrhythmia is known as ventricular tachycardia. Ventricular tachycardia is often associated with underlying structural heart disease, and the prognosis is often concerning because this arrhythmia can lead to cardiac arrest. This is not always true, however, because in patients with no underlying heart disease (idiopathic cause), ventricular tachycardia can have a benign prognosis. Another serious ventricular arrhythmia is

ventricular fibrillation. This rhythm disturbance causes cardiac arrest and, without electrical countershock, is fatal.

Other arrhythmias include ventricular ectopic beats, which can manifest as single ectopic beats, bigeminy (every other beat), trigeminy, quadrigeminy, in a fixed coupled fashion or unrelated to other beats, couplets, triplets, and other forms of nonsustained ventricular tachycardia.

Many potential problems are related to heart rhythm disturbances. Abrupt change in the heart rate, especially with marked slowing or acceleration, can lead to hemodynamic compromise, syncope, and other related symptoms. Rhythm disturbances that are extraordinarily fast or that originate in the ventricles and are associated with structural heart disease can be premonitory signs of cardiac arrest. However, most rhythm disturbances that are seen in clinical practice are benign.

Ectopic Beats

Ectopic beats that trigger palpitations frequently are the result of ventricular ectopic activity (premature ventricular contractions [PVCs]), atrial ectopic activity (premature atrial contractions [PACs]), and atrial arrhythmias such as atrial fibrillation. Ventricular ectopy and atrial ectopy, when not associated with serious underlying structural heart disease, are relatively benign. Although the risk of death may be slightly increased in any patient with PVCs (up to doubling of mortality), the risk remains low in persons with a normal heart. The reason to treat ectopic beats is not to prevent death, but rather to prevent symptoms. Asymptomatic atrial and ventricular ectopy in a patient with no underlying heart disease does not require treatment.

Symptomatic atrial and ventricular ectopy, however, becomes a major problem to treat in clinical practice, for several reasons. First, no good, safe, medical therapies are available.[1–13] Drugs used to suppress ectopy frequently can be proarrhythmic and increase the risk of sudden death or increase the severity of the arrhythmias, and these agents can have numerous other serious complications. Second, the problem can be highly symptomatic and concerning to the patient. It can have a tremendous impact on quality of life. Third, the degree of symptoms from benign arrhythmias varies tremendously, and patients who are highly symptomatic may require several types of therapeutic interventions, which can extend as far as drug therapy and even radiofrequency catheter ablation approaches.

Atrial Fibrillation

Atrial fibrillation is a complex arrhythmia with myriad presentations and therapeutic intervention possibilities. The general approach to atrial fibrillation is threefold: (1) cardiac ventricular rate control, (2) rhythm control, and (3) prevention of thromboembolic events. Although atrial fibrillation is associated with a doubling in mortality, this is not the reason that it is generally treated; yet treatment is directed at prevention of symptoms, and no one has shown that treatment of the arrhythmia alone will decrease mortality (it may even increase mortality). Atrial fibrillation occurs in more than 2.2 million U.S. residents. Ectopic beats are as common, but the extent of their occurrence is not completely known. Not all patients with ectopic beats are symptomatic, and the triggers for ectopic beats can be highly variable. For example, in some patients, caffeinated beverages, chocolate, and even high sugar levels can trigger ectopic activity.[14,15]

The most important aspect of the history is to inquire about the ingestion of stimulants such as caffeine, simple sugars, chocolate, pseudoephedrine, ephedra, guarana, ginseng, gotu cola, yohimbe, and others.

People with paroxysms of atrial fibrillation, or at least those patients who present to physicians, are highly symptomatic. Perhaps these patients do not represent the great majority of patients with atrial fibrillation, but it is not clear how many patients with paroxysmal fibrillation never frequent a health care provider. In addition, patients with symptomatic atrial fibrillation are not always symptomatic during atrial fibrillation. They often have symptoms when they are in normal sinus rhythm and can be asymptomatic during atrial fibrillation. The presence of persistent paroxysmal or permanent atrial fibrillation frequently inspires long-term treatment and consideration of the threefold treatment approach.

Palpitations

Palpitations are among the most common complaints associated with arrhythmias; the differential diagnosis is extensive. Palpitations can be intermittent or sustained, regular or irregular, and even unrelated to an arrhythmia. Catecholamine excess alone can cause a sensation of palpitations without an arrhythmia even being present.[16]

Some causes of palpitations include the following: anxiety; severe viral syndrome; alcohol; stimulants (cocaine, methamphetamine); stimulant medications including pseudoephedrine; drinks containing caffeine, theobromine, or theophylline; poor sleep (or an irregular sleep cycle); and several supplements (including *Ginkgo biloba,* ephedra, ginseng, guarana, horny goat weed, yohimbe, and others). Hormonal changes and excess thyroid hormone can also lead to palpitations.

Palpitations can represent somatization of a psychiatric disorder. Of 125 outpatients referred for ambulatory electrocardiographic monitoring to evaluate palpitations, 34% had an arrhythmia, whereas 19% had a psychiatric disorder, especially major depression or a panic disorder.[17] Those with psychiatric disorders were younger, more disabled, and more hypochondriacal about their health. Their palpitations were more likely to last longer than 15 minutes, were accompanied by other symptoms, were more intense, and were associated with more emergency room visits. Several reports confirmed the high incidence of psychiatric conditions in association with palpitations.[18,19] Nevertheless, careful evaluation of palpitations must rule out organic disease.

Palpitations only rarely are the result of a life-threatening process, although they can be associated with or represent manifestations of underlying ventricular dysfunction or other structural heart disease. Palpitations in a patient with heart disease, especially coronary artery disease, should raise suspicions that the palpitations are the result of an arrhythmia.[20,21]

Approach to the Patient

Perspective

Arrhythmias may have little meaning if they have no prognostic significance, do not alter hemodynamics or cardiac function, and are not symptomatic. Routine screening of an asymptomatic patient is not recommended. Patients typically

seek medical care for palpitations, for an arrhythmia associated with symptoms, for a symptom thought to be caused by an arrhythmia, or for nonspecific symptoms that may result from an arrhythmia.

Initial Evaluation and Diagnosis of the Arrhythmia

The initial evaluation includes a careful, circumspect, and complete history (directed toward the symptoms and any potential relationship with an arrhythmia, as well as an assessment of potential responsible conditions), a physical examination, and a 12-lead electrocardiogram at baseline and, if possible, during the arrhythmia. An unhurried, careful, and complete history is the key to appropriate further evaluation, and the clinician should resist the urge to perform expensive, unnecessary, or potentially risky tests. Several issues should be addressed in the history (Table 27-1).

The electrocardiogram recorded during the arrhythmia or while the patient is symptomatic determines the need for further evaluation and treatment. An ambulatory monitor or an event monitor may be needed, in selected patients, to secure a diagnosis. If the symptoms are sporadic, but occur daily, use of an ambulatory (Holter) monitor is the best approach.[22–25] An event recorder or transtelephonic monitor can help make the diagnosis in a patient with less frequent palpitations. Transtelephonic devices are small, lightweight, and inexpensive. The memory feature allows recording of data without the need for immediate access to telephone transmission. An implantable monitor (Reveal, Medtronic, Minneapolis) is also available.[26] The device can record events triggered by the patient or by preselected criteria automatically. The device can record up to 42 minutes of data. If episodes are associated with exercise or physical or mental stress or when an arrhythmia cannot be documented with ambulatory or transtelephonic monitoring, exercise testing may secure a diagnosis.

TABLE 27-1. Historical Features of Importance in the Evaluation of the Patient

- Which arrhythmia is present?
- Does the arrhythmia cause symptoms?
- Does the arrhythmia have prognostic significance?
- Is the problem life-threatening?
- Does the patient require hospital admission or extensive testing?
- Is specialist consultation required, and, if so, how urgently?
- Is treatment required?

Risk Assessment

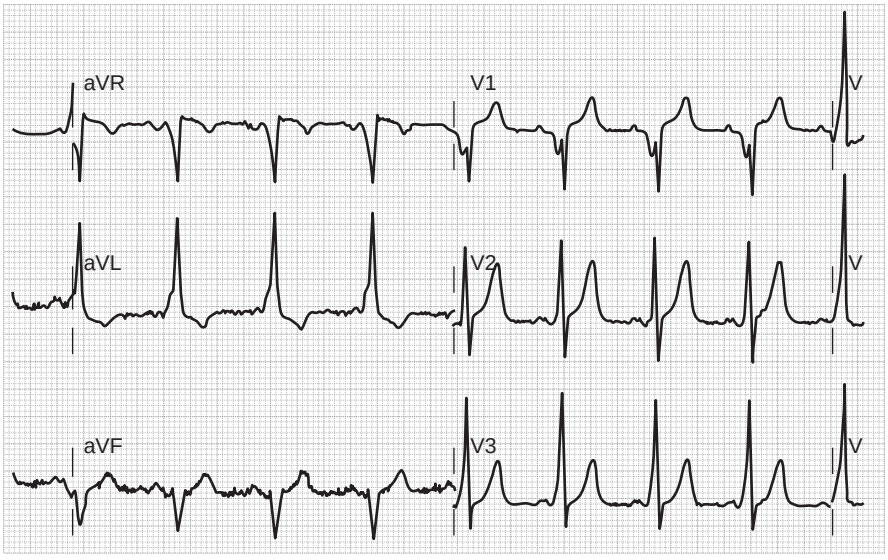
The clinician should determine whether an arrhythmia has prognostic importance: Is it a premonitory sign of death? Several conditions, ventricular tachycardia and the Wolff-Parkinson-White syndrome (Fig. 27-1), are potentially life-threatening. Not all ventricular tachycardias are life-threatening; a patient without heart disease, for example, who has idiopathic sustained ventricular tachycardia (*not* idiopathic ventricular fibrillation) has little chance of dying. In contrast, even a single episode of nonsustained ventricular tachycardia in a patient with coronary artery disease and poor left ventricular function as a result of prior myocardial infarction may be associated with a poor prognosis.[27]

Rarely, an asymptomatic arrhythmia must be treated urgently. Symptoms and their relationship with the arrhythmia require careful assessment. A correlation of the arrhythmia and symptoms is preferred, although not always possible.

Indications for Inpatient Management

Hospital admission is required if the patient has significant underlying heart disease (e.g., cardiomyopathy with congestive heart failure or coronary heart disease with active ischemia), if the arrhythmia is life-threatening and requires rapid reversion (e.g., rapid tachyarrhythmias, polymorphic ventricular tachycardia, prolonged QT interval in a patient

FIGURE 27-1
Six leads of an echocardiograph of a patient with Wolff-Parkinson-White syndrome showing delta waves.



with syncope), or if the arrhythmia is uncontrolled or highly symptomatic. Hospital admission is preferred for older patients, who may have not only underlying heart disease, but also other chronic illnesses such as kidney or liver disease that could affect antiarrhythmic therapy.

Referral to a Specialist

A cardiologist is frequently needed to help manage the complex patient with an arrhythmia; for example, a temporary pacemaker may be needed for a patient with symptomatic bradycardia. Referral to an electrophysiologist may be necessary to institute aggressive acute therapy, such as intravenous amiodarone for life-threatening ventricular tachycardia, antitachycardia pacing for acute reversion of an arrhythmia, or for placement of an implantable cardioverter defibrillator (ICD) or to reprogram a pacemaker or an ICD (Table 27-2).

TABLE 27-2. Reasons for Referral to a Specialist

- Resuscitated ventricular fibrillation
- Sustained ventricular tachycardia
- Atrial fibrillation that is difficult to control or refractory to standard therapies
- Nonsustained ventricular tachycardia
- Symptomatic supraventricular tachycardia that is difficult to control
- Sinus bradycardia (sick sinus syndrome, tachy-brady syndrome)
- Second degree atrioventricular block
- Unexplained ventricular ectopy in the athlete or in a symptomatic patient
- Syncope with a suspected arrhythmic mechanism
- Patients with devices (pacemakers, implantable defibrillators) who are unstable
- Uncontrolled rhythm problems

Integrative Therapy

The decision to start any type of antiarrhythmic therapy depends on the severity and frequency of arrhythmia-related symptoms, the risks of the arrhythmias, and the risks associated with the therapy itself. The need for long-term therapy must be carefully individualized to each patient because the severity and importance of symptoms are highly variable. The symptoms associated with any arrhythmia can have an impact on lifestyle, occupation, driving, and other important daily activities. These issues must be considered for every patient and are evaluated as part of a diagnostic and therapeutic approach.

Diet

Gastric Distention

Dietary interventions in some cases can influence some arrhythmias. A large meal can distend the stomach and stimulate vagal afferents, thus leading to vagal efferent activation causing atrial fibrillation in patients who have vagally mediated atrial fibrillation, hypotension, and bradycardia.

Food as a Trigger

Some foods may even act as triggers, and patients will often report some evidence for this. Alcohol is one of the major triggers for atrial fibrillation and ventricular ectopy.[28,29] Caffeine is frequently another trigger for ectopic beats but not necessarily atrial fibrillation.[14,15] Restriction of alcohol and caffeine may have no effect on arrhythmias. If this is the case, restriction will be of no benefit and may adversely influence the patient's lifestyle. Specific food allergies can trigger a reaction and cause palpitations. Trans fats, particularly of the 18-2 type (found in doughnuts, fried foods, and artificial cheese such as in processed pizza) have been associated with cardiac arrest.[30,31] In contradistinction,[32] omega-3 fatty acids may improve outcomes,[32,33] but data do not indicate an antiarrhythmic effect.[34] Fat balance appears to have an effect on cardiovascular health.[35] Alcohol consumption may enhance the effects of omega-3 fatty acids.[36,37]

The effects of diet on the autonomic nervous system are complex. Several foods increase sympathetic nervous system tone. High levels of sodium also increase the effects of catecholamines and influence ventricular ectopy.[38–43] It may turn out that caffeine, theophylline, and theobromine present in coffee, tea, and chocolate may be inciting factors, or they may possibly have positive benefit.[44–47] Data that coffee causes atrial fibrillation are questionable.[48,49] Trial and error with these food substances is worthwhile, but no particular reason exists to try to eliminate all these foods if they do not have an effect on the arrhythmia. Patients may complain that a specific food triggers a rhythm disturbance by an unknown mechanism. This is not uncommon and is possibly related to some type of allergic reaction or other related issue.

Gastric distention from large meals, excessive caffeine, alcohol, high levels of sodium, trans fats, severe fluctuations in blood sugar levels, and possibly food allergies are potential dietary triggers of cardiac arrhythmias.

Botanical Stimulants of Arrhythmia

Specific supplements can trigger arrhythmias. Ma Huang, from the Chinese ephedra plant, contains catecholamines including ephedrine that can initiate ectopic rhythm disturbances and cause life-threatening problems.[50,51] Investigators have even suggested that ambrotose, ginkgo, and other commonly used substances may exacerbate or even cause arrhythmias.

Diet and Anticoagulation

Diet is very important in arrhythmia management, especially in patients who require anticoagulation for atrial fibrillation or other arrhythmias. If the diet changes markedly with significant alterations in vitamin K levels, the prothrombin time will fluctuate tremendously (Table 27-3).

A balanced diet low in fat and high in roughage that will lead to a moderate level of blood sugar and as little stress as possible on the gastrointestinal tract may improve the arrhythmias.

TABLE 27-3. Assessing the Need for and Risks of Warfarin for Nonvalvular Atrial Fibrillation

Step 1

Is the patient at low or high risk?
Low risk according to the American College of Chest Physicians (ACCP)
None of the following risk factors

- ☐ Age 75 years or more
- ☐ Previous stroke or transient ischemic attack (double risk)
- ☐ Congestive heart failure
- ☐ Hypertension
- ☐ Diabetes

If low risk (zero to one of the above): Treat with aspirin.
If moderate risk (two of the above): Consider warfarin in relation to the risk of bleeding in step 2.
If high risk (three or more of the above): Strongly consider warfarin.

Step 2

Is the patient at high bleeding risk?

- ☐ Age older than 65 years
- ☐ History of gastrointestinal tract bleeding
- ☐ History of hemorrhagic stroke
- ☐ Recent myocardial infarction, hematocrit less than 30, creatinine more than 1.5, or diabetes mellitus

Weigh the potential benefits of warfarin in stroke prevention with the potential risks of bleeding, and make the most appropriate therapeutic decision.

Data from guidelines from the American College of Chest Physicians and Ebell MH. Choosing between warfarin (Coumadin) and aspirin therapy for patients with atrial fibrillation. *Am Fam Physician.* 2005;71:2328–2350.

Exercise

Exercise and physical exertion can trigger various arrhythmias. Maintaining excellent physical health through exercise, however, decreases the effects of the sympathetic nervous system on the heart and the heart rhythm and improves outcomes in almost all circumstances. The sympathetic nervous system often has a major contributory role in the genesis of serious and benign atrial and ventricular arrhythmias. Exercise performed regularly, with enhancement of aerobic capacity, decreases sensitivity to catecholamines, reduces circulating catecholamine levels, decreases sympathetic nervous system tone, and enhances vagal tone. All these effects increase heart rate variability, which decreases the risk of sudden death and the potential for catecholamine-initiated or sympathetically initiated atrial and ventricular arrhythmias (see Chapter 94, Enhancing Heart Rate Variability). Exercise can also modulate other potential rhythm disturbances such as sinus tachycardia. Especially in young women, inappropriate sinus tachycardia and postural orthostatic tachycardia syndrome are potential problems.[52] Inappropriate sinus tachycardia is a condition in which the sinus node appears to be hyperactive; the cause is not completely known. It may be, in part, related to abnormal sympathetic nervous system stimulation, but it could also be an intrinsic problem with the sinus node. Increasing exercise decreases the potential for this problem. Exercise appears to be beneficial in treating many arrhythmias, but it must be used with caution. For patients with malignant arrhythmias, exercise therapy must be prescribed and supervised by a qualified physician who is knowledgeable about the risks, benefits, and methods of monitoring the patient.

Lifestyle

Lifestyle has a major impact on arrhythmias.[53–55] Cigarette smoking and other forms of nicotine have no potential benefit and may be harmful for any individual.[54,56] Nicotine use can exacerbate the risk of sudden death and malignant and benign arrhythmias of all types. Although alcohol may have a beneficial effect on cardiovascular mortality, myocardial infarction, and cholesterol, it has no benefit for any arrhythmia. The combination of alcohol and nicotine is even more likely to trigger an arrhythmia.

Mind-Body Therapy

Autonomic variations can occur with numerous lifestyle interventions, including meditation and other mind-body therapies.[57,58] The influence can be profound and may occur by several potential mechanisms: (1) change in autonomic function, (2) placebo effect, (3) direct effect on the rhythm, (4) change in perception of the importance of the arrhythmias to the patient, and (5) shifting of the attention from the arrhythmia to some other issue.

Biofeedback can decrease the number, frequency, and severity of palpitations related to arrhythmias. The effects of biofeedback have been known for some time.[59–63] Another issue is the simple process of developing awareness that a patient can learn to identify a rhythm disturbance as not a potentially noxious experience. The interpretation of the severity of the rhythm disturbance amplifies the severity of the effects on symptoms. Having a patient face the problem can actually empower the patient to improve his or her perception of the arrhythmia and its implications. Ultimately, properly used psychosocial therapy can reduce the risk of death.[64] Biofeedback devices can also be used to enhance heart rate variability (see Chapter 94, Enhancing Heart Rate Variability).

Meditation

Meditation has been associated with a decreased risk of sudden death in high-risk patients because of a reduction in ventricular fibrillation.[57,58] Meditation may affect the autonomic nervous system in a beneficial way.[65] It may also change the perception of the arrhythmia for patients who have a benign problem.

Meditation and relaxation techniques may also be useful for individuals who have an ICD for life-threatening rhythm disturbances. If the device is activated frequently, it can cause tremendous grief. Meditation and relaxation techniques can improve outcomes in such patients. These techniques may also allow for better patient acceptance of the shocks (see Chapter 98, Recommending Meditation).

Relaxation appears to have a positive benefit. For years, physicians have used benzodiazepines to treat rhythm disturbances such as atrial fibrillation and supraventricular tachycardia by inducing relaxation. If a patient comes into an emergency room with such an arrhythmia and is allowed to relax, the rhythm will often stop spontaneously (see Chapter 93, Relaxation Techniques).

Acupuncture

Data suggest that acupuncture may be antiarrhythmic for atrial fibrillation.[66] Although acupuncture may affect other arrhythmias beneficially, the data are far from definitive.[67] Acupuncture can also trigger inappropriate shocks in patients with ICDs, and this therapy should be avoided in these patients.[68]

Supplements

Coenzyme Q10

Coenzyme Q10, at a dose of 100 to 300 mg a day, may decrease episodes of atrial fibrillation by an unknown mechanism. Coenzyme Q10 can also have an effect on ventricular and atrial ectopy.[69]

L-Carnitine

L-Carnitine, at a dose of 3 g a day or more, can improve mitochondrial function and left ventricular function and may prevent some atrial and ventricular arrhythmias. Several small randomized controlled trials of carnitine showed a reduction in risk of sudden cardiac death and total death in patients with cardiomyopathy. The mechanism is not clear, but it may be that carnitine improves mitochondrial and myocardial function.[70–72] Carnitine has no known adverse effects. It may reduce ischemia and reperfusion-induced arrhythmias and raise the ventricular fibrillation threshold (of unclear significance).[73]

Calcium and Magnesium

Calcium and magnesium, approximately 1 g a day each of a salt (e.g., magnesium sulfate), have been associated with a decrease in arrhythmias. Magnesium can decrease triggered activity and can slow conduction in the AV node.

Magnesium supplementation given to patients in congestive heart failure in a double-blind placebo-controlled trial showed improvements in arrhythmias. Individuals taking 3.2 g per day of magnesium chloride equivalent to 384 mg per day of elemental magnesium had between 23% and 52% fewer occurrences of specific arrhythmias in a 6-week follow-up period.[43] Although some data suggested that magnesium has a beneficial effect on atrial fibrillation,[74] other data did not support its use.[75] Magnesium may also be associated with reduction in the risk of sudden death in women.[76]

Copper and Zinc

Three cases were reported in which ventricular premature beats disappeared, and PVCs decreased, after copper supplementation at a dose of 4 mg per day.[41] Investigators discovered that zinc made the arrhythmias worse and that extra zinc can lead to copper deficiency. The use of copper has a potential problem, however, in that high copper levels can lead to atherosclerosis.

Selenium

A deficiency in selenium can cause heart problems including arrhythmias. No good data, however, are available to suggest that selenium supplementation in patients with low selenium levels will improve arrhythmia status.[38,77]

Potassium

Potassium supplementation is extraordinarily important, especially if a patient is taking drugs that lower potassium levels. Potassium has been implicated in all types of rhythm disturbances, and potassium deficiencies can lead to torsades de pointes. Anyone with long QT interval syndrome, and specifically those patients who take drugs that lower potassium levels, clearly should take potassium supplements. This can also be done though potassium in the diet, including fruits and vegetables that contain high potassium concentrations (see Chapter 87, The DASH Diet).

Omega-3 Fatty Acids

Omega-3 fatty acids appear to influence several myocardial channels that can affect arrhythmias.[78–82] Specifically, omega-3 fatty acids appear to have an effect on calcium and potassium channels.[83] In men with symptomatic PVCs, omega-3 fatty acids were shown to decrease the risk of PVCs by approximately 70% when supplementation was in the form of fish oil,[84,85] but data are conflicting.[86]

Fish oil was also shown in the second Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI2) prevention trial to be associated with a decreased risk of total death and sudden death. This study included 11,324 Italians who had had a myocardial infarction within the preceding 3 months. These patients were randomized to approximately 850 mg of omega-3 polyunsaturated fatty acids (2836), vitamin E (2830), or neither (2828). Patients who were given fish oil had a 45% reduction in sudden death and a 20% decrease in mortality.[83]

The Lyon Diet Heart Study and the Physicians' Health Study both showed a benefit to the use of fish oil. The Diet and Reinfarction Trial (DART) included 2033 men with acute myocardial infarction who were randomized to receive or not to receive advice on diets: decreased fat intake to 30% of total energy, at least two weekly portions (200 to 400 g) of fatty fish (or 1.5 g fish oil capsules if unable to take fish), and cereal fiber to 18 g daily. Patients who were given "fish advice" survived substantially longer and significantly better.[87]

These data inspired the Fatty Acid Antiarrhythmia Trial, which is a randomized placebo-controlled trial of 3 g of fish oil compared with cod-scented olive oil, to look at the incidence of recurrent ventricular arrhythmias in patients who have ICDs and are at risk for sudden death. Many of these patients have malignant ventricular arrhythmias leading to shocks from their device. The aim of this study was to decrease the number of shocks. Fish oil was effective in this study, but data were conflicting.[88]

The data on fish oil in arrhythmias and improving outcomes in patients with heart disease are extensive.[89–91] Although the data in some cases conflict, fish oil is associated with improved autonomic influences,[92–94] reduction in atrial fibrillation[95] (especially after cardiovascular surgery,[96] but not in all studies[97]), reduction in risk of all-cause mortality, reduction in symptomatic ventricular ectopy, and reduction in depression (depression is associated with increased mortality after myocardial infarction).[98] Although some data show benefits for atrial fibrillation,[99] a placebo-controlled study showed no value of fish oil.[100]

In addition, data on patients after myocardial infarction have not shown benefit, likely because present therapy is already so good.[101] The higher-risk patients may be the ones who benefit the most.[102] Concerns also exist about the toxins in some of the supplements, including dioxins, polychlorinated biphenyls, polybrominated diphenyl ethers, and chlorinated pesticides.[103]

Omega-3 fatty acids are available in various forms, not only fish oil.[104] Certain plant oils can be metabolized

into omega-3 fatty acids, including flaxseed oil, which also has other potential benefits,[105] including those on mood. Because omega-3 fatty acids can improve mood, they may also have an autonomic affect that can decrease the sensation of arrhythmias or decrease arrhythmias altogether.

For dosing omega-3 fatty acids, educate the patient to read labels. If you are recommending 1000 mg of omega-3 fatty acids, the user needs to look at the amount of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) per serving size. If the label notes 300 mg of EPA and 200 mg of DHA per two capsules (serving size), the patient would need to take four capsules daily to obtain 1000 mg of omega-3 fatty acids.

Vitamins

A long-standing case of sick sinus syndrome was reported to resolve with supplementation of 800 units per day of vitamin D.[106] However, it is not clear that vitamin D was the cause of this change.

Data indicate that vitamin C given postoperatively to patients at risk for atrial fibrillation and to patients who undergo coronary artery bypass graft surgery may lead to a marked reduction in atrial fibrillation,[107–111] but these data have not been confirmed. By whatever mechanism, vitamin C appears to have antiarrhythmic properties and can prevent atrial fibrillation, at least in some patients. The mechanism may be by clearance of free radicals or by an antiinflammatory effect.

Botanicals

Many of the original antiarrhythmic drugs were derived from herbal therapy: quinidine (a stereoisomer of quinine from cinchona bark), lidocaine, amiodarone (from khellin, derived from the herb *Ammi visnaga*), and digoxin (from foxglove) are a few.[112] Data suggest that several other herbal preparations may have antiarrhythmic effects.

Ciwujia or Siberian ginseng (*Acanthopanax senticosus* Harms), which is used for athletic performance and weight loss, may have antiarrhythmic effects. Ciwujia was studied in isolated rat hearts with transient coronary occlusion.[113] Ciwujia extract reduced reperfusion-induced ventricular fibrillation and ventricular tachycardia. It also reduced the number of cells with abnormal action potential configurations. Ciwujia may reduce the incidence of malignant arrhythmias.[113] Siberian ginseng can cause an apparent increase in digoxin levels.[114] Whether this finding represents a false serum elevation, whether ginseng converts to digoxin in vivo, or whether ginseng alters the metabolism of digoxin is unclear.

Angelica and *Ginkgo biloba* may have a protective influence during myocardial ischemia and reperfusion.[115] In a rat model, the incidence of ventricular premature beats and the total incidence of arrhythmia were greatly reduced.[116]

Licorice root has an antiarrhythmic property.[117] Zhi Gan Cao (prepared licorice) injection can antagonize arrhythmias induced by chloroform, catecholamines, aconitine, strophanthin-K, and barium chloride. Licorice root may slow the heart rate, prolong PR and QT intervals, and antagonize the positive chronotropic response induced by catecholamines. Another component of licorice, sodium 18 beta-glycyrrhetinate, strongly counteracts arrhythmia induced by chloroform, lengthens the appearance time of arrhythmia induced by $CaCl_2$, slightly retards the heart rate of rats and rabbits, and partly antagonizes the acceleration effect of isoproterenol on rabbit hearts. The clinical significance of these experimental findings is unclear.[118]

Various herbs are now considered potentially useful by some practitioners to treat ventricular and supraventricular arrhythmias. Motherwort contains bufenolide, glycosides (stachydrine), and alkaloids. A dose between 4 and 5 g of motherwort can decrease palpitations, presumably by a mild beta-blocking affect, although the exact mechanism that motherwort exerts on the heart to decrease ectopic beats is unclear. No randomized controlled trial has been performed using motherwort.

Khella (*Ammi visnaga*) has significant antiarrhythmic effects. In the 1950s, a compound known as khella was derived from the *Ammi visnaga* plant. It was used to treat angina resulting from coronary heart disease, with significant improvement in those patients. Khella has also been used over the years by naturopaths to decrease palpitations. Khella is the original substance from which a very potent antiarrhythmic drug, amiodarone, was derived.[119–121]

Hawthorn berry has been used to treat atrial fibrillation, and it may have an effect on other rhythm disturbances as well.[114] Hawthorn contains hyperoside (vitexin, rhamnose), rutin, and oligomeric procyanidins. A dose of 160 to 900 mg of the water ethanol extract is recommended. Exactly how this herb works is unknown, but it may act on the sodium-potassium adenosine triphosphatase pump similar to digoxin. More likely, hawthorn acts as a phosphodiesterase inhibitor. Hawthorn may reduce the risk of sudden death and helps treat patients in heart failure.[122]

Rhodiola may have had some antiarrhythmic effects in a rat model in which arrhythmias were induced by epinephrine and calcium chloride.[123] Rhodiola can increase the ventricular fibrillation threshold,[124] and although this effect may be beneficial, the meaning is uncertain. The antiarrhythmic effect of rhodiola may result from activation of the opioid system and stimulation of kappa-opioid receptors.[125] Rhodiola may affect intracellular calcium handling,[126] and it may even exacerbate palpitations in some instances.

Data suggest that garlic, agrimony, celery, ginger, berberine, corkwort, *Stephania tetandra* root, astragalus, *Fissistigma glaucescens,* Xin Bao, Bu Xin, Yu Zhu, and Mai Dong, among others, are antiarrhythmic under various experimental conditions and for various arrhythmias. At the present time, however, the data are not definitive enough to recommend treatment with any of these herbal therapies for a specific arrhythmia.

Pharmaceuticals

The standard first-line drug therapy approach for benign PVCs, PACs, and episodes of atrial fibrillation is often a beta-adrenergic blocking drug. This drug alters the autonomic nervous system tone on the heart, although the effectiveness of this approach is unclear. Good data suggest that it is not effective whatsoever. Further, side effects are common when using these therapies for ectopic beats.

For atrial fibrillation, various antiarrhythmic drugs are available. Their use depends on the underlying heart disease, link to the episodes, age of the patient, severity of symptoms, and the difficulty in maintaining sinus rhythm. Discussions of antiarrhythmic drug use, anticoagulation, and rate control drugs for atrial fibrillation are beyond the scope of this chapter, but several good references are available.[127]

For ventricular ectopy and PVCs, if beta blockers do not work, various antiarrhythmic drugs can be used, including, for normal hearts without any evidence of ischemic heart disease, class IC antiarrhythmic drugs such as propafenone and flecainide.[5,6] One concern about these antiarrhythmic drugs, like any antiarrhythmic drug, is they can triple the mortality rate if underlying heart disease is present. The use of these drugs is never completely safe, and they can have other, so-called proarrhythmic effects.[1–8]

Numerous other antiarrhythmic drugs can be used, but each one of them has significant side effects. The use of these drugs is discouraged for benign ventricular ectopy unless the patient is severely symptomatic.

Although antiarrhythmic drugs can suppress arrhythmias, the important issues of proarrhythmia and side effects must be considered. All antiarrhythmic drugs have the potential to increase ectopy or induce, or aggravate, monomorphic ventricular tachycardia, torsades de pointes, ventricular fibrillation, conduction disturbances, or bradycardia. This is known as proarrhythmia.[1–8] The use of antiarrhythmic drugs should be reserved for clinicians who are expert in their use.

The risk of proarrhythmias from medication is greatest in those who need the most protection, specifically those patients with depressed left ventricular function with an ejection fraction less than 30%.

Risk-to-Benefit Ratio

The goal of therapy for any arrhythmia is to eliminate symptoms or prevent a potentially serious outcome, primarily a life-threatening arrhythmia and sudden death. These goals must be balanced against the risks associated with antiarrhythmic therapy, including proarrhythmia and the side effects of individual drugs.

No study has shown that ventricular ectopy suppression in any group of patients with asymptomatic arrhythmia improves survival. The only reason to treat is to suppress symptoms from the arrhythmias as long as treatment does not worsen the arrhythmias and the prognosis.

Antiarrhythmic Drug Therapy and Dose Titration

Therapy with some antiarrhythmic drugs is best initiated in the hospital, primarily to monitor for early proarrhythmia. The decision to hospitalize depends on the presence and severity of structural heart disease, the indication for treatment (e.g., cause of the arrhythmia and type and severity of associated symptoms), and the drug used. If the patient has a life-threatening arrhythmia, drug initiation and dose titration should be performed in the hospital. Follow-up 24 hour ambulatory electrocardiographic monitoring is recommended on a regular basis, for example every 6 months, to assess for continued drug efficacy and safety. An American College of Cardiology/American Heart Association task force published guidelines for the use of ambulatory monitoring in the assessment of antiarrhythmic drug efficacy.[22]

With the advent of newer approaches to the management of serious and sustained arrhythmias, therapy is moving to device-based treatment (implanted defibrillators and pacemakers) and to ablation (to cure the arrhythmias). The use of antiarrhythmic drugs has changed drastically over the years. If a patient has such an arrhythmia, referral to a specialist is in order.

Ablation Therapy

Another potential treatment that is nonpharmacologic is ablation therapy. Occasionally, ablation therapy can be used to remove focal triggers for rhythm disturbances in the atrium or ventricles for eliminating PACs and PVCs.

Occasionally, a patient with ventricular bigeminy does not perfuse with the PVC and therefore has an underlying rapid ventricular rate but without adequate perfusion, especially during the PVC. Such a patient can develop tachycardia-mediated cardiomyopathy, and heart failure will ensue. By treating the PVC, this problem can be eliminated. Ablation therapy is also used to treat various supraventricular tachyarrhythmias. In fact, atrial fibrillation, especially when paroxysmal, can be treated by ablating focal ectopic beats that often originate from the pulmonary veins.

Conclusion

The problem of arrhythmia management is complex and multifaceted. Treatment depends on the arrhythmia, its implications, the symptoms, and the effect on the patient. Patients with serious rhythm disturbances must be referred to a specialist, especially if the arrhythmias are potentially life-threatening. If not, an approach to improve outcomes should involve change in lifestyle and exercise. Following these dietary recommendations may be useful. If this is not enough, mind-body effects can be substantial. Consider meditation. Acupuncture can have a beneficial effects as well. Several herbal preparations may influence the presence of an arrhythmia, but care must be taken because some supplements such as Ma Huang can worsen an arrhythmia or even create a new, life-threatening one.

Prevention Prescription

- Avoid arrhythmia triggers if identified and definable (e.g., excess caffeine intake).
- Encourage regular aerobic exercise as long as it does not trigger arrhythmias.
- Urge risk factor reduction to prevent the development of structural heart disease (treatment of hypercholesterolemia, hypertension, smoking, excess ethanol intake).
- Moderate balanced caloric intake and maintenance of appropriate weight.
- Prevent stress. Incorporate meditation, yoga, and bioenergy techniques.
- Maintain a regular sleep-wake cycle with at least 7 to 8 hours of sleep nightly.
- Consider supplementing with 1 to 2 g of fish oil and encourage two to three servings of fish each week.
- Avoid the use of drugs or supplements that stimulate or mimic the effect of catecholamines (e.g., over-the-counter decongestants, ephedra [Ma Huang], caffeine).

Therapeutic Review

The treatment of arrhythmias cannot be easily standardized and does not fit into any clearly defined algorithmic pathway. The reason for this is the diverse presentations of arrhythmias, the complexity of management, the great span of problems ranging from completely benign to clearly life-threatening, the lack of randomized controlled clinical data in some instances, the difficulty in diagnosing problems, and the overlap with many other syndromes. Despite these caveats, some rational commonsense recommendations can be set forth to manage patients who have suspected cardiac arrhythmias.

For Patients With Palpitations

- Diagnosis is crucial, and arrhythmias can range from sinus rhythm to various types of ectopy to supraventricular or ventricular tachycardia.
- If no arrhythmia is documented, consider anxiety or panic attacks and treat accordingly.
- Encourage stress reduction techniques such as meditation and yoga. B1

For Patients With Symptomatic Ectopy or Premature Ventricular Contractions

Lifestyle

- Determine the severity of the symptoms and their relation to the arrhythmia. Assess underlying conditions.
- Determine the risk to the patient.
- For proven benign ectopy, discuss the risks of drug therapy and suggest alternatives first.

Nutrition

- Eliminate dietary or other apparent triggers (caffeine, alcohol, trans-fatty foods, blood glucose fluctuations). B1

Mind-Body Therapy

- Promote mind-body interventions such as meditation, yoga, Reiki, or qi gong. B1
- Counsel the patient about the benign nature of the condition. Patients who understand will be able to tolerate the arrhythmia better.

Exercise

- Determine the relation to exercise, and consider a tailored exercise program. B1 B1

Supplements and Botanicals

- Suggest omega-3 fatty acids: 2 to 3 g/day of eicosapentaenoic acid plus docosahexaenoic acid essential fatty acids B1
- Magnesium supplementation: 300 to 1000 mg daily C2
- Consider herbal approaches: motherwort, 4 to 5 g of dried above-ground parts daily B2
- Consider carnitine: 3 g daily; and then coenzyme Q10: 100 to 300 mg daily with a meal B1 B1

Pharmaceuticals

- Drug therapy: only if resistant to foregoing measures B2
- Beta blockade (titrated upward): consider extended-release metoprolol (Toprol XL), 50, 100, or 200 mg daily; or atenolol, 50 to 100 mg daily B1
- Calcium channel blockers (diltiazem or verapamil): 120 to 360 mg/daily B2
- Antiarrhythmic drugs: used as last resort (if no structural heart disease, flecainide, propafenone, sotalol are the first choices; then amiodarone, but only in resistant, highly symptomatic cases; risks may outweigh benefits) B2

Ablation Therapy

- Suggest ablative therapy for motivated patients willing to take the excess risk. (Counsel patients that symptoms are benign.) B3

For Patients With Paroxysmal Atrial Fibrillation

Lifestyle and Risk Factors

- Correlate symptoms with the arrhythmia. Determine the presence of underlying conditions, including hyperthyroidism.
- Assess the risk to the patient and the need for rate control, anticoagulation, and maintenance of sinus rhythm (see Table 27-3).

Nutrition

- Determine triggers, if possible. If a relationship is determined, eliminate caffeine, alcohol, and any potentially offending drug. A1
- If arrhythmia occurs at night, consider changes in diet (no large meals causing gastric distention). B1

Exercise

- If arrhythmia is exercise related, consider an exercise program.

Mind-Body Therapy

- Promote mind-body interventions such as relaxation techniques.
- Counsel patients and educate them about the disease process. B1

Continued

Acupuncture

- Suggest acupuncture (not well tested but perhaps effective). C-1

Supplements and Botanicals

- Omega-3 fatty acids: 1 to 2 g of fish oil daily B-1
- Magnesium supplementation: 300 to 1000 mg daily C-1
  - Hawthorn berry: 160 to 900 mg daily C-2
  - Motherwort: 4 to 5 g daily C-2
  - Coenzyme Q10: 100 to 300 mg daily with a meal B-1

Pharmaceuticals

- Beta blockade (to control rhythm and rate): see earlier for dosage A-2
- Calcium channel blockade (to control rate, diltiazem or verapamil): 120 to 360 mg daily B-2
- Digoxin (little effect, but may help in combination with a beta blocker and is safe if used carefully at proper doses) B-2
- Antiarrhythmic drugs depend on the patient and the conditions. The risk-to-benefit ratio is complex and depends on other diagnosed conditions, symptoms, and antiarrhythmic drugs. Amiodarone is the most effective drug but has the greatest risk of side effects. Propafenone and flecainide can triple the risk of death in patients with underlying heart disease and are contraindicated in patients with coronary disease or impaired ventricular function. A-3

Ablation Therapy

- Ablation of the pulmonary veins or parts of the left atrium B-3
- Ablation of the atrioventricular node with a pacemaker (patient remains in atrial fibrillation) not completely effective B-3
  - Ablation of other inciting arrhythmias B-3

KEY WEB RESOURCES

CHADS2 Score for Atrial Fibrillation Stroke Risk: http://www.mdcalc.com/chads2-score-for-atrial-fibrillation-stroke-risk	This tool calculates the need for warfarin (Coumadin) or aspirin to reduce the risk of stroke in patients with atrial fibrillation.
Surgical Risk Prediction: http://www.surgicalaudit.com/riskcalc.asp	This tool assesses surgical risk of patients seen for preoperative physical examinations.
Risk Assessment Tool for Estimating 10-Year Risk of Developing Hard Coronary Heart Disease: http://hp2010.nhlbihin.net/atpiii/calculator.asp?usertype=prof	This tool from the National Cholesterol Education Program assesses 10-year cardiovascular risk.
emWave by HeartMath: http://www.heartmath.com; and StressEraser: http://stresseraser.com	These biofeedback tools help enhance heart rate variability.
Integrative Medicine Program, University of Wisconsin School of Medicine and Public Health: http://www.fammed.wisc.edu/sites/default/files//webfm-uploads/documents/outreach/im/handout_omega3_fats_patient.pdf	This is a patient handout on omega-3 fatty acids.

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References are available at expertconsult.com.

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Chapter 28

Asthma

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Pathophysiology

Asthma, a common chronic respiratory disorder, affects more than 22 million persons in the United States.[1] Asthma is known to be a complex inflammatory process that involves many cell types and cellular elements. Interactions among these cells along with genetic disposition cause asthma symptoms. The symptoms are usually recurrent episodes of wheezing, cough, chest tightness, and breathlessness from widespread but variable airflow obstruction characterized by complete or partial reversibility either spontaneously or with treatment. This chronic inflammation leads to bronchial hyperresponsiveness to various stimuli and results in the clinical manifestations and severity of asthma and the subsequent response to treatment.

Research into the immunologic basis for asthma has shown that, in genetically susceptible individuals, airborne allergens are taken up at the mucosal surface and selective peptides are generated that then influence T cells to develop into type 2 helper T (Th2) cells. The expansion of the proinflammatory Th2-cell population causes a cascade of cytokines to be released, in addition to the up-regulation of adhesion molecules, which trap and activate passing leukocytes, specifically eosinophils, basophils, and monocytes.[2] Finally, these Th2 cells induce the production of allergic antibody immunoglobulin E (IgE), ultimately resulting in the clinical manifestation of allergy and asthma.

Risk Factors and Triggers

Investigators believe that asthma often begins in childhood and may result from an interaction of several factors (Fig. 28-1). Studies of genetic links in families with more than one member with asthma have shown certain regions of chromosomes 5q and 11q to be of interest. However, studies have also shown that in different populations these links are not simple, and susceptibility seems to be determined by several genes that have an effect in different aspects of asthma. Genes have been identified that are linked to the Th2 cytokine signaling pathway, Th2-cell differentiation, airway remodeling, adaptive immune responses, and IgE levels. Thus, the natural course of asthma varies considerably according to asthma phenotype and environmental influences.[3]

Asthma symptoms can be triggered by several factors (Table 28-1). Infections with viruses such as respiratory syncytial virus and rhinovirus have been thought to be triggers not only because of their ability to cause airway swelling and obstruction but also for their influence on the cellular response of the immune system, thus making it more asthma prone. Other key factors associated with poor asthma control include overestimation by patients and physicians of asthma control, improper technique in using inhaled medications, and overall nonadherence to therapies; these factors may lead to increased exacerbations, more hospitalizations, and higher mortality rates.[4] Understanding current asthma guidelines, measuring lung function, and monitoring medication use, in addition to improving adherence and education, would improve asthma control.

Integrative Therapy

Environment

Reducing exposure to environmental triggers such as dust mites and cockroaches, to which many patients with asthma are sensitive, is important. House dust mites, which are microscopic insects that live off dead skin cell flakes, are all around us even though we cannot see them. The mites and their waste products can be allergenic. To limit exposure to dust mites, especially in the bedroom where they are most common, one should (1) enclose pillows and mattresses in airtight polyurethane covers or use

FIGURE 28-1
The condition of a patient's asthma may change with the environment, activities, and other factors. When the patient is well, monitoring and treatment are still needed to maintain control.

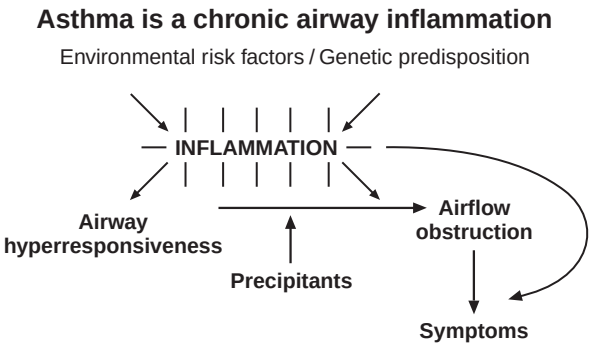

TABLE 28-1. Triggers for Symptoms of Asthma

- Allergens such as house dust mites, pets, and pollens
- Colds and viral infections
- Exercise
- Gastroesophageal reflux disease (stomach acid flowing back up the esophagus)
- Medications and foods
- Emotional anxiety
- Air pollutants such as tobacco smoke, wood smoke, chemicals, and ozone
- Occupational exposure to allergens, vapors, dust, gases, and fumes
- Strong odors and sprays such as perfumes, household cleaners, cooking fumes, paints, and varnishes
- Air pollutants such as ozone

fiberfill products instead of down or foam pillows, (2) remove carpeting (hardwood or linoleum floor is better) and curtains, (3) wash sheets and stuffed toys (for pediatric patients) in hot water every week, and (4) clean bedrooms frequently with a vacuum that has a high-efficiency particulate air (HEPA) filter. Cockroaches and their feces represent another trigger for asthma, so cleanliness is important to decrease their presence; in addition, it helps to wash floors and counters frequently, to eliminate cockroach debris. Other important control measures include eliminating exposure to tobacco smoke and removing pets from the home.

Nutrition

Diet therapy or nutritional advice is the most common "alternative" therapy that is given by allopathic physicians for patients with asthma. In theory, diet could modulate intestinal flora, affect immune maturation, and interact with underlying genetic disposition in the development and even the origin of asthma. The literature is difficult to summarize, however, because of the design of many of the studies and the lack of systematic approaches that include the means of diagnosis.[5] Clinicians have long thought that eliminating certain "allergenic" foods and decreasing exposure to foods such as dairy products (believed to be associated with increased mucus production) will help with chronic asthma symptoms and their severity.[6] The easiest way to conduct an elimination diet is to pick a food to which the patient appears to be sensitive, such as nuts or eggs, and then eliminate it from the diet for 2 weeks. At the end of 2 weeks, gently reintroduce the food into the diet. If a significant change occurs, such as bloating or headaches, the patient may indeed be sensitive to that particular food (see Chapter 84, Food Intolerance and Elimination Diet). Few studies have supported these claims, although one study did suggest a reduction in symptoms in an adult asthmatic patient after adoption of a restricted diet. Some epidemiologic studies suggest that dietary habits influence lung function. The populations with a higher intake of polyunsaturated fatty acids (omega-6 fatty acids) have a higher prevalence of asthma, eczema, and allergic rhinitis.

The following are the nutritional recommendations for patients with asthma:

1. Eliminate potential allergens:
   a. Any food associated with a history of intolerance (gastrointestinal disturbance or eczema)
   b. Sulfites (especially in dried fruits)
   c. Food additives (aspartame, benzoates, and yellow dye no. 5)
   d. Dairy products (for a trial period, as mentioned previously)
2. Increase intake of fruits and vegetables because they are rich in antioxidants, levels of which have been shown to be low in patients with chronic lung problems such as asthma.
3. Increase intake of omega-3 fatty acids by eating cold-water fish (e.g., sardines, herring, and salmon) and reduce intake of omega-6 fatty acids by eliminating vegetable oils and instead using olive oil (see Chapter 86, The Antiinflammatory [Omega-3] Diet).

If intake of dairy products is decreased or eliminated (especially in children), a calcium supplement should be considered.

Exercise

Although exercise in itself can induce symptoms in patients with asthma, numerous studies have shown that asthma can be better controlled in patients who exercise regularly. No study illustrates the superiority of one type of exercise over another. Investigators had long assumed that swimming may be beneficial because the environment is moister, and cold, dry air may actually exacerbate asthma symptoms. Studies did not support this concept, however. Instead, any exercise that the patient will do on a regular basis that does not increase symptoms should be encouraged. In addition, some studies suggest that swimming in highly chlorinated pools or in indoor pools with possible mold exposure may exacerbate asthma symptoms.[7]

The older the patient, the better he or she does with asthma by following an exercise regimen. This effect may, in part, have to do with the better self-image and overall improved health associated with regular exercise in adults.

Breathing Exercises

Breathing exercises and breathing retraining have been used in the management of asthma (Buteyko, yoga, physical therapy). One specific form of breathing therapy, known as the Buteyko breathing technique, has been thought to help asthma by decreasing the respiratory rate and allowing the carbon dioxide concentration in the lungs and blood to rise, thus resulting in bronchodilation. This technique dates back to 1952, when Dr. Buteyko theorized that "hidden" hyperventilation caused asthma symptoms. In vitro studies indicated that having a low alveolar carbon dioxide pressure could result in bronchoconstriction and greater airway resistance. Results of other studies suggested that this breathing technique may be beneficial, but the studies were small. One study did measure end-tidal carbon dioxide ($ETCO_2$) and found no correlation between $ETCO_2$ and breath-holding time; the investigators postulated that this technique may help by improving the biomechanics of breathing.[8] A systematic review concluded that "no reliable conclusions can currently be drawn concerning the use of breathing exercises for asthma in clinical practice."[9] A larger randomized control trial did show that after 6 months of using the Buteyko technique, most subjects in both groups had improved asthma control, and those using Buteyko had an additional benefit of reducing their inhaled corticosteroid use.[10]

Yoga

Yoga embodies many of the previously discussed therapies for improving the health of patients with asthma. Because it is a form of exercise, it has a cardiovascular component. This mind-body method involves using regulated breathing exercises (pranayama), and relaxation and meditation are also included in many yoga practices. One study in adults showed that yoga helped decrease medication use and lower anxiety,[11] and another study showed that yoga reduced airway hyperresponsiveness and improved some aspects of quality of life.[12] A study in 132 adults with mild asthma who were randomized into a yoga group and a control group showed that, after 8 weeks, the yoga group had significantly improved lung function. Both groups continued their regular pharmacologic treatments[13] (see Chapter 89, Breathing Exercises).

Botanicals

Use of botanicals is one of the oldest and most widely used therapeutic approaches in all asthma care worldwide. Historical theories and treatments used in breathing disorders have persisted over thousands of years.[14] Although the amount of knowledge and information regarding herbal or botanical treatment of asthma is large, a significant portion is not based on any well-designed or well-performed clinical studies.[15] In one study, the use of herbal remedies was associated with lower adherence to conventional medications, especially inhaled corticosteroids.[16] Many of the botanicals used are similar to pharmaceuticals in their chemical properties. Many botanicals are used traditionally, and tradition varies by culture.

Boswellia (Boswellia serrata)

Boswellia (also known as salai guggal or Indian frankincense) is a botanical used frequently in Ayurvedic medicine and traditionally used for inflammatory disorders such as asthma and arthritis. Boswellic acid, the major constituent of *Boswellia,* is thought to inhibit 5-lipoxygenase and leukotriene synthesis, and this may be the mechanism for its antiinflammatory properties. *Boswellia* may enhance the effectiveness of conventional leukotriene modifier medications (see later). One small placebo-controlled study in adults did show that subjects taking *Boswellia* had fewer exacerbations and improved lung function.[17]

Dosage

A common dosage recommendation is 300 mg three times/day.

Precautions

Few precautions have been reported, except for occasional gastrointestinal effects such as epigastric pain, heartburn, nausea, and diarrhea.

Coleus (Coleus forskohlii)

Coleus is a fairly uncommon botanical in the United States, but it has a long history of use for respiratory and asthma problems in India in the Ayurvedic medicine tradition. A member of the mint family, *Coleus forskohlii* grows wild on the mountain slopes of Nepal, India, and Thailand. Traditionally, it was used for numerous purposes, including treatment of rashes, asthma, bronchitis, insomnia, epilepsy, and angina. It is thought to act much like theophylline and has been studied as an effective bronchodilator. Coleus has been shown to increase intracellular cyclic adenosine monophosphate levels and to stabilize cells that release histamine, although its clinical value is still to be determined.[18] One study showed that an inhaled dose of forskolin powder from an inhaler device increased lung function by improving forced expiratory volume in 1 second (FEV_1) in patients with asthma.[18]

Dosage

A common dosage recommendation for coleus is 50 mg two or three times/day of an extract standardized to contain 18% forskolin, or a 10-mg dose using an inhaler device.

Precautions

No precautions have been reported, but coleus should be used with caution with antihypertensive (beta blocker) and anticoagulant therapy. Pregnant women should not take coleus.

Ma Huang (Ephedra sinica)

Ma Huang, also known as Chinese ephedra and Chinese joint fir, has been commonly used as an asthma remedy in China for thousands of years. The pharmaceutical ephedrine (derived from *Ephedra sinica*) was used in asthma therapy until the advent of more specific beta-agonist medications. Ma Huang may be part of many combinations of other botanicals, including licorice and other antiinflammatory agents. Botanicals and supplements containing ephedra alkaloids have now appeared in many preparations for losing weight and increasing energy.

Dosage

Ephedra is not recommended for use in the treatment of asthma because of warnings from the U.S. Food and Drug Administration (FDA) and reports of serious side effects,

especially when it was used in combination with caffeine and other stimulants, such as bitter orange.

Precautions

Ma Huang botanicals and its combination products have the most serious potential for side effects. Deaths associated with its use have been reported. Central nervous system problems such as nausea, vomiting, sweating, and nervousness, along with heart palpitations, tachycardia, hypertension, anxiety, and even myocardial infarction, also have been reported.[19]

> Complications, including death, have been reported when Ma Huang is taken in high doses or with caffeine-containing products. Death has even been noted with only one use of this substance.

Licorice (Glycyrrhiza glabra)

Licorice, also known as liquorice, sweet wood, and sweet root, has been used as a cough remedy and asthma treatment. The active ingredient is glycyrrhizin, also called glycyrrhizic acid. Its effect in treating asthma derives from the antiinflammatory nature of licorice and the enhancement of endogenous steroids. Licorice is also thought to be an expectorant, aiding in the expulsion of mucus from the bronchial passages, as well as a demulcent, which can be soothing to irritated airways and bronchioles.

Dosage

Licorice is available in several forms such as dried root, which can be used as an infusion or decoction. The dried root dose is usually 1.0 to 5.0 g three times per day. If a licorice tincture is used (1:5 strength is common), the dose is 2 to 5 mL three times a day. Finally, the standardized extract (containing 20% glycyrrhizic acid) dose is 250 to 300 mg three times a day.

Precautions

The side effects are minimal if less than 10 mg of the glycyrrhizic acid is taken daily and prolonged use is avoided. Long-term use, however, can cause headache, hypertension, dizziness, edema, and other signs of aldosteronism (through the binding of mineralocorticoids). Licorice may also cause low serum potassium and should be avoided in patients taking cardiac glycosides, blood pressure medications, corticosteroids, diuretics, or monoamine oxidase inhibitors. A deglycyrrhized licorice (DGL) is available, but its effectiveness has not been well studied, and it may not be as effective as other products with glycyrrhizin.

Pycnogenol

Pycnogenol (a proprietary mixture of water-soluble bioflavonoids extracted from French maritime pine) has been used for its antiinflammatory properties in conditions such as asthma. Pycnogenol is a blend of several bioflavonoids—catechin, epicatechin, taxifolin, oligomeric procyanidins, and phenolic fruit acids such as ferulic acid and caffeic acid. This preparation is thought to exert its effect by blocking leukotrienes and other cytokines that increase inflammation and cause asthma symptoms. A study in children with asthma showed that Pycnogenol improved pulmonary function and reduced the need for rescue medications.[20]

Dosage

Pycnogenol is supplied in 30-, 50- and 100-mg tablets. The usual dosage is 30 to 100 mg/day for maintenance therapy. The manufacturer recommends 1 mg/kg/day.

Precautions

No serious side effects have been reported, but Pycnogenol is recommended to be taken with or after meals because it has an astringent taste. Reports exist of minor side effects, including gastrointestinal discomfort, headache, nausea, and dizziness, which resolve when the botanical is discontinued.

Herbal Mixtures

Japanese combination herbs and remedies (Kampo) such as Saiboku-to blend black cumin, chamomile, cinnamon, cloves, rosemary, sage, spearmint, and thyme into a botanical combination that reduces asthma symptoms. This combination is thought to be effective because of antiinflammatory properties of blocking 5-lipoxygenase and inhibiting platelet-activating factor (PAF).[21] PAF is produced by several inflammatory cells, including eosinophils, thus causing airway hyperreactivity, microvascular leaks, increased airway secretions, and epithelial permeability. Other trials using traditional Chinese medicine herb mixtures also demonstrated a potential for improving asthma control. These mixtures included ASHMI (a traditional herbal mixture) and Ding Chuan Tang, and both showed improvement in asthma control and airway reactivity.[22,23]

Dosage

These combination herbal preparations are usually prepared as a tea, taken two to four times/day, depending on the particular mixture and brand used.

Precautions

No problems with these combination therapies have been reported.

Supplements

Vitamin and Mineral Overview

In addition to botanical and herbal preparations for the long-term treatment of asthma, vitamins and minerals are used frequently. As with most of the treatments mentioned thus far, few studies support their use, but historically they have been thought to help with asthma and chronic respiratory symptoms.

Vitamin C

Vitamin C has been studied in asthma, and although the results were mixed, one randomized trial did demonstrate reduced asthma symptoms. Vitamin C was also found to be protective against exercise-induced asthma.[24] Another study using vitamin C in 201 patients with asthma for 16 weeks did not show any clinical benefit.[25] Investigators believe that vitamin C inhibits histamine release and promotes vasodilation by increasing production of prostacyclin. A review of 9 studies with 330 participants was analyzed, and the investigators concluded that evidence is insufficient at this time to recommend vitamin C in the treatment of asthma.[26]

Dosage

The dose is 250 to 500 mg once or twice a day.

Vitamin D

As with vitamins C and E, numerous studies looked at vitamin D levels and their correlation with asthma. In a survey of 616 children, serum vitamin D levels were associated with airway reactivity, hospitalizations, and the use of antiinflammatory drugs.[27] Lower vitamin D levels were also shown to be inversely associated with recent upper respiratory tract infections, which are a common trigger of acute asthma.[28] Taking supplemental vitamin D to help prevent upper respiratory tract infections could help decrease asthma exacerbations.

Dosage

Recommended doses are 400 mg/day for children younger than 4 years of age and 600 mg/day for adults.

Precautions

The range for a safe dose of vitamin D is unknown, but an excess of vitamin D may cause abnormally high levels of calcium in the blood that may damage bones, soft tissues, and kidneys.

Vitamin B_6

In a double-blind randomized study, vitamin B_6 was shown to improve peak flow rates in a group of adults with severe asthma.[29] In patients with low serum pyridoxine (vitamin B_6) levels, supplementation helped decrease episodes of wheezing. Lowering of serum vitamin B_6 levels may be a side effect of common asthma medications.

Dosage

The recommended dose range is 50 to 100 mg/day.

Precautions

High doses—usually more than 500 mg/day—and prolonged use of vitamin B_6 have been associated with peripheral neuropathy.

Vitamin E

Intake of vitamin E is recommended in the diet or through supplementation because patients who have a high antioxidant intake have fewer pulmonary problems. Poorly controlled asthma has been shown to be associated with low vitamin E levels.[30]

Dosage

The recommended dose is 400 units/day of mixed tocopherols.

Precautions

The risk of all-cause mortality may be increased with prolonged use of doses greater than 400 units daily.

Magnesium

Magnesium's role in decreasing bronchospasm has been investigated in both the conventional medical and the complementary and alternative medicine communities. Intravenous magnesium is now commonly used for serious asthma symptoms (status asthmaticus). The use of oral magnesium has been studied. In adults, magnesium was shown to decrease symptoms but not to improve pulmonary function in one study and to have no benefit in another.[31] In a more recent study of 55 adults taking 340 mg of magnesium a day for 6 months, objective measurements of lung function, including bronchial reactivity to methacholine and peak flow measurements, improved, as did subjective measures of asthma control and quality of life.[32]

Dosage

The dose is 200 to 400 mg/day. Magnesium gluconate and magnesium glycinate are the forms least likely to cause diarrhea.

Precautions

One problem with using oral magnesium is the tendency of the preparations to cause diarrhea.

Selenium

Selenium is another potent antioxidant used in many inflammatory conditions, including asthma. One randomized placebo-controlled trial conducted for 14 weeks in 24 patients with asthma found evidence of clinical improvement but no effect on objective markers such as lung function.[33]

Other studies showed inconsistent results. This inconsistency may result from the complex relationship between selenium and asthma because selenium can augment the oxidative stress that accompanies asthma, but it also exerts a significant influence over various immune responses.[34]

Dosage

The dose is 100 to 200 mcg/day.

Precautions

When selenium is consumed in amounts exceeding 400 mcg/day, symptoms of toxicity may appear, including nausea, vomiting, abdominal pain, fatigue, irritability, and weight loss.

Fish Oil

The use of antiinflammatory medication is now the standard in asthma treatment. If the diet could be altered to decrease the propensity for development of inflammatory precursors, conditions such as asthma would be less problematic. The use of omega-3 essential fatty acids in adequate amounts in the diet may limit leukotriene synthesis by blocking arachidonic acid metabolism. A rich source of omega-3 fatty acid is fish oils. Because eating cold-water oily fish (mackerel, sardines, herring, salmon, and cod) is not common in most Western diets, the use of fish oil capsules has become more standard. Epidemiologic studies in populations that do eat this type of diet have shown it to reduce the risk of asthma significantly and improve pulmonary function. The vegetarian sources of omega-3 fatty acids (flaxseed oil, canola oil, and soy oil) are used even less in most diets, so the study of fish oil in asthma has been investigated.[35]

In one prospective study, dietary supplements of omega-3 fatty acids given to infants who had a high risk for developing asthma showed a small reduction in wheezing episodes in the first 18 months, but by age 5, this association was no longer present.[36,37]

Dosage

One 500-mg capsule is taken two to three times/day. Benefit may not be evident for several months.

Pharmaceuticals

Bronchodilators

Bronchodilators have long been used to help alleviate the bronchospasm and difficulty with breathing that are associated with asthma "attacks." Bronchodilators belong to several different classes. Commonly used beta agonists are albuterol and salmeterol or formoterol. A different beta agonist that is similar to albuterol is levalbuterol (Xopenex), which may have fewer cardiovascular side effects. In addition are the methylxanthines (theophylline and aminophylline). The methylxanthines are used as second- or third-line drugs because they have more significant side effects and their use requires serum level monitoring.

Dosage

Albuterol: two to four puffs of a metered-dose inhaler (MDI), one to three times/day as needed

Levalbuterol: one inhalation vial (three strengths) per nebulizer three times/day; or by MDI, two puffs one to three times/day as needed

Salmeterol or formoterol (long-acting beta-agonist): one actuation of the dry powder inhaler (DPI) twice a day

Methylxanthines (theophylline): dosage dependent on age and weight

Precautions

Beta agonists may cause rapid or irregular heartbeat, insomnia, and nervousness. The anticholinergic medications have few side effects, except for occasional dry mouth or headache. The theophylline-type medications may cause tremor, shakiness, nausea, and vomiting. Overdose of methylxanthines can cause serious problems, such as seizures and cardiac arrhythmias.

Antiinflammatory Medications

Antiinflammatory medications are considered the most important components of the pharmacologic approach to asthma care. Several categories of these medications are available, usually listed as steroidal and nonsteroidal. The steroidal MDIs and DPIs include fluticasone, beclomethasone, mometasone, ciclesonide, and budesonide. Newer proprietary preparations that have been shown to reduce the need for higher doses of the steroidal preparations are combinations of an inhaled steroid (fluticasone, budesonide, or mometasone) with a long-acting bronchodilator (salmeterol or formoterol). Oral preparations, such as prednisone, prednisolone, and methylprednisolone, are also available. The nonsteroidal medications include the leukotriene inhibitors montelukast and zafirlukast. These medications act by blocking certain pathways of airway inflammation once exposure (allergic, irritant, infectious, or emotional or exercise) has occurred. The oral steroids are the most potent agents and have the greatest potential for significant side effects.

Dosage

Leukotriene inhibitors differ by the specific type used. The dosage of montelukast, for example, is 10 mg/day for adults and 5 mg/day for children (chewable tablets). For a child younger than 5 years, 4 mg/day is recommended (not to be used in children younger than 12 months).

Dosages for steroidal inhalers are usually two puffs (or one actuation of the DPI) twice/day. Oral steroids are usually taken at 1 to 2 mg/kg or 20 to 40 mg/day (adults) for varying amounts of time. A short "burst" would be 3 to 5 days in total.

Precautions

Nonsteroidal medications have few side effects. Leukotriene inhibitors may cause headache, and some cause hepatic dysfunction, so liver function should be monitored. The steroidal medications, especially the oral preparations, may cause problems with decreased height velocity (in children), immune suppression, hypertension, cataracts, and hirsutism (if taken long term). The inhaled forms have rare side effects and have been followed long term in children[38]; they may, however, cause hoarseness, cough, and oral candidiasis unless a spacer is used or thorough mouth rinsing is practiced. Combination medications (corticosteroids plus a long-acting beta agonist such as fluticasone and salmeterol) have a black box warning given by the FDA because of the possibility that some patients may actually do worse when using these types of medications, with more asthma exacerbations and even death.

The newer antiinflammatory steroidal inhalers, used alone or in combination with a long-acting bronchodilator, constitute the most innovative pharmacologic approach to chronic asthma care.

Biomechanical Approaches

Massage

Massage therapy is an ancient treatment, dating back to the second century in China. It was referred to as the "art of rubbing" and was common until pharmaceuticals began to be heavily used instead, starting in the 1950s. Little material in the literature has investigated the efficacy of massage, and the studies performed before the 1990s had problems with sampling, lack of controls, sample size, and inappropriate use of statistical analysis.[39] Since then, several studies have investigated the use of massage in many areas of medicine that use methods to support the effectiveness of massage. Most of these studies have been conducted by the Touch Research Institute at the University of Miami Miller School of Medicine in Florida. Asthma has been studied in children, and investigators showed that daily massage improved airway caliber and control of asthma.[39] A decrease in anxiety and improved attitude toward the subject's asthma were also noted.

Dosage

The time and duration of massage therapy for the average patient with asthma are not known. The study that showed improvement used once-a-day massage for 30 days. The person doing the massage may be another family member or friend who has been taught massage techniques or a massage therapist.

Osteopathy

Osteopathy is another system of medical care that embraces the body as a whole and in which structure and function are closely interrelated. One main premise is that because osteopathy emphasizes that all body systems, including the musculoskeletal

system, operate in unison, a disturbance in one system can alter functions of the other systems. Several main categories of osteopathic manipulative treatment (OMT; e.g., craniosacral, strain-counterstrain, and myofascial) involve more than 100 different individual treatments. OMTs in asthma have been used for both chronic and acute symptoms. OMT is used to increase vital capacity and rib cage mobility, improve diaphragmatic function, enhance clearing of airway secretions, and improve autoimmune function. One report proposed that the use of OMTs in the emergency department setting could alleviate acute symptoms.[40] In a randomized controlled trial in 5- to 17-year-old patients with asthma, 90 patients received OMT, and 50 were in the control group. Peak flow improved more in the OMT group than in the control group (measurements were taken before and after OMT).[41] A movement has also been started by the American Osteopathic Association to use OMT in the basic management of asthma.[42]

Dosage

The findings of the osteopathic practitioner will determine the form of OMT. Again, the form chosen may affect any part of the body, depending on the physical examination. Often, just helping the patient use various parts of the chest in breathing may help.

Chiropractic

Chiropractic, the third largest regulated health care profession in North America, has been involved in health care for conditions such as asthma since the late 1800s. The theory of chiropractic care is based on the idea that the properly adjusted body is essential for health. Through the use of spinal manipulation therapy for the removal of subluxations, the life force is influenced, and good health is attained.[43]

Some studies involving chiropractic treatments in asthma showed overall improvement in lung capacity. Other findings documented abnormal spinal mechanics associated with asthma. Chiropractic adjustments may produce immediate relaxation of the neck musculature and overall may improve respiratory function. Other chiropractic theories hold that various adjustments may affect respiratory symptoms through the action of treating the subluxations found and subsequent nerve function. Three randomized controlled studies showed benefit in subjective measures, such as quality of life, symptoms, and bronchodilator use; however, the differences between controls and treated groups were not statistically significant.[44]

Dosage

The dosage of chiropractic care depends on the practitioner.

Precautions

Reported complications of chiropractic manual treatments have been documented, but none were found in the treatment of asthma. Chiropractic care often involves repeated use of radiographs, thus making frequent radiation exposure an issue for some patients.

Manual Therapy

A systematic review of more than 450 citations assessed 3 randomized trials of manual therapies in asthma.[45] The manual therapies included physical therapy, respiratory therapy, chiropractic therapy, and osteopathic therapy. The reviewers concluded that evidence is insufficient to support the use of manual therapies in patients with asthma and suggested the need to conduct adequately sized randomized controlled trials that examine the effects of manual therapies on clinically relevant outcomes. Currently, evidence is insufficient to support or refute the use of manual therapy in patients with asthma.[45]

Mind-Body Therapy

Mind-body therapies have been used in the treatment of asthma in various ways. They are at times referred to as cognitive-behavioral therapies and encompass several approaches. No one therapy has been shown to be superior over another; however, some therapies appear to be more acceptable to individual patients. Discussing several types of therapy with the patient and the family will enhance the success of mind-body interventions. Research in this area started in the early 1960s, and approaches have included relaxation therapy, breathing exercises, biofeedback, and hypnosis and guided imagery.

The theory behind using these therapies is to improve the inflammatory process that can be triggered by the autonomic nervous system through emotions. Numerous studies in both children and adults have shown higher levels of anxiety and even at times panic when asthma symptoms are perceived. In addition to anxiety, stress has been shown to influence the immune response and may promote a higher sympathetic activity, augment IgE production, cause a shift from a Th1 to a Th2 allergic-type response, and promote airway inflammation without overt symptoms.[46] Studies have also shown that using different types of cognitive-behavioral therapies may decrease symptoms and medication use and may reduce the inflammatory response of airway cells.[47,48]

Hypnosis and Guided Imagery

Hypnosis has been used for achieving relaxation, relieving pain, helping with physical discomfort (even chronic pain), and altering moods. It is multidimensional and helps patients develop a heightened concentration of an idea or image. The process may be brief or may involve complex instructions, depending on the subject, the goal, and the therapist. Hypnosis has been shown to be effective in patients whose asthma is mild and those whose symptoms have an emotional component. Studies showed that "motivated" patients had decreases in symptoms and medication use, as well as improvements in pulmonary function.[49]

Guided imagery involves a form of self-hypnosis in which the patient uses an image of her or his own creation after an initial relaxation period to help reduce asthma symptoms. This method is especially effective in children with an active and vibrant imagination. They often can be taught this technique in less than half an hour and do well with their asthma symptoms after a few practice sessions. Guided imagery starts with initial relaxation (using diaphragmatic breathing—"belly breathing") and then progresses to an imagery session. The subject develops an image and then focuses on taking control or command of the perceived airway or lung problem by using this image. An example is moving from a closet to the outdoors, where the child could once again breathe. This emotion-mediated format enables disclosure and subsequent reframing for the child and allows independence from the chronic illness (see Chapter 95, Guided Imagery, and Chapter 92, Self-Hypnosis Techniques).

Dosage

As with relaxation, these therapies are best if used often and especially if used when asthma symptoms are initially mild. This approach prepares the patient for dealing with worse symptoms during an attack.

Disclosure and Journaling

Much like the findings in rheumatoid arthritis, some evidence has indicated that just having the patient with asthma discuss the symptoms may decrease the severity and frequency of the asthma. Journaling, in which one writes about asthma in a journal three to five times a week for 20 to 30 minutes, has been shown to reduce both symptoms and medication use. In one study, patients wrote in their journals about a stressful event that they had not discussed with others or that had been unresolved; the control group just wrote about daily events.[50] The investigators reported a 13% improvement in lung function, as measured by the FEV_1, in patients who wrote about a stressful experience compared with the control group (see Chapter 96, Journaling for Health).

Other Therapies to Consider

Knowing where to put bioenergetic modalities—traditional Chinese medicine (TCM), healing touch and prayer, and homeopathy—in the stepwise approach to asthma care is difficult. These modalities could really fit anywhere in the treatment plan from the most mild to the most severe asthma. These methods should be used in conjunction with the previously discussed therapies if the patient has moderate or severe symptoms, but they are appropriate as first-line treatment in the interested patient with mild or intermittent asthma.

Traditional Chinese Medicine

TCM has been practiced for several thousand years and takes many forms. The basis, however, is the understanding of the connections among body, mind, and spirit in health and disease. The belief in an unseen vital energy that affects the patient's health and in the flow of this energy or qi (chi) through the appropriate channels is the basis of this practice. The practitioner can affect this flow or intensity by manipulating the balance through the use of acupuncture, Chinese herbs, diet, and physical therapy. TCM can successfully treat many medical conditions.

Acupuncture and other forms of TCM are thought to be beneficial in the treatment of asthma. Clinical observations showed that acupuncture and individually mixed Chinese herbs were effective, although clinical trials have not supported these observations. The National Institutes of Health 1997 Consensus Development Conference on Acupuncture recommended acupuncture for many conditions, including asthma.[51] One review showed modest improvement in asthma symptoms by using acupuncture,[52] and another study suggested that acupuncture before exercise protected against exercise-induced asthma symptoms.[53] A systematic review of 11 studies for acupuncture and asthma concluded that evidence is insufficient to make recommendations about the value of acupuncture in asthma treatment. The review went on to recommend further research because of the complexities and different types of acupuncture.[54]

Dosage

The dosage of acupuncture is practitioner dependent, and the effects of TCM usually take several treatments to appear.

Precautions

Adverse side effects of acupuncture are rare but have been reported, including pneumothoraces.

Healing Touch and Prayer

Healing touch and other touch therapies such as therapeutic touch, Reiki, and Johrei are defined as the consciously directed process of energy exchange during which the practitioner uses touch or "nontouch" as a focus to facilitate healing. Prayer, which does not even require touch or the presence of the healer to help with symptoms and medical condition, has been used in nearly every culture for centuries. Few studies have investigated this type of energy healing in the patient with asthma. One small study using "hands-on" healing in adult asthmatic patients did show some reduction in medication use.[55]

Dosage

Dosage depends on the modality (healing touch, therapeutic touch, Reiki, Johrei, prayer); all have different approaches, and practitioners use various assessments.

Homeopathy

Homeopathy is thought to be an energy medicine because it is not based on the usual physical laws found in science, but rather on the premise that the use of "remedies" that would cause the same symptoms (principle of like cure) and are very dilute (the more dilute, the more potent; law of dilution) is the most powerful treatment. Practitioners believe that the dilution in water actually imparts healing energy, and this energy, combined with the patient's vital force or energy, is used in healing.

Several studies have shown efficacy of homeopathic remedies in the treatment of both asthma and allergies.[56] The study in asthma showed a reduction in symptoms but no real difference in pulmonary function. A review of the research in homeopathy for treating asthma (6 trials with a total of 556 subjects were included) concluded that not enough evidence exists to assess the possible role of homeopathy in asthma reliably at this time.[57]

The remedies depend on the particular patient's symptom pattern and should be individually assessed by an experienced homeopath to select the correct constitutional remedy. Some of the commonly used homeopathic remedies are as follows:

Arsenicum album: used for asthma with restlessness and anxiety
Ipecac: used for chest constriction and cough
Pulsatilla: used for chest pressure and air hunger
Sambuscus: used for asthma symptoms that awaken one in the night

Dosage

The dosage depends on the individual and on the guidance of the practitioner (see Chapter 111, Therapeutic Homeopathy).

Precautions

Homeopathy is thought to be safe owing to the extreme dilution, and the treatments are inexpensive.

Prevention Prescription

- Eliminate potential allergens and triggers in the environment.
- Increase fruit and vegetable intake, along with that of omega-3–rich fats, which are found in cold-water fish, nuts, greens, and ground flaxseed.
- Follow an exercise regimen, and consider other types of activities that incorporate both exercise and meditation, such as yoga and martial arts.
- Take controller medications, such as inhaled steroids and leukotriene-modifier medication, routinely until asthma is no longer persistent and the medications can safely be decreased or discontinued.
- Consider adding a multivitamin with antioxidants (vitamins C, D and E, B-complex, selenium) to the diet.
- Botanicals may be helpful in controlling and decreasing asthma symptoms but are best taken under the guidance of a health care provider with experience in using them.
- Mind-body therapies such as relaxation, visualization, and self-hypnosis may decrease asthma exacerbations and reduce the need for asthma medications.
- Stress reduction in the home, work place, and school may prevent or decrease asthma symptoms and airway inflammation.

Therapeutic Review

The following is a summary of therapeutic options for treating asthma. If a patient is having persistent symptoms (daily wheezing, shortness of breath, difficulty sleeping, or difficulty exercising) or severe symptoms (even if intermittent), it is best to prescribe more aggressive therapy such as the beta-agonist drugs and antiinflammatory medications as controller medications. For the patient who has mild to moderate or intermittent symptoms, this stepwise approach may be considered.

Lifestyle

- As with many chronic illnesses, asthma prevention would be the best treatment. Unfortunately, changing a person's lifestyle, including the environment, is difficult. Because of the cultural and regional differences just in the United States, patient populations differ in how they approach a chronic illness and even in the way they use medical care.

Environmental

- Reducing exposure to asthma triggers can be therapeutic in itself. Such things as house dust mite reduction, frequent cleaning, use of HEPA filters, avoidance of secondhand smoke, and removal of all pets from the home will help decrease the "irritability" of the airways. A1

Nutrition

- With elimination of allergenic-type foods such as dairy products (at least for a trial period), shellfish, foods with nitrites, sulfites, added food coloring, and artificial sweeteners, asthma symptoms often diminish. Patients should consider increasing intake of organic fruits and vegetables for their antioxidant contribution, as well as foods rich in omega-3 fatty acids while decreasing those containing omega-6 fatty acids (vegetable oils). B1

Supplements

- Vitamin B_6: 100 mg/day B2
- Magnesium: 200 to 400 mg/day B2
- Fish oil: 1 g (eicosapentaenoic acid plus docosahexaenoic acid) twice daily B2
- Vitamin D: 400 units for children younger than 4 years of age and 600 units daily for adults B2
- Vitamin C: 250 mg twice daily B2
- Vitamin E: 400 units a day or less of mixed tocopherols B2

Mind-Body Therapy

- These techniques can be very rewarding in the treatment of asthma, and breathing and relaxation are excellent places to start. B1
- Guided imagery and hypnosis therapies are readily available in most communities and also help decrease symptoms, medication use, and physician or urgent care visits. Usually, these methods should be used regularly (once or twice daily) until familiar to the patient; they can then be used as needed for asthma symptoms. B1
- Journaling is also recommended, and patients should spend at least 20 minutes writing about their asthma or other stressors in their lives three times per week. B1
- Cognitive therapies should not be used in place of medications, especially if symptoms are moderate or severe. If the patient is using a peak flow meter, these therapies can be used if peak flow values are in a safe range.

Exercise

- Not only will routine exercise help with asthma (three to five periods of exercise lasting a minimum of 20 minutes per week), it will also help with self-esteem, weight loss, and cardiovascular health. Exercise B1

should be used with caution in patients with exercise-induced asthma.

Botanicals

- Coleus: 50 mg three times/day 
- Kampo (also known as Kanpo) is a mixture of Chinese herbs and found in powder form such as Easy-Breather Tea (Yama's Herbs, New York): 3 rounded teaspoons in warm water two to three times/day 
- Pycnogenol: 30 to 100 mg/day or 10 mg/kg/day, taken two to three times/day 

Pharmaceuticals 

- For patients with mild to moderate symptoms that are persistent, starting with pharmaceuticals with antiinflammatory properties such as fluticasone, two puffs of the 110 metered-dose inhaler (110 mcg/inhalation) twice daily, or budesonide, one actuation twice daily, will improve symptoms in most patients while the other interventions mentioned previously can be started. For acute symptoms, one should use albuterol, two puffs twice daily, or levalbuterol, two puffs twice daily. These medications should be considered as first-line therapy if a patient has persistent or severe symptoms.
- Other medications, such as leukotriene modifiers (montelukast 10 mg daily), may also be considered. 

Biomechanical Approaches

- As adjuncts to other modalities and depending on the patient's preferences, massage, osteopathic manipulative treatment, and chiropractic therapies may be very beneficial. All three have different approaches and regimens, but finding a practitioner who is familiar with treating patients with asthma is the key. 

KEY WEB RESOURCES

Buteyko a…z: http://www.buteyko.com/	For learning more about the Buteyko method, this Web site has information on the breathing method, including an instructional DVD for purchase.
Allergy and Asthma Network, Mothers of Asthmatics: http://www.aanma.org/	This nonprofit patient education and advocacy organization provides consumer-friendly information about asthma and allergies.
Guidelines for the Diagnosis and Management of Asthma: http://www.nhlbi.nih.gov/guidelines/asthma/	The National Institutes of Health through the National Heart, Lung and Blood Institute has published evidence-based guidelines for the treatment of asthma, including several extensive sections on patient and family education and environmental control.
Allergy Solutions, Inc.: http://www.allergysolution.com/default.asp	This company sells products for patients with allergies and asthma, including HEPA filters and pillow and mattress covers.

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Chapter 29

The Allergic Patient

Randy J. Horwitz, MD, PhD

More than 20% of U.S. citizens—approximately 50 million people—are estimated to suffer from an allergic condition, and they spend $8 billion annually for prescription drugs to treat allergic symptoms.[1] A nationwide survey found that more than half (54%) of all U.S. citizens test positive to one or more allergens.[2] Although acute and chronic allergic diseases may not rank as a leading cause of mortality in the population, they do constitute a leading cause of work and school absenteeism, and they contribute to significant social and economic costs.

This chapter considers general integrative approaches to the patient with atopy, or environmental allergies, whether seasonal or perennial. Separate chapters in this book deal with some of the more prominent allergic and allergy-related conditions (e.g., asthma, atopic dermatitis, food intolerance, and multiple chemical sensitivities). Some commonalities link these seemingly disparate disorders, however, and knowledge of these common principles may be helpful in devising treatment recommendations for patients with allergies.

Pathophysiology

The wide range of allergic conditions observed in the clinical setting and described in the literature may lead one to believe that an infinite number of discrete mechanisms is responsible for allergic symptoms. Despite the diversity in end-organ effects, however, much of the underlying pathophysiology in allergic diseases is remarkably similar. In addition, such knowledge enables the physician to recognize, and even anticipate, adverse reactions. Knowing that some patients with an anaphylactic reaction or asthma exacerbation may experience a late-phase allergic response, for example, compels the physician to continue intensive therapy until the reaction has completely subsided.

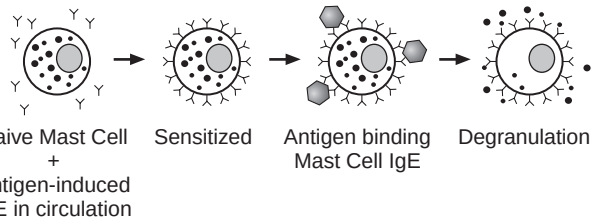
The term allergy, in common usage, connotes a variety of reactions that range from mildly debilitating to life-threatening. In conventional medicine, however, allergy specifically describes a precise cascade of biochemical reactions that, in genetically predisposed (or atopic) individuals, may result in specific physical symptoms, such as rhinorrhea, sneezing, wheezing, bronchoconstriction, and even life-threatening vasodilation and hypotension (anaphylaxis). Some distinct stages in the development and promulgation of the allergic reaction are well described.

The two-step process by which a genetically susceptible (i.e., atopic) individual initially becomes allergic to a substance begins with *sensitization* (Fig. 29-1). During the initial stage of sensitization, the individual develops significant amounts of immunoglobulin E (IgE) antibodies against an inhaled, ingested, or injected substance. Long-lived memory B cells, which are capable of producing more of this specific IgE antibody immediately when stimulated, appear in the circulation, largely through the action of "allergic" cytokines. The newly formed IgE antibody adheres either to circulating blood basophils or to mast cells located in the mucosal layers of the skin, the gastrointestinal tract, and the respiratory system. Millions of IgE molecules of different specificities (directed against different allergens) are present on the surface of each mast cell and basophil. An individual is considered sensitized only after sufficient levels of IgE antibodies directed against a specific substance have been produced and are bound to the surfaces of these cells. The process of sensitization does not produce any of the symptoms that we equate with allergic disease—in fact, a person is usually unaware of these initial molecular and cellular changes. Not until reexposure to the allergen do allergic symptoms manifest.

Immunoglobulin E acts as a bridge that cross-links a specific antigen on the surface of mast cells and basophils to release mediators that foster inflammatory activity.

The second step in the allergic process is the reactivity phase. The allergic reaction requires that a sensitized person be reexposed to the allergen, which now acts as a bridge, cross-linking the IgE molecules on the surface of

FIGURE 29-1
Allergic sensitization and reactivity (degranulation). The process of sensitization and degranulation in mast cells begins with production of antigen-specific immunoglobulin E (IgE) in genetically predisposed individuals. Initial binding of specific IgE to the naive mast cell surface "primes" the cell for activity. Subsequent binding of a specific allergen to the mast cell triggers complex intracellular biochemical events, leading to degranulation and subsequent mediator release.



each basophil and mast cell. This bridging phenomenon induces changes within the cell, typically through the action of multiple complex protein kinase cascades. Ultimately, this cross-linking process leads to degranulation of the mast cell or basophil, a process that releases both preformed mediators (e.g., histamine, serine proteases, and proteoglycans) and newly synthesized compounds (e.g., eicosanoids and cytokines). The activities of these mediators of allergic inflammation are readily observable in a patient experiencing an allergic reaction. Histamine dilates blood vessels and thus causes localized edema in tissues such as the skin and mucosal membranes, as well generalized urticaria. Cytokines lead to the ingress of additional cells to the area of the initial reaction, such as $CD4^+$ T cells and eosinophils in the lung tissue of an individual experiencing an asthma exacerbation. Overall clinical symptoms vary from negligible rhinorrhea to sudden death (severe anaphylaxis), depending on the degree of exposure and the sensitivity of the person exposed to the allergen. Most cases lie somewhere between these extremes. Although the cellular and molecular events for all immediate hypersensitivity reactions are similar, differences in target organ responses ultimately dictate the clinical patterns of disease activity once a reaction has been induced.

Allergic reactions also produce an inflammatory reaction; indeed, one of the most important research findings from the past few decades is the recognition that most of the pathophysiologic processes of diverse allergic reactions have a common inflammatory pathway. Elucidation of this pathway has resulted in more precise, targeted therapies with which to control allergic inflammation. In the past, treatment with systemic corticosteroids was the only antiinflammatory intervention available. Although remarkably effective, these steroids provide relief at the expense of severe, long-term adverse effects, including bone loss, myopathy, and even psychiatric disturbances. Fortunately, the identification of biochemical intermediates and enzymes in the inflammatory cascade reduced the need for such powerful and nonspecific drugs and led to targeted therapies for interrupting the allergic inflammatory cascade, or at least controlling the allergic symptoms, until the triggered reaction eventually attenuates.

Although analogues for specific pharmacologic activities exist in the conventional and alternative therapeutic realms, the overall approach to treatment more clearly differentiates the two approaches to care. Whereas a conventional physician tends to treat each disease state (and symptom) separately and specifically, an integrative practitioner may additionally consider measures to diminish an atopic predisposition. These additional therapies are described in this chapter and in the chapters on specific allergic diseases.

Integrative Therapy

Nutrition

Specialized Allergen Avoidance Diets

The avoidance of specific foods or food additives that are found to be responsible for gastrointestinal or anaphylactic allergic reactions, such as peanuts in sensitive individuals, is an obvious intervention. Such elimination diets are useful for both true food allergies and food sensitivities (see Chapter 84, Food Intolerance and Elimination Diet). Food avoidance is also useful when one is attempting to control less severe, nongastrointestinal allergies. For example, patients who are troubled by recurrent sinus infections or mild to moderate refractory asthma symptoms often benefit from certain dietary modifications. Usually, these avoidance diets are specific to an individual, but some common classes of foods have been popularly linked to allergic exacerbations, such as dairy products and animal proteins. These foods seem to be associated with a worsening of allergic symptoms in many patients, though published clinical data in this area are scant. A handful of small studies refuted the association between milk and mucus production or allergic symptoms,[3] but biologically plausible hypotheses support such an association.[4] In either case, a brief trial (4 to 6 weeks) of dairy avoidance is helpful to discern such an association in selected individuals.

Omega-3 Fatty Acids

Alterations in the dietary intake of fats are known to affect the fatty acid composition of cell membranes.[5,6] This fact is especially pertinent to inflammatory conditions, because catabolism of cell membrane–derived fats is an initial step in inflammatory mediator production through the arachidonic acid cascade. Omega-3 supplementation decreases the ratio of omega-6 to omega-3 fatty acids in the inflammatory cell lipid membrane and thus creates less substrate for mediator production.[5,6] This process, in turn, decreases the production of many potent bioactive compounds (e.g., leukotrienes) that are intimately involved in allergic inflammation. The level of inhibition of leukotriene production by dietary modification rivals that of pharmacologic agents[7] (see Chapter 86, The Antiinflammatory Diet).

Increased dietary omega-3 intake is a useful clinical intervention, as is a trial of omega-3 supplementation. Published reports used doses of 3.2 g eicosapentaenoic acid (EPA) and 2.2 g docosahexaenoic acid (DHA) daily as a supplement to a standard diet.[5] In one clinical trial, 26 patients with asthma were placed on defined diets of varying omega-3 to omega-6 content.[8] More than 40% of subjects showed marked improvement in airway hyperresponsiveness when they consumed a diet with an elevated omega-3 content. These responders

to dietary interventions could be readily identified through analysis of the leukotriene composition of their urine, a measure that predicted which patients were likely to improve with dietary intervention.[8]

Dietary Antioxidants

The association between dietary antioxidant intake and the allergic response has been the subject of much study over many years. Many positive and negative reports exist in the literature, fairly equally divided, thus precluding definitive and global conclusions. Some findings are worthy of mention, however, particularly a few examining vitamin C and selenium intake. A case-control study using a food frequency questionnaire in 1500 people found that apple consumption and dietary selenium intake were negatively associated with asthma prevalence.[9] Further evidence for a role of selenium in modulating allergic diseases is that selenium functions as a cofactor for glutathione peroxidase, which helps prevent peroxidation of cell membranes by consuming free peroxide in the cell. In one report, children with asthma had significantly lower red blood cell glutathione peroxidase activity than a healthy control group.[10] Finally, patients with asthma have higher amounts of oxidized glutathione in their airways, a finding perhaps indicating that patients with asthma are subject to greater oxidative stress.[11]

A study in children found that higher intakes of cooked vegetables, tomatoes, and fruit were protective factors for symptoms of shortness of breath and wheeze during a 12-month observation period.[12] Consumption of citrus fruit, in particular, had a protective role for these symptoms, which may be related to vitamin C intake. In the same study, consumption of bread, butter, and margarine were all associated with an increased risk of shortness of breath and wheezing.[12] These findings are not universally accepted, however, because data in the literature are conflicting.

Finally, no conclusive consensus evidence indicates that antenatal supplementation of any vitamin or mineral during pregnancy will reduce the probability of atopy or asthma later in life for children.[13,14] By definition, these studies are difficult to perform, and the number of confounding variables is extremely high.

Supplements

Quercetin

Quercetin is a bioflavonoid (a plant pigment responsible for the colors found in fruits and vegetables) obtained from diverse sources, including apples, buckwheat, onions, and citrus fruits. Most data supporting its role in attenuating allergic reactivity have been obtained from in vitro studies, as well as from animal models of allergic disease. In vitro, quercetin stabilizes the membranes of mast cells and reduces the release of preformed histamine.[15,16] In animal models, quercetin is able to suppress anaphylactic responses in sensitized rats,[17] and it inhibits asthmatic inflammation in guinea pigs and rats.[18]

Quercetin must be used as a preventative—taken before allergen exposure. Thus, the activity of quercetin is similar to that of cromolyn, a drug that is often prescribed for allergy and asthma prevention (see later). Quercetin also inhibits the production of enzymes responsible for manufacturing the potent leukotrienes.[19] Practitioners usually recommend that quercetin be used regularly during an individual's entire allergy season, or year-round for those with perennial allergies.

> Quercitin is similar to cromolyn in its mechanism of action. Both are mast cell stabilizers.

Dosage

The dose of quercetin is usually 400 to 600 mg of a coated tablet one to three times daily between meals (adjust dose for clinical response). Quercetin is not soluble in water, however, so it is a poorly absorbed nutrient. Bromelain, a protein-digesting enzyme extracted from pineapples, increases the absorption of quercetin, as does vitamin C. Therefore, quercetin is typically sold blended with one or both additives.

Precautions

None are reported.

Magnesium

Magnesium is now a standard of care in the emergency treatment of acute asthma exacerbations, and it is usually administered as an intravenous solution. Magnesium has been shown to improve forced expiratory volume in 1 second (FEV_1) in that setting. Inverse associations are also reported between intracellular magnesium levels and asthma severity.[20] Despite this association, little convincing literature supports a role for long-term magnesium replenishment in the care of mild to moderate asthma. Some published reports note an improvement in asthma symptoms for those subjects with higher magnesium intake,[21] while others link dietary magnesium intake with an increased risk of asthma and wheezing in children.[22]

Dosage

Magnesium glycinate seems to be less irritating to the gastrointestinal system. The typical dose is 400 mg daily.

Precautions

Side effects are primarily gastrointestinal. At standard doses, magnesium exerts laxative effects.

> Some forms of magnesium supplementation have prominent laxative effects. The clinician must be wary of prescribing magnesium citrate, oxide, or hydroxide in a patient for whom diarrhea is a problem.

Botanicals

Butterbur (Petasites hybridus)

Butterbur has traditionally been used to treat migraine headaches but also asthma and bronchitis, because it is thought to reduce mucus production. A study of 132 people with seasonal rhinitis (hay fever) found that an extract of this herb was as effective as cetirizine (Zyrtec), a commonly prescribed, mildly sedating antihistamine, and had fewer

side effects (especially less sedating). The study lasted only 2 weeks and required four to five doses of the herb daily.[23] More recently, mechanisms of action were more carefully delineated in a mouse model of asthma.[24] In this study, butterbur was shown to inhibit leukotriene activity and reduce allergic airway inflammation and bronchial hyperreactivity by specifically inhibiting allergic cytokine formation (interleukin-4 [IL-4] and IL-5, and RANTES [regulated on activation, normal T expressed and secreted]).

Dosage

Petasites extracts are typically standardized to contain a minimum of 7.5 mg of petasin and isopetasin. The adult dosage ranges from 50 to 100 mg twice daily for the treatment of migraine headaches. A high-quality, standardized product prepared in Germany is Petadolex. It is prepared using a carbon dioxide extraction, and its content of pyrrolizidine alkaloids is lower than the limits of detection (the German government requires content to be less than 1 mg daily by dosage). In the rhinitis study, participants took one butterbur extract tablet (standardized to 8.0 mg of total petasin per tablet) four times daily. The 50-mg Petadolex tablet is standardized to contain 7.5 mg petasins and may also be used up to four times daily in adults.

Precautions

The main concern in using butterbur is finding a preparation that is free of harmful pyrrolizidine alkaloids. These compounds are capable of causing toxic reactions in humans, primarily venoocclusive liver disease.

Stinging Nettle (Urtica dioica)

Stinging nettle has enjoyed a long history of use as an antiallergy preparation, and it is also used in the therapy of prostatic hypertrophy. The "stinging" hairs and leaves of this plant contain histamine, serotonin, acetylcholine, and 5-hydroxytryptamine, compounds that typically are the cause of allergic symptoms. Some investigators attribute the antihistaminic properties of ingested nettles to an autocoid, or feedback inhibition of histamine and histamine-related compounds. Studies have revealed that nettle extract also inhibits the release of tryptase, a mast cell mediator of allergic inflammation, as well as other proinflammatory mediators, such as cyclooxygenase-1 (COX-1), COX-2, and prostaglandin D_2 synthase (PGDS).[25] More important may be the inhibitory effect of nettle on the transcription of inflammatory genes. Nettle extracts have been shown to inhibit the activity of nuclear factor-kappaB (NF-κB)—a transcription factor, or on-off switch, responsible for the expression of many inflammatory genes (e.g., IL-1, IL-2, IL-6, IL-8, tumor necrosis factor, adhesins, major histocompatibility class I, inducible nitric oxide synthase, and COX-2).[26]

Clinically, few trials have been conducted. In one randomized double-blind study, 57% of patients rated nettles effective in relieving allergic rhinitis symptoms, and 48% said that nettles equaled or surpassed previously used allergy medications in effectiveness.[27]

Dosage

The typical dosage is 300 to 350 mg of a freeze-dried extract used one to three times daily, as needed.

Precautions

Rare allergic reactions and possible gastrointestinal upset have been reported.

Pharmaceuticals

Cromolyn

Cromolyn is a prime example of a drug whose active ingredient was isolated from a botanical source with a historical record of effectiveness. Isolated from an extract of the khella plant *(Ammi visnaga),* cromolyn demonstrates potent mast cell–stabilizing activity in vitro. When used prophylactically, in advance of allergenic exposure, cromolyn can markedly reduce the rate and degree of mast cell degranulation and thus allergic symptoms. Cromolyn is available by prescription in a nebulized form for inhalation (Intal), as a liquid for oral use in gastrointestinal allergic conditions (Gastrocrom), and without a prescription as a nasal preparation for allergic rhinitis (NasalCrom). Nebulized cromolyn is useful in treating children with asthma and was a mainstay of asthma antiinflammatory medications before the development of inhaled corticosteroids.

Dosage

For the treatment of allergic rhinitis, the dosage is one spray of nasal spray (NasalCrom) into each nostril three to six times/day until the condition is better and then one spray in each nostril every 8 to 12 hours. This preparation can also be used prophylactically approximately 20 to 30 minutes before allergen exposure (e.g., exposure to a cat). For asthma, one ampule (20 mg) is used by nebulizer three to four times daily.

Precautions

Cromolyn is quite safe, and adverse reactions are extremely rare.

Antihistamines

Antihistamines bind to the H_1 histamine receptor and inhibit allergic reactions at the level of the target organs; that is, they do not prevent the initiation of the classic allergic response but can inhibit (or at least reduce) the effects of histamine, a key biochemical mediator of allergy. Many different chemical classes of antihistamines are available, but most clinicians prefer the first- and second-generation pharmaceutical agents.

First-generation antihistamines are safe, over-the-counter preparations that are effective in reducing allergic symptoms, but at the expense of significant central nervous system effects. First-generation compounds tend to be highly lipophilic and readily cross the blood-brain barrier, thus causing sometimes marked sedation. In addition, anticholinergic effects, such as urinary retention, may inhibit the use of these drugs in patients with prostatic hypertrophy or urinary hesitancy from other causes. Because of the longer history of use of first-generation antihistamine products, many practitioners recommend them in certain higher-risk circumstances, such as in pregnancy. Examples of first-generation compounds are diphenhydramine (Benadryl), clemastine (Tavist), and chlorpheniramine (Chlor-Trimeton).

Second-generation antihistamines typically have fewer anticholinergic and antimuscarinic side effects than first-generation agents and are equally effective. The mechanism

of action is similar in first- and second-generation drugs, although more research has focused on presumptive antiinflammatory activity of the second-generation compounds. For example, desloratadine down-regulates various inflammatory mediators, including the generation and release of IL-4 and IL-13 by human basophils.[28] Examples of second-generation antihistamines include cetirizine (Zyrtec), loratadine (Claritin), and fexofenadine (Allegra).

Although many advertisements have been devoted to identifying specific and superior uses for differing brands of antihistamines (e.g., better efficacy in treating urticaria or rhinitis), much of this information represents marketing efforts because large head-to-head published comparisons of drugs for specific allergic conditions are lacking.

Finally, topical antihistamines are available as nasal sprays. Although systemic absorption is less than with oral preparations, similar adverse effects can occur. Bitter taste limits use in many patients. Examples of topical antihistamines include azelastine (Astepro) and olopatadine (Patanase).

Dosage

The standard dose of antihistamine varies with the particular compound. Follow the label directions.

Precautions

Patients should not operate heavy machinery or automobiles while they are taking even mildly sedating antihistamines. A 2000 study compared driving coordination in subjects given standard doses of a first-generation antihistamine (diphenhydramine) with that in subjects given alcohol, fexofenadine, and placebo. Remarkably, diphenhydramine had a greater impact on driving performance than alcohol.[29] In addition, urinary retention, confusion, dizziness, drowsiness, dryness of mouth, or convulsions (seizures) may be more likely to occur in older adults who take the older antihistamines.

Nasal Corticosteroids

Topical (nasal) corticosteroids are relative newcomers to the allergic rhinitis pharmacopeia. They are regarded as first-line therapy for moderate to severe rhinitis symptoms, especially nasal congestion, for which they seem to outperform antihistamines.[30] A brief period (perhaps weeks) often elapses before maximal effects are appreciated. These drugs function as topical antiinflammatory agents and reduce allergic inflammation locally in the nasal mucosa and sinus passages. Many of the newer preparations are regarded as safe because they exhibit first-pass metabolism and thereby lessen the possibility of systemic absorption and long-term adverse effects.

Dosage

The dosage varies with each preparation. Typically, one spray in each nostril daily is sufficient for maintenance. Occasionally this dose is doubled for short periods during peak allergy weeks.

Precautions

Common side effects include epistaxis (up to 10%). Concern also exists about growth rate declines in prepubescent children, but this observation was noted in very few reports. Higher rates of posterior subcapsular cataracts were also reported. Concerns about systemic absorption of these steroid compounds and the long-term effects remain, although several studies showed only mild adrenal inhibition.

> I have observed cases of septal perforation as a result of improper spraying of these products in the nares. Advise patients to aim the "nozzle" of the canister or bottle away from the nasal septum (i.e., toward the outside of the nostril).

Immunotherapy

Allergic desensitization is an effective adjunct to drug therapy in selected patients. It is generally reserved for those individuals who show no response to other therapies or for whom life-threatening reactions can occur with unpredictable frequency (e.g., insect sting anaphylaxis). Immunotherapy in the United States usually consists of the subcutaneous administration of gradually increasing amounts of allergic material, given at regular intervals ("allergy shots"). The mechanism by which the injections diminish allergenic sensitivity is not completely clear, but their effectiveness has been demonstrated in cases of allergic rhinitis (and for some types of asthma as well). This therapy is believed by some to be a last resort because the potential for an adverse reaction is always present, and the reaction itself can be life-threatening. From 1985 to 1993 in the United States, 52.3 million administrations of immunotherapy resulted in 35 deaths. These numbers equate to a mortality incidence of less than 1 per million, which is quite low but perhaps unacceptable for patients treated for a non–life-threatening condition such as allergic rhinitis.[31] Moderate to severe systemic reactions are fairly common and warrant close patient supervision immediately after the administration of a desensitization injection.

A newer immunotherapy modality that is rapidly gaining popularity is sublingual immunotherapy. Popularized in Europe when subcutaneous immunotherapy was deemed too dangerous for regular use, sublingual immunotherapy is similar to the subcutaneous route except that the allergen extract is given as drops that the patient self-administers under the tongue (sublingually) on a daily basis. The sublingual route has been shown to be efficacious in numerous studies, and it is very safe, with few mild reactions reported and no deaths.[32] It can be used for aeroallergens as well as for foods.

Mind-Body Therapy

Numerous studies documented the value of mind-body approaches to many allergic conditions. Classic studies from the late 1960s demonstrated that many patients with moderate to severe asthma exhibit severe symptoms when they are exposed to saline mists that they believed were potent allergens. Even more remarkable was their prompt recovery with use of a saline inhaler that they believed to be a beta agonist.[33,34] Even standard skin test reactions that produce classic wheal-and-flare reactions to subcutaneously introduced allergens can be modulated by mind-body techniques. In one

study, patients with dust mite sensitivity who were skin tested after viewing a humorous video demonstrated lower wheal-and-flare reactivity to dust mite allergen than did patients viewing a control video (weather documentary).[35] Finally, a randomized controlled study examined the effectiveness of the addition of self-hypnosis to a pharmacologic regimen for allergic rhinitis. Allergic symptoms in 79 patients with "hay fever" showed significant improvement over the course of two pollen seasons compared with those in control groups.[36]

Traditional Chinese Medicine

Until recently, relatively few controlled studies examined the role of acupuncture or Chinese herbs as part of a traditional Chinese medicine approach to allergies. Now, however, owing to several ground-breaking studies, this is perhaps the most exciting area for future innovation. Researchers purified and dissected several ancient Chinese herbal formulations for both asthma and food allergies and uncovered some remarkable results. An herbal preparation, tested in an animal model of asthma, was shown to be as effective an antiinflammatory agent as corticosteroids, but through a novel mechanism and with potentially fewer adverse effects.[37] A similar research initiative by the same workers led to the discovery of a Chinese formula that was completely protective in an animal model of peanut allergy.[38] The therapy also proved to be long lasting. This finding is remarkable because few, if any, therapies exist for this potentially fatal condition.

A human study demonstrated the superiority of a regimen of acupuncture plus Chinese herbs (versus placebo) in the treatment of seasonal allergic rhinitis.[39] The study assessed rhinitis symptoms with several validated scales, which showed significant improvements in quality of life and symptom control in patients who received a standard regimen of acupuncture along with a standardized herbal decoction. The therapy was found to be well tolerated and safe in this study population.

Prevention Prescription

- Use environmental modification, including reduction of dust mite allergen (mattress and pillow encasements, removal of carpeting as possible, replacement of curtains with shades), removal of allergenic pets from the home (or at least the bedroom), purchase of a high-efficiency particulate air (HEPA) filter, and planning of activities to avoid exposure to early morning peak pollen counts.
- Follow an antiinflammatory diet. Avoid processed foods, partially hydrogenated oils, white sugar, and flour. Replace vegetable oils with olive or canola oil for cooking. Avoid excessive amounts of saturated fat, such as those found in red meat, fried foods, and dairy products.

Therapeutic Review

The following is a summary of general therapeutic options for allergies (e.g., allergic rhinitis). If a patient presents with severe respiratory or anaphylactic symptoms, stabilizing pulmonary function or allergen exposure risk with potent conventional therapies is prudent before introducing supplements or botanical preparations. For the patient with mild to moderate allergy symptoms, however, this stepladder approach is appropriate.

Remove Environmental Triggers From the Home

- With perennial allergens (e.g., dust mites), washing bedclothes weekly in hot water, encasing mattresses and pillows in mite-impermeable covers, and removing carpeting from rooms (especially bedrooms) may be helpful. Regular vacuuming of carpeted areas by someone without allergies is also suggested. B1
- Pet-sensitive individuals are a special case. The ideal solution, removal of the pet from the household, is typically not an option with pet lovers. In this case, removing pet access to the bedroom is helpful. B2
- A high-efficiency particulate air (HEPA) filter is useful for light, floating allergens, such as cat allergens; it is less effective with dog allergens. A1

Avoid Peak Pollen Exposure Outdoors

- Outdoor pollens are ubiquitous; avoidance is nearly impossible. Pollen-sensitive patients can avoid significant exposure by limiting outdoor activities between 5 and 10 AM and on dry, windy days, when airborne pollen levels are highest. C1

Nutrition

- Decrease dairy (milk protein) and total protein intake. Plant proteins may be preferable. C1
- Consume omega-3–rich fats found in cold-water fish, nuts, greens, and ground flaxseed. Consider the addition of pharmaceutical-grade (distilled) fish oil capsules or liquid supplements. B1
- Increase water intake dramatically to maintain adequate hydration. B1
- Increase intake of natural bioflavonoids and antioxidants by eating more organic fruits (especially berries) and vegetables. B1

Continued

Mind-Body Therapy

- Clinical hypnosis may markedly attenuate allergic reactivity. C1
- Consider a trial of homeopathy, which is particularly helpful in individuals with multiple chemical or drug sensitivities. This form of therapy is safe for adults and children. C1

Traditional Chinese Medicine

- Acupuncture therapy with or without Chinese herbal therapy can be used for allergic rhinitis. Most studies used artificially standardized regimens; individualized therapy may be more efficacious. B1
- Chinese herbal therapy and acupuncture can be helpful for asthma control. B1

Supplements

- Quercetin: 400 to 600 mg one to three times daily C1
- Magnesium glycinate: 400 mg daily C2
- Vitamin C: 250 mg twice daily C2

Botanicals

- Freeze-dried stinging nettles: 300 to 500 mg one to three times/day B2
- Butterbur (Petadolex): 50 to 100 mg twice daily B2

Pharmaceuticals

- Cromolyn sodium: nasal spray, one spray/nostril three to four times daily; nebulizer, 20 mg (one ampule) two to four times daily A1
- Second-generation antihistamines (oral) A2
  - Loratadine: 10 mg daily
  - Fexofenadine (Allegra): 180 mg daily or 60 mg twice daily
  - Cetirizine (Zyrtec): 5 to 10 mg daily
- Nasal antihistamines A2
  - Azelastine (Astepro), olopatadine (Patanase): one to two sprays/nostril twice daily
- Nasal corticosteroids (may be added if other natural and pharmacologic interventions fail or if nasal congestion or recurrent sinusitis is a prominent problem) A2
- Fluticasone nasal (Flonase): two sprays/nostril daily
- Budesonide nasal (Rhinocort): one to four sprays/nostril daily

Immunotherapy

- This is typically reserved for those patients with more severe or refractory symptoms, life-threatening allergic reactivity, or coexisting conditions (e.g., asthma, sinusitis). A3
- Consider sublingual immunotherapy before subcutaneous immunotherapy. A1

KEY WEB RESOURCES

World Allergy Organization: http://www.worldallergy.org/index.php	This international allergy organization publishes excellent position papers that are highly regarded in the field. The articles are free to all. Look at the sublingual immunotherapy reviews as well.
Allergychoices, Inc.: http://www.allergychoices.com/	This group is the oldest practice in the United States that trains physicians in sublingual immunotherapy. The Web site also contains some good explanations of the theory.
Allergy Control Products: http://www.allergycontrol.com/; and National Allergy: http://www.natlallergy.com/	These two vendors are among the oldest sources for allergy supplies for consumers. They also send health care practitioners order forms and discounts for patient use.
NeilMed Pharmaceuticals, Inc: www.neilmed.com	This company is a great source of nasal irrigation supplies and information for patients and also sends samples to health care practitioners.

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References are available at expertconsult.com.

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Chapter 30

Multiple Chemical Sensitivity Syndrome

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Pathophysiology

Multiple chemical sensitivity (MCS),[1,2] renamed idiopathic environmental intolerance by its skeptics, is an acquired, chronic, often disabling polysymptomatic condition.[1] The core symptom of MCS consists of flares of illness from exposures to low levels of multiple different chemicals from the environment. MCS involves a two-step process of initiation, followed by elicitation. Typically, patients present with complaints of elicitation, which the clinician may or may not observe directly. Survey data indicate that although the population of patients will report similarly high current reactivity to multiple environmental chemicals and foods at the elicitation phase (the precise eliciting agents and symptom manifestations vary among individuals), the initiation process by history ranges from a single identifiable high-dose chemical exposure to a series of lower-dose exposures to no identifiable chemical initiator at all.[3] Limited data suggest that pesticide-initiated MCS may lead to somewhat more severe clinical pictures than does MCS initiated by indoor remodeling (likely more solvent-related MCS).[4]

Heterogeneous Mechanisms

The pathophysiology of MCS is not well understood. Various investigators have proposed a range of mechanisms, many of which are nonexclusive, and none of which by itself explains the entire clinical presentation. However, the clinician must be aware of the various hypotheses to advise patients on the plausibility of potential treatments they may encounter before rigorous evidence is available on benefit versus risk.

Table 30-1 summarizes the proposed mechanisms of MCS. Leading possibilities, for which some systematic evidence in animals and human subjects exists, include the following: (1) time-dependent or neural sensitization of central dopaminergic pathways[5,6]; (2) neurogenic inflammation involving trigeminal nerve effects mediated by C-fiber irritation, especially in the nasopharyngeal region, leading to sinusitis, or neurogenic vasodilation leading to migraine headache[7–9]; (3) elevated nitric oxide/peroxynitrite as an underlying molecular process contributing to sensitizing and inflammatory events[10,11]; (4) chronic systemic inflammation triggered by exogenous agents[12–14]; and (5) classical conditioning.[15–17] In a simplistic mind-body dualism, proponents and skeptics of MCS have framed the discussion for years as though biogenic and psychogenic mechanisms were mutually exclusive.[18–20]

However, the data support the likelihood that MCS is a mechanistically heterogeneous syndrome with variable degrees of biologic and psychological mechanisms in play.[21,22] To date, the data suggest that various biologic mechanisms contribute to MCS,[14] and psychological mechanisms superimpose their effects[17] and interact with biologic factors in many, but not all, cases.[23,24] For example, controlled animal studies demonstrated that repeated low-level exposures to environmental chemicals such as formaldehyde,[6] toluene,[25] or lindane[26] can sensitize psychomotor activity and, in certain situations, corticosteroid release, as well as increase or delay extinction of classically conditioned fear.[26,27] Thus, the chemical exposures themselves can facilitate classical conditioning processes and can thereby render dualistic models of MCS inaccurate and irrelevant: it is mind and body, rather than mind or body.

Individual difference factors in animals that enhance the ability to become sensitized include parental preference for abusable substances (genetics),[28] female gender (related in part to the progesterone-to-estrogen ratio),[29] hyperreactivity to novel environments,[30,31] and preference for sucrose rather than plain water.[32–35] Human self-report and laboratory studies have repeatedly shown parallel findings in persons with chemical intolerance, including familial substance abuse problems, greater prevalence of women affected, hyperreactivity of acoustic startle blink responses to novel noise stimuli during chemical exposure, and higher scores

TABLE 30-1. Proposed Mechanisms for Multiple Chemical Sensitivity

MECHANISM	STRENGTH OF SUPPORTING EVIDENCE
Time-dependent or neural sensitization	++
Neurogenic inflammation	++
Elevated nitric oxide/peroxynitrite	++
Non-IgE antibodies to food (IgM, IgG)	++
Classical conditioning	++
Misattribution of psychiatric symptoms*	?

IgE, IgG, IgM, immunoglobulins E, G, and M, respectively.
*Psychiatric symptoms are present in a substantial subset of patients with multiple chemical sensitivity, but causality pathways are not well established. Competing hypotheses include the following: (1) mood problems cause environmental chemical reactivity; (2) environmental chemical reactions cause mood problems; (3) some additional factor causes both environmental chemical reactivity and mood problems; (4) patients misattribute their mood-related symptoms to environmental chemical reactions; and (5) mood and chemical reactivity are often concomitant but unrelated.

for carbohydrate and other food cravings on validated questionnaires.[5]

Multisystem Symptoms, Inflammatory Events, and Amplified Reactivity

The key phenomena involve a capacity for nonimmunologically mediated hyperreactivity or amplified responsivity to low-level environmental stimuli from multiple classes of agents (chemicals, drugs, foods, electromagnetic factors). Manifestations include multisystemic inflammatory events and other disturbances of function in target organs, which can include most areas of the body (e.g., central nervous system, heart, airways, gastrointestinal system, and musculoskeletal system). The pattern of symptoms is idiosyncratic to the patient, not to the exogenous agent. In other words, in contrast to conventional toxicants such as heavy metals, the same triggering agent in MCS can cause very different sets of symptoms in different patients; and structurally unrelated agents can cause the same symptoms in a given patient. Thus, although genetic polymorphism data (see later) suggest impaired capacity for metabolic clearance of environmental toxicants in some patients with MCS, classical toxicologic mechanisms also fail to account for the clinical picture in MCS.

Most patients with MCS also report multiple adverse reactions to common foods such as corn, egg, wheat, yeast, milk, beef, tomato, and potato, as well as food additives (colorings, preservatives).[36] Anaphylactoid reactions are less common than are multisystemic symptoms similar to those reported in adverse reactions to environmental chemical triggers. Immunoglobulin E (IgE) antibody mediation is unlikely, based on the evidence, but IgM and IgG antibodies to certain foods in some patients (e.g., those with irritable bowel syndrome) have been demonstrated.[37]

Clinically, MCS overlaps other controversial syndromes such as fibromyalgia and chronic fatigue syndrome.[38] Case definitions vary, but they typically include symptoms of central nervous system dysfunction such as difficulty concentrating, fatigue, migraine headache, irritability, and other mood instability. Arthralgias, irritable bowel syndrome, and rhinitis, as well as sinusitis, ovarian and breast cysts, and menstrual disorders are also common in MCS.[39] Family histories of patients with MCS are notable for an increased prevalence of heart disease and hypertension, diabetes mellitus, sinusitis and rhinitis, and substance abuse, especially alcoholism (e.g., 20% versus 6%).[40,41]

Population-based studies placed the prevalence of MCS in the general population at 2.5% to 4%.[42] Other surveys indicated that 10% to 30% of the general population will self-report some nondisabling problems (e.g., breathing or headache difficulties) during exposures to low levels of environmental chemicals such as scented products.[43,44] Demographically, women report intolerance to environmental chemicals more often than do men, and women comprise 70% to 80% of patients with MCS.[45] The typical age at the time of diagnosis is in the 30s to 40s.[39] Systematic studies suggested that psychiatric comorbidities are common but not universal among patients with MCS, with rates ranging from approximately 25% to 69%, depending on subsets studied.[46] Persons with concomitant MCS, fibromyalgia, and chronic fatigue syndrome have the highest rates of comorbid depression, at 69% (versus 27% in chronic fatigue syndrome alone).[47]

Genetic Polymorphisms

Compared with patients with MCS who can identify an initiating past chemical exposure, the subset of chemically intolerant patients who cannot identify a specific higher level chemical exposure event that initiated their condition presents with higher lifetime rates of psychiatric problems, especially anxiety and depression. The subset of MCS patients (n = 11) whose symptoms overlap those of panic disorder exhibits panic-like symptoms during controlled challenges with carbon dioxide, which is a marker of poor indoor air quality, and has cholecystokinin-B receptor alleles, a genetic polymorphism associated with panic diagnoses in persons who do not have MCS.[48] Patients with MCS and normal controls do not differ for a gene coding for the D4 dopamine receptor associated with personality disturbances.

Furthermore, in a larger case-control study of women meeting strict reproducible case definition criteria for MCS (N = 203), researchers documented significant differences in genotype distributions for cytochrome P-450 isoenzyme CYP2D6 and *N*-acetytransferase-2 (NAT2).[49] Odds ratios for being CYP2D6 homozygous active and NAT2 rapid were significantly higher in cases than in controls. Cases also differed from controls for the odds for being heterozygous for paraoxonase 1-55 (PON1-55) and PON1-192. In addition, other studies linked heterozygosity for the PON1 polymorphisms with neurologic symptoms in 1991 Gulf War veterans with chronic illnesses, which partly overlap fibromyalgia and MCS. More recent articles questioned the consistency of the genetic findings in MCS.[14,50] Taken together, however, the genetic polymorphism and biochemical findings suggest that some patients with MCS have inherent susceptibilities to less effective detoxification mechanisms for exogenous substances

and increased sensitivity to carbon dioxide triggers (panic-like pictures).

The clinical data raise the possibility of additional individual differences in genetic profiles of patients with MCS in terms of family histories of alcoholism. Although various investigators return to hypothesizing that MCS is "simply" a variant of somatization disorder in psychiatry, such a label does not expand the potential therapeutic armamentarium to help these patients. Mainstream psychiatry has few treatments to offer persons with somatization disorder other than well-structured, predictable contacts with physicians to minimize health service overuse, unnecessary diagnostic tests, and drug side effects. Early twin adoption studies suggested that the daughters of men with alcoholism develop somatoform disorder—but not necessarily alcoholism per se—at higher rates than do controls.[51] In view of the data showing that family histories of patients with MCS include a higher prevalence of alcoholism,[40] the evidence points to potential mechanistic clues that could lead to treatments adapted from the seemingly unlikely area of addiction research. Clinically, patients with MCS report poor tolerance of drugs and alcohol, but addictive-like responses to craved foods, especially those with wheat, yeast, milk, corn, and sugar constituents.[1]

Addiction and Time-Dependent Sensitization

The leading candidate mechanism for MCS from addiction research is time-dependent or neural sensitization.[5,6] This type of nonimmunologic sensitization involves progressive amplification of host behavioral and neurochemical responses to repeated exposures to the same, initially novel or threatening stimulus. Sensitization of the dopaminergic mesolimbic pathway may mediate the development of cravings for drugs of abuse, including alcohol, and sucrose (which cross-sensitizes with stimulant drugs). Both animal studies using formaldehyde, toluene, and pesticides and human research on persons with low-level chemical intolerance demonstrated that low-level environmental chemical exposures initiate mesolimbic sensitization or its psychophysiologic correlates. These correlates include sensitized responding in electroencephalographic alpha or beta frequency activity and progressive increases in blood pressure of human subjects with chemical intolerance versus normal controls.

At the physiologic limits, sensitized systems in animals exhibit a bidirectional or oscillatory capacity.[52] In other words, the response magnitude increases progressively to some biologic ceiling and then reverses direction. Overall, then, patients with MCS may have a biologic susceptibility to sensitize, a process that permits development of addictions to certain foods (in which the craving response remains below the ceiling), as well as intolerance for chemicals (and drugs) (in which the response has reversed into adverse reactions and avoidance or addiction).

Integrative Therapy

Overview

In a useful 2003 study, researchers asked more than 900 persons with self-reported MCS to rate the degree of help versus harm they had experienced in the course of trying each of 101 different treatments to recover from their condition.[53] Thus, although the formal clinical trial evidence for any therapies in MCS per se is very limited, the data from the patients themselves offer revealing information on which to base a treatment plan. Table 30-2 summarizes the top-rated most helpful and bottom-rated most harmful treatments from the patient treatment survey study of interventions tried by these patients with MCS. The reader also is encouraged to review the original article for the comprehensive list of 101 options, with numbers of patients who tried each one.

The evidence indicates that self-management strategies, not supplements or practitioner-administered treatments, are most helpful to the largest proportion of these patients. The most valuable condition-specific options involve reduction of environmental exposures and dietary management (with a rotation diet). Among the nonspecific interventions, spiritual and mind-body approaches, such as prayer and meditation,[23,54] also rank high as much more useful than harmful. Notably lower ranked are supplements and treatments provided by practitioners (acupressure could be either self- or other-administered), although many of these options were rated as more helpful than harmful. Another article proposed use of high-dose vitamin D_3 supplementation for its presumptive antiinflammatory effects,[11] but no studies of this possibility in MCS have been conducted.

Most therapies that would fall into the broad category of complementary and alternative medicine rated at least slightly more helpful than harmful. At the beginning of treatment, however, many patients with MCS do not tolerate botanical agents or nutritional supplements. They also have great difficulty traveling even short distances to appointments with practitioners because of intolerance of vehicle exhaust. As a result, lifestyle and self-management changes are the mainstays of treatment in MCS.

Overall, the coping issues that patients with MCS face include a sense of loss of control, impingement by environmental hazards at every turn, and intolerance of many exogenous substances considered nontoxic as well as toxic by the larger community. As a result, an integrative provider may provide the most help to a patient with MCS by facilitating self-empowering actions, including obtaining advice from other patients, online support groups (for patients who can tolerate being around computers, with necessary modifications such as low-emission screens and well-ventilated boxes to redirect off-gassing of volatile substances from heated plastic components), and other educational resources.[55] For example, support groups were rated as much more helpful than harmful (8.7) by the 520 individuals who had tried them in the 2003 study.[53]

Self-care lifestyle, mind-body therapy, and constitutional treatments are more helpful and less harmful for environmentally ill patients than are other classes of treatment, such as biochemical therapies. Pharmaceutical drugs, especially antidepressants and anxiolytics, reportedly cause more harm than benefit for a large proportion of individuals.

TABLE 30-2. Patient Ratings of the Most Helpful and Most Harmful Treatments for Multiple Chemical Sensitivity (*N* = 917 Patients)

	NUMBER OF PATIENTS WHO TRIED TREATMENT	RATIO OF HELP-TO-HARM RATINGS*
Most Helpful (Tried by at Least 300 Patients)		
Chemical-free living space	820	155.2
Chemical avoidance	875	118.6
Prayer	609	48.3
Meditation	423	19.2
Acupressure	308	14.9
Air filter	786	13.7
Rotation diet	560	12.7
Lactobacillus acidophilus	661	12.7
Change of residence	513	11.7
Most Harmful (Tried by at Least 100 Patients)		
Sertraline	148	0.1
Fluoxetine	183	0.3
Amitriptyline	149	0.3
Other antidepressants	306	0.5
Diazepam	125	0.5
Alprazolam	134	0.6

*A help-to-harm ratio of more than 1 implies more helpful than harmful effects; a help-to-harm ratio of less than 1 implies more harmful than helpful effects. See the original article for more details on other therapies. (Adapted from Gibson PR, Elms AN, Ruding LA. Perceived treatment efficacy for conventional and alternative therapies reported by persons with multiple chemical sensitivity. *Environ Health Perspect.* 2003;111:1498–1504.)

Much of the research literature has concerned itself with arguing about the reality of the patients' condition and the presence or absence of psychiatric labels. The treatments that patients rated as most harmful were common antidepressant drugs and two benzodiazepines, the conventional treatments most widely used for the depression and anxiety comorbidities that researchers have identified in these patients. Overall, the evidence suggests that these patients need help with emotional disturbances, but they require alternative, nonpharmaceutical approaches to treatment. Psychotherapy to cope with MCS (6.0) rated with a higher helpful-to-harmful ratio than did psychotherapy to cure MCS (1.4).

Apart from the patient-oriented survey study, the controlled data on any of the interventions described here are minimal. In that sense, all the treatments fall into the category of therapies to consider rather than ones with sufficient evidence. Some short-term studies in children with attention deficit disorder, migraine, and epilepsy support comprehensive dietary elimination programs of offending foods,[56–59] but long-term prospective studies in which an intervention leads to clinical improvements are not available in this field. Some retrospective studies and studies documenting changes in proxy variables such as brain neuroimaging scan patterns support the inference of exposure-dependent, reversible changes in brain function in patients with food or chemical intolerances who have neuropsychiatric symptoms.[60,61] A more recent positron emission tomography scan study found no resting baseline differences between patients with MCS and healthy controls,[62] but no newer controlled study has reported on neuroimaging findings during acute or repeated intermittent chemical exposures. Patients with MCS exhibit significantly greater temporal summation of hyperalgesic responses to intradermal capsaicin compared with controls.[8]

Lifestyle

Chemical Avoidance Programs

The essential feature of chemical avoidance programs is for patients to spend most of their time in chemically less contaminated environments, especially indoors at home and at work.[21] Many affected persons have to work at home or in alternative workspaces. Comprehensive avoidance is key, because continued ambient exposures fluctuate and maintain sensitized states.[63] This approach involves changes in heating and cooking systems (preferring all-electric homes

to those with natural gas heat or gas stoves), minimization of volatile organic compounds by using low-outgassing materials such as ceramic tile rather than carpet, glass and metal furniture without glues, untreated cotton-based rather than synthetic fabrics in clothing and home furnishings, glass and stainless steel cookware and dishes rather than plastics; and nonscented products for cleaning and personal hygiene.

Items that have chemical odors are allowed to age outdoors away from living space air, to permit outgassing away from the affected person. Any clothing with residual chemical treatments is washed repeatedly and aired out before use to remove any excess residues. Undyed fabrics are preferable to dyed fabrics for clothing and home furnishings. No pesticide or herbicide use is permitted indoors or outdoors in the vicinity of the affected person. Chemical avoidance reportedly restores a limited amount of ability to tolerate environmental chemicals, but it typically requires at least a year before substantial gains are made.

Patients also often move from homes in more polluted areas to locations in less polluted outdoor air environments, where pesticide and herbicide spraying by neighbors is less common. Many of these patients also report mold sensitivity, and relocating to a home that is mold free is crucial for improvement. Many patients also find air filters helpful to reduce particulate, chemical, dust, and mold levels in indoor environments, but filters alone without significant avoidance programs are rarely effective.

Precautions

Social isolation, marital and family disruption, depression, and suicidality are clinical side-effect risks of avoidance programs. Financial losses also develop from overzealous attempts to change home living environments and avoid chemical exposures in a workplace. Interventions to minimize these risks are essential components of any avoidance program.

Nutrition

Rotation Diets

Comprehensive rotation diets involve eating each food no more often than once in 4 to 7 days. Such diets usually start with foods that the patient has eaten less frequently, such as turkey, rice, yams, and nuts (not peanuts). Members of the same botanical food family (e.g., tomato and potato; wheat and rye) are not combined or eaten in close time proximity, to avoid triggering craving reactions or adverse food reactions. Many patients tolerate few foods at first, and meals can consist of a large quantity of a single food by itself, without seasonings or other foods. Rotation diets can reveal "masked" food intolerances, in which the foods that are responsible for chronic symptoms are craved and eaten too often for the cause-and-effect relationship to emerge.

Temporary avoidance of an offending food for 4 to 7 days "unmasks" the process, and challenge tests of the single food typically trigger an enhanced adverse reaction on first reingestion if sensitivity persists. Frequent eating of a food reinstates the masking and chronic symptoms at a lower-grade level. Complete avoidance of an offending food and use of a full rotation diet for months to years clinically restore the ability to tolerate some of the originally offending foods. The ability to tolerate once offending foods can return as early as 3 months after complete avoidance (see Chapter 84, Food Intolerance and Elimination Diet).

If the range of tolerated foods is sufficient to allow selection of antiinflammatory diet foods, these are preferred. Such foods include various less contaminated fishes, organic vegetables, fruits, and nuts on a rotation schedule (see Chapter 86, The Antiinflammatory Diet).

Precautions

Undernutrition and malnutrition, including weight loss, are common. Some effort to provide macronutrient and micronutrient supplements (made without common allergens such as wheat, soy, milk, yeast, corn) is appropriate. Some products provide macronutrients in elemental food products (e.g., amino acids rather than proteins with their higher antigenic potential). Many patients do not tolerate any such supplements, however, for long periods after the initial diagnosis.

> Food elimination and rotation diets often foster nutritional deficiencies. However, most environmentally ill patients do not tolerate supplements early in their course. Phase in appropriate multivitamin, multimineral supplementation later in the overall treatment program, as hyperreactivity gradually fades.

Exercise

In view of the evidence that exercise can improve mood as a nonpharmaceutical intervention, aerobic exercise can be a valuable adjunct. For patients with MCS who have comorbid fibromyalgia or chronic fatigue syndrome, data suggest that even walking as exercise is helpful in reducing symptoms.

Precautions

Some patients cannot tolerate outdoor environments because of ambient air pollution from vehicle exhaust, pesticides, and herbicides. Provisions for exercising in a chemically less contaminated outdoor or indoor environment will be necessary. Some patients with panic disorder may find their symptoms triggered by stimuli that increase sympathetic discharge or lead to a buildup of carbon dioxide (see Chapter 88, Writing an Exercise Prescription).

Mind-Body Therapy

Prayer, Meditation, Yoga, Self-Hypnosis, Imagery, and Journaling

With or without a spiritual or religious aspect, setting an intention to heal, meditation, and various other mind-body interventions can help patients find a sense of meaning and purpose in their lives, as well as regain a sense of self-efficacy, despite their health problems.

Precautions

As with any relaxation program, some patients with anxiety disorders can experience a paradoxical worsening of anxiety during induction of a relaxed or altered state of consciousness.

Energy-Based Therapy

Healing Touch, Reiki, Faith Healing, Polarity Balancing, Craniosacral Work, Acupuncture, and Classical Homeopathy

As an adjunct to avoidance programs alone, constitutionally oriented treatments (e.g., acupuncture and classical homeopathy) have some likelihood of gently, gradually, and persistently reducing the individual's pervasive hyperreactivity to environmental chemicals, foods, and other potentially useful treatments such as supplements. However, patients with MCS are also extremely sensitive and reactive to subtle energy-based therapies. A preclinical study comparing individuals with elevated levels of self-rated chemical sensitivity showed greater variability, exposure to exposure, from repeatedly sniffing a given homeopathic remedy solution, compared with less chemically sensitive controls.[64] Referrals to practitioners with extensive experience in working with highly sensitive patients are highly preferable. Trying one therapy at a time is safer than combining multiple interventions in this class, at least until the effects of a given treatment stabilize.

Forms of these interventions in which the extent of each treatment can be adjusted and titrated are more likely to help than are treatments that are nonindividualized or heroic attempts at treatment. For example, for classical homeopathy, LM potencies whose dosing frequency, amount of dilution, and number of successions can be adjusted daily in the course of treatment are usually preferred over a single high-potency remedy dosing program.

Precautions

Practitioners who are inexperienced in working with this population or who attempt overly aggressive treatments in each encounter are likely to be harmful to patients. Treatment courses are more often long term and gradual, to avoid injuring the individual.

Manual Manipulation

Patients reported that chiropractic with applied kinesiology, followed by massage and traditional chiropractic, were the more helpful versus harmful forms of manual therapies. Patients with more musculoskeletal symptoms may benefit more directly than those with other manifestations of chemical and food intolerances.

Precautions

No specific precautions are necessary, other than awareness that most patients with MCS will not tolerate scented lotions or oils during massage.

Supplements

In addition to *Lactobacillus acidophilus* (12.7), patients rated other supplements as helpful, with a help-to-harm ratio of at least 5.0, as follows: magnesium supplements (8.6); intravenous magnesium (5.8); vitamin C and E supplements (5.5/5.4); mineral supplements other than calcium, magnesium, or chromium (6.4); and milk thistle seed (5.0). The emerging focus on testing multiple antioxidant therapies to reduce oxidative stress and offset chronic inflammation in many different conditions may be a useful consideration in the population with MCS as well.[14]

Practitioners must often delay introducing supplements into the treatment regimen until the patient has experienced some degree of improved tolerance of exogenous substances from constitutional intervention such as acupuncture or LM potencies of classical homeopathy or from prolonged chemical avoidance and elimination or rotation diet programs.

Dosage

Doses vary widely among patients with MCS. The basic rule of thumb for dosing supplements (or drugs) in this population is to treat as though the patient were geriatric regardless of chronologic age (i.e., impaired in liver or renal clearance of, or idiosyncratically highly sensitive to, most exogenous substances). Thus, the guiding principle is start low, go slow in dosing. Doses at one fourth to one half of usual adult doses often make sense for initial trials.

Precautions

Products made without excipients, colorings, flavorings or other additives, or common food allergens (no wheat, dairy, yeast, soy) are generally better tolerated. Patients tolerate supplements with food colorings and other additives less than they do simpler compounds. Use of a compounding pharmacy to individualize tolerated encapsulation materials (e.g., in clear gelatin capsules) may facilitate the patient's ability to tolerate a given substance.

Detoxification

Experts debate the validity of evidence that patients with MCS as a group all have an elevated body burden of environmental chemicals such as volatile organic compounds or heavy metals. Some proponents of detoxification recommend sauna to foster removal of stored toxicants through the skin and other organs.

Heat stress detoxification induces release of fat-stored toxicants. Sauna procedures are not standardized; temperatures, humidity, and duration of administration all vary greatly among different approaches.

One contemporary sauna-based detoxification program (the Hubbard program) involves multiple components: physical exercise; sauna; nutritional supplementation with niacin, as well as vitamins A, D, C, E, B complex, calcium, magnesium, iron, zinc, manganese, copper, potassium, and iodine; water, salt, and potassium repletion; polyunsaturated oil; calcium and magnesium supplements; and a regular balanced meal and sleep schedule (see Chapter 104, Detoxification).

Precautions

Both liver function and kidney function must be monitored. Extreme heat activates sweating and increases circulation at the skin, as well as increases metabolic rate, water and electrolyte losses, and heart rate.

Pharmaceuticals

Despite some case reports of benefit from antidepressant agents and one specific anticonvulsant drug, gabapentin, controlled studies are not available in this area. The only drug with a patient-rated ratio of help-to-harm ratio of 2.0

was nystatin, taken for its presumptive antifungal properties. Fluconazole (Diflucan) rated 1.9, and ketoconazole (Nizoral) rated 1.2. As noted earlier, most psychopharmacologic drugs caused more harm than benefit from the patients' perspective.

For the subset of patients with MCS who have documented elevated levels of heavy metals, oral chelation medications may be indicated, in consultation with a clinical toxicologist knowledgeable in using these drugs.

Dosage

Try geriatric doses (one fourth to one half of usual adult doses) of any pharmaceutical agents to start. Doses are titrate by patient tolerance.

Precautions

Patients with MCS generally tolerate medications of all types poorly. The help-to-harm ratio ratings are much lower than for many other types of intervention.

Prevention Prescription

- Choose home and work settings away from highly polluted locations, such as away from major highways.
- Avoid routine use of toxic pesticides and herbicides in and around the home and work environment. Seek safer, less toxic alternatives to deal with pests.
- Ventilate indoor areas undergoing remodeling and do not attempt to spend extended periods of time in the areas until remodeling has been completed and the area has been well ventilated for days to weeks (or even months).
- Avoid any indoor environment that becomes contaminated with molds; find alternate housing or workspace immediately.
- Eat organic and chemically less contaminated foods whenever possible, in a diversified diet plan (in terms of botanical food families).
- Drink environmentally uncontaminated, clean water (tested for consistent purity).
- After acute unavoidable exposure to a toxic chemical that could initiate chemical sensitization, take detoxification steps (discard clothing, wash skin thoroughly, spend extended periods in clean open air; use any facilitating agents as recommended by clinical toxicologist [e.g., vitamin C to acidify urine for some toxicants]) and seek treatment with acupuncture or similar constitutional treatment to rebalance system before the sensitized state takes hold.
- Furnish home and office with glass, metal, less treated woods, and natural fabrics such as cotton rather than synthetics.
- Wear untreated or chemically less treated clothing, especially from natural fabrics such as cotton.
- Avoid or minimize regular use of scented products in home and for personal hygiene.

Therapeutic Review

Avoidance or Minimizing of Environmental Chemical Exposures

- Take a comprehensive environmental history and recommend comprehensive avoidance of likely offending substances. B1

Rotation Diet of Less Frequently Eaten Foods

- Eliminate craved foods for at least 3 months; establish a rotation diet for testing and treatment of less frequently eaten foods. B1

Exercise

- Encourage low-impact aerobic exercise, especially for people with overlapping conditions of chronic fatigue syndrome and fibromyalgia. C1

Spiritual and Mind-Body Interventions

- Recommend the specific types (e.g., prayer, meditation, support group, yoga, hypnosis, guided imagery, mindfulness meditation, supportive psychotherapy) on the basis of patient's preferences and personality type (e.g., persons high in trait absorption may prefer meditation over biofeedback). B1

Constitutional Energy-Based Therapy

- Acupuncture, classical homeopathy, Ayurveda, or a specific energy therapy such as healing touch or qi gong may help gradually and gently lessen susceptibility to environmental substances. Try one type of intervention at a time, and allow adequate time in terms of 6 to 12 months for benefits to emerge unless risks predominate. C1

Manual Manipulation Therapy

- Massage, osteopathy, and chiropractic may be helpful adjuncts, especially in patients with musculoskeletal manifestations of environmental intolerances. Avoid the concomitant use of scented lotions and oils. C1

Supplements

- Patients report good help-to-harm ratios from *Lactobacillus acidophilus,* magnesium, vitamins C and E (presumably mixed tocopherols, but no data exist), and milk thistle seed. Consider adding other antioxidant supplements promoting C2

Continued

glutathione production such as vitamin C 250 mg and *N*-acetylcysteine 200 mg once or twice a day. Use a geriatric dosing program of one fourth to one half of the usual adult dose, to start.

Detoxification

- Consider referral for oral chelation therapy for patients with a documented heavy metal body burden.
- Consider sauna detoxification referral with appropriate support of electrolytes and nutrients during procedures.

Pharmaceuticals

- Minimize the use of drugs. Patients rate most psychopharmacologic interventions (antidepressants, anxiolytics) as more harmful than helpful, but some find nystatin or fluconazole (Diflucan) for presumptive systemic *Candida*/yeast infection more helpful than harmful. Use a geriatric dosing program of one fourth to one half of the usual adult dose, to start.

KEY WEB RESOURCES

Chemical Injury Information Network: http://www.ciin.org/index.html	This organization offers patient education on potentially toxic chemicals for people with MCS and includes a library of information on chemical health issues.
Chemical Sensitivity Foundation: http://chemicalsensitivityfoundation.org/	This organization focuses on raising public awareness of MCS.
Create Healthy Homes: http://www.createhealthyhomes.com/index.php	This company offers information on testing your home for substances that could trigger sensitivity and tips on creating a healthy home.
MCS Global Recognition Campaign: http://www.mcs-global.org/	This group has helpful resources regarding high-efficiency particulate air (HEPA) filters, masks, food, and building materials for the sensitive individual.

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Chapter 31

Insulin Resistance and the Metabolic Syndrome

Edward (Lev) Linkner, MD, and Corene Humphreys, ND

The syndrome of insulin resistance (IR) and the metabolic syndrome were coined in the 1980s by Gerald Reaven, MD, an endocrinologist at Stanford Medical School in California. Other names used to describe the condition include syndrome X, prediabetes, dysmetabolic syndrome, and cardiometabolic syndrome.[1]

Metabolic syndrome is associated with a constellation of risk factors for atherosclerosis and type 2 diabetes mellitus (DM), including[2]:

- Elevated fasting glucose
- Elevated triglycerides
- Reduced high-density lipoprotein (HDL) cholesterol
- Hypertension
- Central obesity

When three or more of these risk factors are present, a person qualifies for metabolic syndrome. Following a joint scientific statement by several major organizations, a set of defined cutoff values were determined for all components, with the exception of waist circumference (Table 31-1).[3] According to the National Cholesterol Education Program Adult Treatment Panel III, a waist circumference of more than 40 inches (101 cm) in men and more than 35 inches (89 cm) in women is one of the defining criteria for metabolic syndrome.[4] These values apply to Western cultures only. For information on other ethnic groups, refer to the 2010 article by Lear et al[5] that outlines existing and proposed waist circumference and waist-to-hip ratios. Additional abnormalities include endothelial dysfunction, a procoagulant state, and a proinflammatory state. Table 31-2 provides a list of abnormalities associated with IR.[2,6–8]

IR is the most common clinical finding associated with metabolic syndrome and is thought by many investigators to represent the underlying cause of this condition. IR is defined as a decreased cellular sensitivity to insulin and varies by the cell type, the organ, and the particular metabolic pathway.[1] Research suggests that IR is associated with an inflammatory state and that such activation of inflammatory pathways sustains IR and ultimately leads to the development of metabolic syndrome.[9]

Prevalence

Information on this topic can be found online at expertconsult.com

Pathophysiology

The etiology of IR and metabolic syndrome is multifactorial and encompasses genetics, nutrient deficiencies, and metabolic defects, as well as lifestyle and environmental factors. The pathophysiology includes a complex cascade of events that occurs intracellularly. Insulin is the major hormone whose action is necessary for proper tissue development, growth, and maintenance of glucose homeostasis.[12] It also affects lipid metabolism by increasing lipid synthesis in the liver and the adipocytes. IR has decreased responsiveness in the tissues to appropriate circulating levels of insulin and is the major factor in the pathogenesis of the metabolic syndrome (Fig. 31-1). Therefore, IR in muscle causes reduced glucose disposal from the bloodstream, and IR in liver causes greater glucose production. Impairment of insulin secretion by the pancreatic beta cells is a critical feature that leads to hyperglycemia when the amount of insulin secreted and the timing of the insulin response to glucose are defective.[13]

The incidence of prediabetes and type 2 DM has reached epidemic proportions. According to the 2010 UnitedHealth report, more than half the U.S. population will be afflicted by 2020. Currently, DM is estimated to affect approximately 26 million U.S. residents. Although 67 million U.S. residents are thought to have prediabetes, more than 60 million are not aware that they have the condition. The cost to the public health system if current trends continue is estimated to be 3.23 trillion U.S. dollars. Investigators believe that this financial forecast can be mitigated through diet and lifestyle changes. If such interventions were adopted on a national scale, it could lead to savings of up to 250 billion dollars over the following 10 years.[10]

The increased prevalence of IR, metabolic syndrome, and type 2 DM is thought to stem from the global rise in obesity. Visceral fat is now understood to be involved in numerous metabolic, endocrine, and immune functions, all of which can increase the risk of cardiovascular disorders.[11] Metabolic syndrome is associated with a twofold increased risk of cardiovascular disease and a fourfold risk of developing type 2 DM when compared with people without the condition.[4]

TABLE 31-1. Criteria for Clinical Diagnosis of the Metabolic Syndrome

MEASURE	CATEGORICAL CUT POINTS
Elevated waist circumference	Population- and country-specific definitions
Elevated triglycerides (drug treatment for elevated triglycerides is an alternate indicator)	150 mg/dL or higher
Reduced HDL cholesterol (drug treatment for reduced HDL cholesterol is an alternate indicator)	Less than 40 mg/dL for males and less than 50 mg/dL for females
Elevated blood pressure (drug treatment for elevated blood pressure is an alternate indicator)	Systolic 130 mm Hg or higher and/or diastolic 85 mm Hg or higher
Elevated fasting glucose (drug treatment for elevated glucose is an alternate indicator)	100 mg/dL or higher

From Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation*. 2009;120:1640–1645.
HDL, high-density lipoprotein.

TABLE 31-2. Abnormalities Associated With Insulin Resistance[7,8]

Some Degree of Glucose Intolerance
- Impaired fasting glucose
- Impaired glucose tolerance

Abnormal Uric Acid Metabolism
- ↑ Plasma uric acid concentration
- ↓ Renal uric acid clearance

Dyslipidemia
- ↑ Triglycerides
- ↓ High-density lipoprotein cholesterol
- ↓ Low-density lipoprotein particle diameter
- ↑ Postprandial lipemia

Hemodynamic Changes
- ↑ Sympathetic nervous system activity
- ↑ Renal sodium retention
- ↑ Blood pressure (50% of patients with hypertension have insulin resistance)

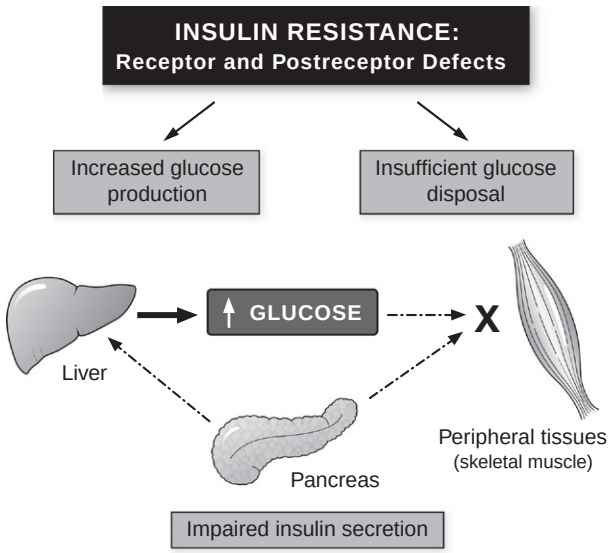
Hemostatic Changes
- ↑ Plasminogen activator inhibitor-1
- ↑ Fibrinogen

Endothelial Dysfunction
- ↑ Mononuclear cell adhesion
- ↑ Plasma concentration of cellular adhesion molecules
- ↑ Plasma concentration of asymmetric dimethyl arginine
- ↓ Endothelial-dependent vasodilatation

Reproductive Disorders
- Polycystic ovarian syndrome
- Low testosterone in men

Data from Corona G, Monami M, Rastrelli G, et al. Testosterone and metabolic syndrome: a meta-analysis study. *J Sex Med*. 2011;8:272–283; and Reaven G. Metabolic syndrome: pathophysiology and implications for management of cardiovascular disease. *Circulation*. 2002;106:286–288.

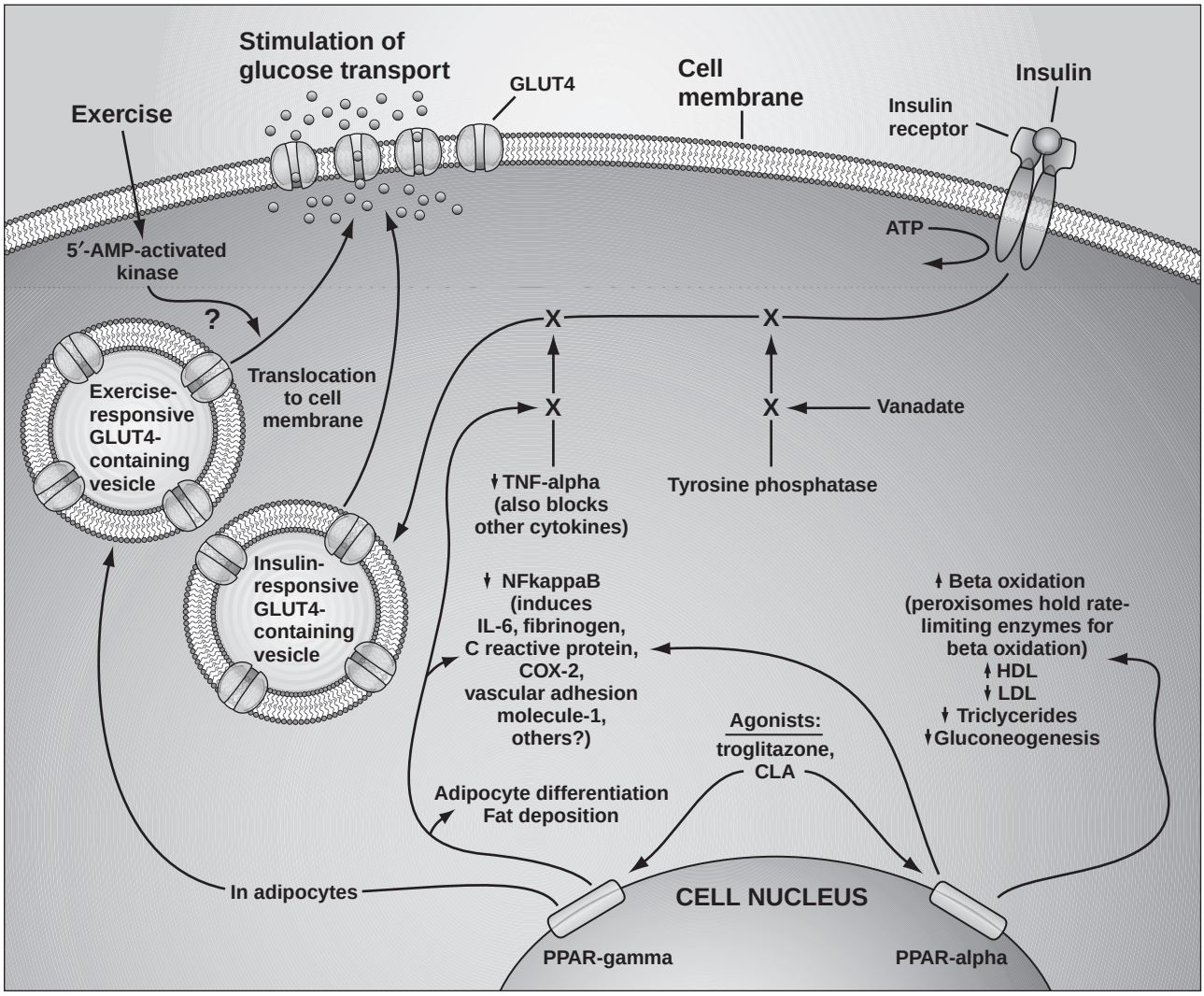
FIGURE 31-1
Sites of the three major pathogenic defects that lead to type 2 diabetes mellitus. Insulin resistance in muscle causes reduced glucose disposal from the bloodstream, and insulin resistance in liver causes greater glucose production. Impairment of insulin secretion by the pancreatic beta cells is a critical feature that leads to hyperglycemia when the amount of insulin secreted and the timing of the insulin response to glucose are defective.



The key targets for insulin actions are predominantly skeletal muscle (75%), cardiac muscle, adipose tissue, and the liver. In the liver, insulin in healthy subjects inhibits the production and release of glucose by blocking gluconeogenesis and glycogenolysis. Defects in glucose transport or in hexokinase II pathways may be the principal impairment of muscle glycogen synthesis. In vivo studies with nuclear magnetic resonance spectroscopy showed that the defect in muscle glycogen synthesis is caused by a defect in muscle glucose itself.[14] The glucose transporter 4 (GLUT4) is the major carrier of glucose into the cell. Stimuli such as insulin and exercise promote GLUT4 activity by embedding it into the cell membrane. Peroxisome proliferator-activator receptors (PPARs) are nuclear hormone receptor transcription factors that cause target genes to be expressed and play an essential role as regulators of insulin action[13] (Fig. 31-2).

Past definitions of IR generally considered it only in terms of the negative effects on glucose metabolism. Such effects include hyperglycemia following a high-carbohydrate meal and overstimulation of the pancreatic beta cells to produce more insulin.

FIGURE 31-2
Insulin signaling pathways. AMP, adenosine monophosphate; ATP, adenosine triphosphate; CLA, conjugated linoleic acid; COX, cyclooxygenase; GLUT, glutamine transporter; HDL, high-density lipoprotein cholesterol; IL, interleukin; LDL, low-density lipoprotein cholesterol; NFkappab, a B cell–specific transcription factor (nuclear factor kappa B); PPAR, peroxisome proliferator-activator receptor; TNF, tumor necrosis factor.



Eventually, these cells are unable to produce enough insulin to maintain normal blood glucose. This inability of the beta cells to produce sufficient insulin generates the transition from IR to type 2 DM.[15] It is crucial to understand that even though the beta cells are dysfunctional, IR still occurs at the cellular level (Fig. 31-3). As further research in the pathophysiology of IR has emerged, the traditional glucocentric view of IR has evolved to include a lipocentric concept as well. Scientists have discovered that abnormalities in fatty acid metabolism cause inappropriate buildup of fat in muscle tissue, the liver, and other organs. Lipotoxicity, with an amplified plasma free fatty acid concentration, is a hallmark of IR. Subsequently, these lipids are associated not only with an abnormal accumulation, but also with increased fat oxidation with further damage to the cell.[16,17]

A likely site of IR may involve the insulin receptor itself. This receptor belongs to the receptor tyrosine kinase family, which also includes molecules such as insulin-like growth factor I receptor (IGF-IR) and the insulin receptor–related receptor (IRR). Therefore, impairment of this insulin-stimulated glucose uptake may also result from the up-regulation of certain proteins that inhibit these signaling pathways. Furthermore, protein-tyrosine phosphatases (PTPases) may also have a role as negative regulators of this insulin-signaling cascade. A combination of down-regulation of some receptors and up-regulation of others may be a key element in the pathophysiology of IR.[13]

A chronic, low-grade inflammatory condition also has a central pathogenetic role in IR. Research has shown that these proinflammatory cytokines and acute-phase reactants are associated with many of the features of metabolic syndrome. These inflammatory cytokines promote IR through site-specific serine phosphorylation of insulin substrate family.[16]

Therefore, IR, mostly in skeletal muscle, manifests as a reduction in insulin-stimulated glycogen synthesis resulting from decreased glucose transport. Once this occurs, lipid accumulates in many cells, most importantly the liver and pancreas, and causes oxidative damage and destructive cellular metabolism. These multiple defects in insulin signaling

FIGURE 31-3
Natural history of diabetes, depicting the rising blood glucose level with progressive beta cell dysfunction.

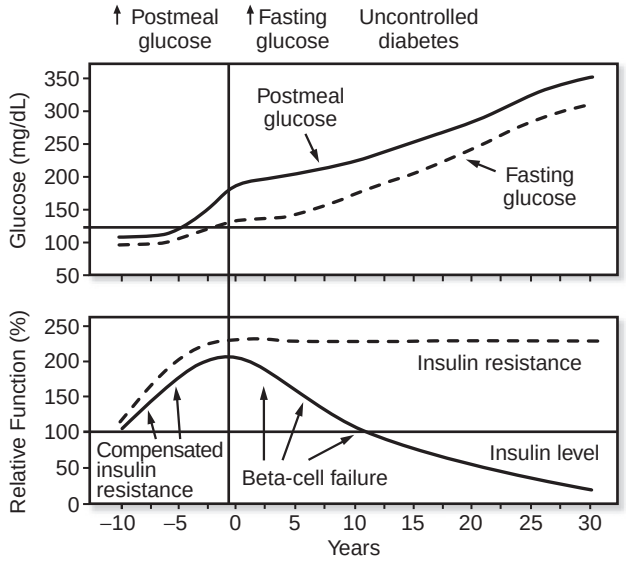


TABLE 31-3. Comorbidities of the Metabolic Syndrome

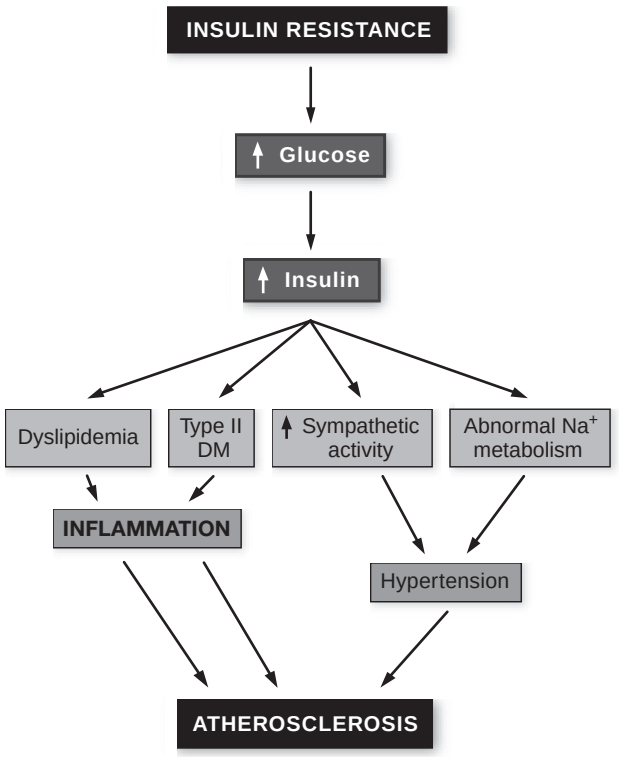
- Alzheimer disease[19]
- Atrial fibrillation[20]
- Baldness[21]
- Cancer
  - Breast cancer[22]
  - Colorectal cancer (men)[23]
  - Endometrial cancer[24]
  - Pancreatic cancer[25]
  - Thyroid cancer[26]
- Cardiovascular risk[27]
- Chronic fatigue syndrome[28]
- Chronic kidney disease[29]
- Cognitive impairment[30]
- Coronary artery disease[31]
- Depression[32]
- Erectile dysfunction[33]
- Gestational diabetes[34]
- Gout[35]
- Hypothyroid and subclinical hypothyroidism[36]
- Kidney stones[37]
- Nonalcoholic fatty liver disease[38]
- Peripheral artery disease[39]
- Psoriasis[40]
- Sleep apnea[41]

are accountable for the downstream impaired glucose metabolism in most tissues[13,18] (Table 31-3[19–41]). These pathways are summarized in Figure 31-4.

Impact of Environmental Toxins on Metabolic Syndrome and Type 2 Diabetes Mellitus

Newer research points to the role of environmental toxins as etiologic factors in the pathogenesis of IR and type 2 DM. The organic compound bisphenol A (BPA) has been found to have an association between IR and type 2 DM. BPA is used to make polycarbonate and epoxy resins and is found primarily in food and beverage containers. BPA has been used commercially since 1957, and more than 90% of U.S. residents are estimated to have detectable levels in their urine. Findings from the 2003 to 2004 National Health and Nutrition Examination Survey (NHANES) revealed an increased prevalence of liver enzyme abnormalities, DM, and cardiovascular disease with higher urinary concentrations of BPA. After adjustment for confounding variables, the investigators noted a 39% ($P < .001$) increased risk of

FIGURE 31-4
Summary of insulin resistance and its effects. DM, diabetes mellitus; NA^+, sodium.



type 2 DM with every 1 standard deviation increase in BPA concentrations in the urine.[42]

Persistent organic pollutants (POPSs) may also play a role in the pathogenesis of metabolic syndrome and type 2 DM. Fatty foods, pesticides, and solvents are the main sources of POPs. Because they are lipophilic, these substances are highly resistant to degradation. Some of the most common POPs found in humans include dioxins, polychlorinated biphenyls, dichlorodiphenyldichloroethylene, trans-nonachlor, hexachlorobenzene, and hexachlorocyclohexanes.[43] In the 1999 to 2002 NHANES report, higher concentrations of POPs (mainly pesticides and herbicides) were associated with an increased prevalence of type 2 DM. Subjects in the highest category (more than the 90th percentile) of exposure, as compared with the lowest category (less than the 25th percentile), had a 38-fold ($P < .001$) increased prevalence of type 2 DM. Obesity was not a risk factor for type 2 DM in people with undetectable levels of POPs.[44] A year later, the same research group found a positive correlation between POPs (in particular organochlorine pesticides) and metabolic syndrome.[45] According to a *Lancet* editorial, the findings from Lee et al may imply that "virtually all of the risk of DM conferred by obesity is attributable to persistent organic pollutants, and that obesity is only a vehicle for such chemicals."[43]

Inorganic arsenic is another environmental toxin that appears to be associated with type 2 DM and metabolic syndrome. The primary sources of inorganic arsenic are contaminated drinking water, from naturally occurring arsenic in rocks and soils, and food.[46] Organic arsenic is predominately derived from the ingestion of fish and shellfish and is considered nontoxic, given that it is excreted unchanged in the urine.

Results from the 2003 to 2004 NHANES cross-sectional study revealed a positive association between increasing levels of total urinary arsenic and type 2 DM. Subjects with type 2 DM had 26% higher total arsenic levels than did subjects without DM. In the fully adjusted model comparing subjects in the 80th versus the 20th percentiles of total urine arsenic (16.5 versus 3.0 g/L), the odds ratio for DM was 3.58.[47] No association between organic arsenic and DM was found. Investigators believe that 8% of the public water systems in the United States exceed the U.S. Environmental Protection Agency's standard of 10 mcg/L for drinking water.[47] Wang et al[48] also found an increased prevalence of metabolic syndrome in subjects with elevated hair arsenic levels. After adjustment for confounding variables, subjects with hair arsenic in the 2nd tertile (0.034 mcg/g) had a statistically significant increased risk of metabolic syndrome (odds ratio, 2.54; 95% confidence interval [CI], 1.20 to 5.39; $P < .015$).

Metabolic syndrome is primarily a phenotypic disorder (92%), as opposed to a genotypic disorder (8%).

Insulin Resistance: A Disease of the Liver or the Pancreas?

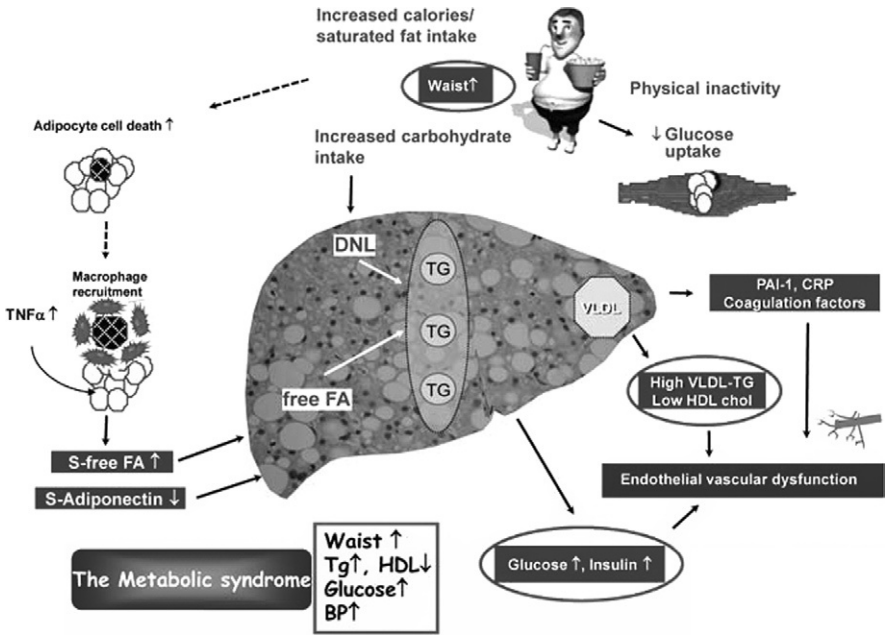
Perhaps the liver can be considered the primary factor that produces IR, and the pancreas is an innocent bystander. This hypothesis was supported in a 2007 article by Lim et al,[49] who found a positive association between body mass index and type 2 DM risk only when serum gamma-glutamyltransferase levels were elevated. Liver inflammation and liver IR caused by toxins, xenobiotics, infection, dietary elements (refined carbohydrates, fructose, and fats), and genetic factors end up flooding the body with harmful inflammatory molecules.

Under normal circumstances, insulin stimulates appropriate glucose uptake into cells, inhibits hepatic gluconeogenesis, and decreases adipose tissue lipolysis. Furthermore, insulinsignaling pathways centrally in the brain increase satiety and thus prevent extra glucose production in the liver. In the patient with IR, the liver facilitates the release of free fatty acids directly from adipose tissue, increases hepatic production of very-low-density lipoproteins, and decreases HDL cholesterol. An increase also occurs in the manufacture of free fatty acids, inflammatory cytokines, and adipokines, thus leading to mitochondrial dysfunction and eventually impaired insulin signaling, increased hepatic gluconeogenesis, and poor glucose uptake in skeletal muscle[50] (Fig. 31-5).

Chronic inflammation associated with visceral obesity produces IR in the liver itself, which is characterized by the manufacture of abnormal adipokines and cytokines, including tumor necrosis factor-alpha (TNF-alpha), interleukin-1 (IL-1), and IL-6, as well as free fatty acids, leptin, and resistin. These inflammatory molecules inhibit insulin signaling in the hepatocytes, with subsequent impaired insulin signaling at the insulin receptor and insulin receptor substrate (IRS) levels.[51] Dysfunction of IRS proteins leads to postprandial hyperglycemia, increased hepatic glucose production, and eventually dysregulated lipid synthesis.[52]

At the same time, proinflammatory mediators from adipose tissue migrate through the bloodstream to the increasingly compromised liver, thus triggering a release of adipokines

FIGURE 31-5
Causes and consequences of insulin resistance and pathogenesis of the metabolic syndrome. BP, blood pressure; CRP, C-reactive protein; DNL, de novo lipogenesis; FA, fatty acid; HDL, high-density lipoprotein cholesterol; PAI-1, plasminogen activator inhibitor-1; TG, triglyceride; TNF, tumor necrosis factor; VLDL, very-low-density lipoprotein cholesterol. (From Yki-Jarvinen H. Liver fat in the pathogenesis of insulin resistance and type 2 diabetes. *Dig Dis.* 2010;28:203–209.)



to all organs.[53] The accumulated adipose deposition in the liver causes a vicious cycle that leads to further liver resistance and the flooding of even more inflammatory mediators.[54]


More information on this topic can be found at expertconsult.com.

Nonalcoholic Fatty Liver Disease

A fatty liver resulting from nonalcoholic causes has become the most common liver disorder seen today. Nonalcoholic fatty liver disease (NAFLD) ranges from steatosis to nonalcoholic steatohepatitis (NASH), which may progress to end-stage cirrhosis.[56]

The fat that goes to the liver is derived from free fatty acids released during lipolysis of visceral adipose tissue. Free fatty acids are the primary sources of hepatic triglycerides that cause NAFLD, whereas hepatic de novo lipogenesis and ingested dietary fat are secondary contributors. Lipid excess, in turn, overwhelms the oxidative capacity of the liver, thus generating reactive oxygen species and increased lipid peroxidation and proinflammatory cytokines.[57] The significant rise in dietary fructose is thought to be one of the major contributors to the obesity epidemic. Fructose is an extremely lipogenic sugar that affects hepatic metabolism by altering gene expression patterns (including liver PPAR-gamma) and increasing portal endotoxin concentrations through Toll-like receptors.[58] Increased fructose intake (e.g., high-fructose corn syrup) is also associated with hepatic IR and fibrosis severity in NASH. High dietary intake of saturated fat is also implicated in NAFLD.[56]

The model that DM can develop as a complication of primary liver disease, called hepatogenous diabetes (HD), makes it apparent that liver dysfunction by itself can promote IR and type 2 DM. Hepatic IR has also been shown to cause defective oxidative and nonoxidative muscle glucose metabolism. NAFLD, alcoholic cirrhosis, chronic viral hepatitis, and hemochromatosis are the most common diseases associated with hepatic IR.[59] A defective insulin response in the liver also adds to the development of clotting disorders resulting from hepatic overexpression of plasminogen activator inhibitor-1 (PAI-1). This up-regulation of PAI-1 expression has been demonstrated in various in vitro and animal liver injury models, as well as in clinical trials.[60,61]

Consolidating all these facts shows that the liver is metaphorically "on fire," spreading inflammation and harmful molecules throughout the body, including the pancreas, which can ultimately lead to beta cell failure. In working with this lipotoxic liver injury hypothesis, a holistic approach must include reducing the burden of fatty transportation to the liver as well as lowering de novo synthesis.[62]

Diagnosis

Metabolic syndrome can be diagnosed with the criteria described in Table 31-1. Outside a research laboratory, the standard of practice is to conduct a 2-hour glucose and insulin tolerance test (GITT), which can easily be ordered through any outpatient laboratory. The protocol is as follows: (1) 2 days of carbohydrate loading, (2) obtaining blood specimens for fasting glucose and insulin measurements, and (3) a 75-g glucose drink. Thereafter, blood specimens for glucose and insulin measurements are obtained (but not always necessarily) at half-hour intervals for the first hour, followed by a final specimen 2 hours later. For most patients, just the fasting and 2-hour measurements are sufficient. Essentially, this is the standard glucose tolerance test (GTT) with concomitant insulin testing. One caveat is that the clinician should make sure that the laboratory used is familiar with diagnostic procedures involving insulin, which is a very unstable hormone in vitro. If only a fasting insulin specimen is obtained, a false-negative diagnosis may be made. Without regular drawing of blood specimens for measurement of insulin, the test is no longer functional. The clinician must learn how the body's insulin serves to manage glucose once it has been ingested. With most laboratories, baseline fasting insulin should normally be less than 15 microunits/mL, and 2 hours following a 75-g glucose load it should be less than 30 microunits/mL.

Even though the most accurate and functional test is the 2-hour GITT, other possibilities for the diagnosis include the following:

- The triglyceride-to-HDL cholesterol ratio: A healthy ratio is less than 2.
- Glycosylated hemoglobin (HbA1c): Values for patients with IR are between 5.7 and 6.4 according to the 2010 American Diabetes Association guidelines.[63]
- Fasting insulin: When this is assessed in isolation, normal values should be less than 15 microunits/mL (140 pmol/L); however, a normal fasting insulin value does not rule out IR. Reference ranges are laboratory specific, so the clinician must check with the clinical laboratory for their specific values. In addition, what is "normal" and what is healthy can be vastly different.

Other markers of importance are elevated high-sensitivity C-reactive protein (hs-CRP), uric acid, small dense low-density lipoprotein cholesterol (sd LDL-C), and inflammatory markers such as IL-6 and IL-8, TNF-alpha, PAF-1, and adiponectin. In working with the hypothesis that IR is a disease of the liver, gamma-glutamyltranspeptidase (GGT) should also be considered because this transaminase enzyme is the most sensitive to detect liver toxicity.

For most clinicians, the 2-hour GITT is the most valuable test for diagnosis and patient education, particularly for normal-weight individuals who may have metabolic syndrome and for women with polycystic ovarian syndrome.

Lifestyle intervention offers the greatest promise for prevention and management of metabolic syndrome.

Integrative Therapy

Lifestyle Factors

Although the cause of IR is multifactorial, lifestyle factors are known to have a profound effect on blood glucose regulation. According to statistics reported in 2009, at least 92% of type 2 DM cases are related to lifestyle choices.[64] Lack of exercise,

Bile acids secreted by the liver also play a role in IR. They produce signaling molecules that are involved with glucose and lipid metabolism. Nuclear hormone receptors such as farnesoid X receptors (FXR), as well as ligands for G-protein–coupled receptors (TGR5), regulate the enterohepatic recycling and biosynthesis of bile acids. These signaling molecules may be the reason that prescription bile acid resins are effective in both IR and type 2 DM.[55]

central adiposity, and a diet high in refined carbohydrates and saturated fats and low in fiber are some of the key lifestyle characteristics associated with IR and type 2 DM. Knowler et al,[65] researchers in the Diabetes Prevention Program, compared lifestyle modification with diet and medication in more than 3000 patients with prediabetes. These investigators assigned patients to three groups who received one of the following: (1) metformin, 850 mg twice daily; (2) a lifestyle modification program with goals of at least 7% weight loss; or (3) placebo. After 3 years of follow-up, the metformin group contained 31% fewer diabetic patients, and the lifestyle modification group contained 58% fewer subjects with DM when compared with the placebo group. Exercise, weight loss, and a healthy diet are the key lifestyle interventions to overcome IR and reducing the risk of type 2 DM.[6]

Exercise

Regular exercise is a vital component of a holistic medical treatment plan and has been shown to reduce the incidence of IR by half.[66] Patients with IR and metabolic syndrome are encouraged to partake in 30 to 60 minutes of moderate-intensity aerobic workouts (e.g., brisk walking) at least five times per week. Resistance training should also be encouraged up to twice weekly.[6] Exercise offers numerous physiologic and mental or emotional benefits. One key benefit is that exercise enhances GLUT4 transporters, which, in turn, helps facilitate glucose entry into the cell while bypassing the need for insulin.[67] This occurs in healthy individuals, as well as those with IR and type 2 DM. Preliminary research also suggests that exercise can improve the inflammatory state associated with IR by reducing proinflammatory chemokines.[68] Other benefits of regular workouts include an increase in lean muscle mass and a reduction in body fat. In addition, this form of therapy promotes a greater sense of well-being and with time becomes an endorphin-inducing experience (see Chapter 88, Writing an Exercise Prescription).

Weight Management

Excessive food consumption, particularly dietary fat and foods with a high glycemic index, is a key pathogenic factor in the pathogenesis of IR and metabolic syndrome.[2] Although most patients with IR are overweight, a small subgroup has a normal body mass index. These people are termed metabolically obese, normal-weight individuals and share the same risks for type 2 DM and cardiovascular disease because they also have increased visceral fat.[69] Increased visceral fat releases an abundance of free fatty acids and sets up a self-perpetuating cycle that increases IR. Affected patients are literally "bathed in cortisol" and can actually look like they have Cushing syndrome. As previously mentioned, this type of fat affects other organs by causing dysfunction and increasing inflammation. Adipose cells are not, as previously believed, just passive depots for energy; rather, they secrete adipokines. Adipose cells also secrete TNF-alpha, adiponectin, resistin, leptin, and other inflammatory substances. These secretions all end up promoting and exacerbating IR. Hu et al[70] found that, irrespective of exercise levels, sedentary behaviors (especially watching television) were associated with significantly elevated risks of visceral adiposity. Studies have shown that even small percentages of weight loss (6% to 10%) can significantly improve IR and reduce the risk of developing type 2 DM by 58%.[65,71]

Nutrition

For the insulin-resistant patient, the dietary focus should be one that is rich in whole grains rather than refined grains, fish and white meat instead of red meat, and plenty of fruits and vegetables along with nuts, legumes, and soy. In 2002, researchers from the Harvard School of Public Health published a set of nutritional guidelines known as the Alternative Healthy Eating Index (AHEI), with an emphasis on the foregoing foods. Results from the Whitehall II Prospective Cohort Study showed that adherence to the AHEI in a middle-aged population was associated with a reversal of metabolic syndrome after 5 years (odds ratio 1.88; 95% CI, 1.04 to 3.41). The effect was more pronounced in subjects with central obesity and elevated serum triglycerides.[72]

The Mediterranean and low glycemic index/load diets are considered the most effective nutritional regimens for metabolic syndrome and insulin resistance.

Mediterranean Diet

Much has been written about the Mediterranean diet, which is rich in vegetables, legumes, soy products, and essential fatty acids. This type of diet is also low in refined carbohydrates and "junk foods." In a randomized trial, Esposito et al[73] compared a Mediterranean diet with a standard diet in 180 patients with metabolic syndrome. After 2 years, only 40 out of 90 subjects on the Mediterranean diet still had features of metabolic syndrome compared with 78 out of 90 participants in the standard diet group. An article by Salas-Salvadó et al[74] also demonstrated a significant reduction in the incidence of type 2 DM with adherence to a Mediterranean diet. In this trial, nondiabetic subjects 55 to 80 years old were randomly assigned to either a low-fat diet (control group), a Mediterranean diet supplemented with 1 L/week of free virgin olive oil, or a Mediterranean diet supplemented with 30 g/day of nuts. All diets were ad libitum. After 4 years, the incidence of type 2 DM was 18% in the control group, 10% in the Mediterranean plus olive oil group, and 11% in the Mediterranean plus nuts group. When pooling the Mediterranean diet groups, the investigators noted a 52% reduction in the incidence of type 2 DM when compared with the control group. Of particular interest was that the reduced incidence occurred in the absence of any significant alterations in body weight or physical activity (see Chapter 86, The Antiinflammatory [Omega-3] Diet).

Low–Glycemic Index Foods

The glycemic index is a system for classifying carbohydrate-containing foods based on the glycemic response. Carbohydrates range from simple sugars to starches and can all be converted to glucose. The rate at which this occurs is governed by the saccharide chain length, with longer chains constituting complex carbohydrates. The glycemic index value for carbohydrates can vary by more than fivefold; starchy foods have a higher glycemic index than nonstarchy foods such as fruits, vegetables, and legumes. Diets that favor high–glycemic index foods are associated with increased 24-hour glucose and insulin levels, as well as higher levels of C-peptide and glycosylated hemoglobin. These effects occur in both nondiabetic and diabetic individuals.[75]

Research has shown the a combination of exercise and a low–glycemic index diet in obese patients with prediabetes not only improves postprandial hyperinsulinemia, but also reduces pancreatic beta cell stress. Conversely, exercise in combination with a high–glycemic index diet impairs the function of beta cells and intestinal K cells despite a similar reduction in weight loss. These findings emphasize the importance of eating low–glycemic index foods that support beta cell preservation, which is a key factor in the prevention of type 2 DM[76] (see Chapter 85, The Glycemic Index/Load).

Fiber

Dietary fiber, either from whole foods or from dietary supplements, is a vital component of the treatment plan for IR and metabolic syndrome. Fiber helps reduce blood pressure and total and LDL cholesterol, and it modifies inflammatory markers. When taken with meals, soluble fibers such as psyllium have been shown to improve postprandial glycemic index and increase insulin sensitivity. Psyllium appears to work by reducing glucose absorption from the intestine and increasing GLUT4 protein expression in muscles. Regular consumption of dietary fiber also promotes weight reduction by enhancing satiety. Oats and barley are other examples of soluble fiber that have U.S. Food and Drug Administration (FDA)–approved health claims for reducing the risk of heart disease.[4]

Cooking Techniques

Information on this topic can be found online at expertconsult.com

Therapeutic Foods

Blueberries are rich in phenolic compounds and anthocyanins and have demonstrated certain health benefits, including improved cognition and reduced cardiovascular and cancer risk. Preliminary research suggests that they may also exhibit antidiabetic effects. In a double-blind placebo-controlled randomized trial, consumption of the equivalent of 2 cups of fresh blueberries a day improved IR in nondiabetic and obese insulin-resistant individuals.[78] Consuming this quantity of blueberries has also been shown to reduce blood pressure, oxidized LDL cholesterol, and lipid peroxidation in patients with metabolic syndrome.[79]

Apple cider vinegar (20 g diluted in 40 g of water) has been shown to reduce postprandial fluxes in glucose and insulin following a carbohydrate-rich meal. The acetic acid in vinegar acts similarly to medications such as acarbose and metformin by suppressing disaccharidase activity and increasing glucose-6-phosphate concentrations in skeletal muscle.[80] Other forms of vinegar such as white vinegar in a vinaigrette sauce can also be used to lower postprandial glucose (20 to 28 g white vinegar mixed with 8 g olive oil).[81,82]

Foods and Substances to Avoid or Consume in Moderation

Table 31-4 outlines a list of foods and substances that should be avoided, given their direct or indirect role in affecting glucose and insulin metabolism.[2,75,83–85]

Research has shown that low to moderate alcohol consumption (one to two standard drinks per day) increases insulin sensitivity and reduces insulin concentrations in nondiabetic postmenopausal women. Regular alcohol consumption in this cohort, however, also increased the steroidogenic hormones dehydroepiandrosterone sulfate (DHEA-S) and estrone sulfate, which are possible risk factors for breast cancer.[86] Alcohol appears to have a U-shaped relationship with metabolic syndrome in which nondrinkers and heavy drinkers have a similar risk profile. This curious finding may in part be explained by an increase in HDL cholesterol observed in heavy drinkers.[87] Given that the potential risks may outweigh the benefits, teetotalers should not be encouraged to start drinking to reduce their risk of developing type 2 DM.

Smoking is a known health hazard and is associated with an increased risk for type 2 DM and should therefore be avoided.[88]

Mind-Body Therapy

Stress Management

Relaxation techniques are valuable in the treatment of IR because they help stabilize adrenal gland function. Stress management lowers both cortisol levels and blood pressure, increases DHEA, improves immunity, and also reduces anxiety and depression. Patients are therefore less likely to abuse their bodies and tend to feel better about themselves.

TABLE 31-4. Foods to Avoid With Insulin Resistance and the Metabolic Syndrome

FOOD/SUBSTANCE	METABOLIC EFFECT
Refined starchy foods	Instant rice, potatoes, white breads, pasta, cereals such as Rice Krispies and corn flakes, corn chips, and canned foods have a high glycemic index and are known to impair glucose metabolism and increase insulin secretion.[75]
"Fast foods"	These foods are calorie rich, given their high sugar and fat content, and contribute to weight gain, insulin resistance, and hyperlipidemia.[2]
Sugar-sweetened beverages	Soft drinks, fruit drinks, iced tea, and energy and vitamin water drinks are often rich in fructose corn syrup and are associated with weight gain and an increased risk of insulin resistance and type 2 DM.[83] Consuming one to two drinks/day is associated with a 26% increased risk of developing type 2 DM.[84]
Artificial sweeteners	Artificial sweeteners such as aspartame, saccharin, and sucralose are associated with obesity and a twofold increased risk of type 2 DM.[85]

DM, diabetes mellitus.

How we cook our foods can also have an impact on biochemical markers associated with IR and metabolic syndrome. High-heat–treated foods typically found in the Western diet generate harmful compounds known as Maillard reaction products. These compounds have been found to reduce insulin sensitivity and increase plasma cholesterol and triglycerides.[77] Mild cooking techniques such as steaming, poaching, and stewing are recommended instead of roasting, barbecuing, broiling, or frying.

A prescription with an individualized approach involving meditation, relaxation techniques, prayer, visualization, and other stress reducing modalities is indicated.[89]

Stress management and exercise are key therapeutic components.

Depression

A 2009 article by Takeuchi et al[90] suggested that metabolic syndrome may be a predictive factor for the development of depression, but not anxiety. Multivariate analysis indicated that an increase in waist circumference was the main factor influencing the relationship between metabolic syndrome and new-onset depression. Skilton et al[32] also found a positive association between depression (versus anxiety) and metabolic syndrome. In light of their research, these investigators advised screening for depression in patients with this condition.

Supplements

Numerous nutritional supplements have demonstrated a beneficial effect on glucose and insulin metabolism. In general, all adults should take a multivitamin to offset any dietary deficiencies and reduce the risk of developing chronic diseases such as cardiovascular disease. Accordingly, patients with IR and metabolic syndrome should include a multivitamin as a core component of their health regimen. Certain nutrients including antioxidants may be required in therapeutic doses to ensure a physiologic effect in the management of IR and metabolic syndrome.[91–93] Supplementation with the following nutraceuticals should be guided by the patient's overall health, dietary habits, laboratory parameters, and their current IR status.

Vitamin B_6

A deficiency in vitamin B_6 is associated with a decrease in several important enzymes that contribute to gluconeogenesis (the generation of glucose from nonsugar substrates).[94] In patients taking the drug metformin for polycystic ovarian syndrome, vitamin B_6 and folate counteracted the rise in homocysteine levels.[95]

Dosage

The dose is 50 to 100 mg/day.[96]

Precautions

None are noted at the recommended dose.

Folic Acid

A combination of IR and elevated plasma homocysteine levels are associated with cardiovascular risk factors. Research has shown that this patient cohort also has disturbed or reduced folate levels, which are thought to lead to the progression of hypertension.[97] Patients heterozygous or homozygous positive for the methylenetetrahydrofolate reductase single nucleotide polymorphism (MTHFR C677T) would benefit from taking L-5-methyltetrahydrofolate rather than folic acid.

Dosage

The dose is 500 mcg/day.[96]

Precautions

None are noted. High doses of folic acid administered to patients with a concomitant vitamin B_{12} deficiency may correct megaloblastic anemia but increase the risk of irreversible neurologic damage.[98]

Vitamin B_{12}

In patients with metabolic syndrome, taking folate and vitamin B_{12} decreased IR and improved endothelial function. Homocysteine levels also improved with these nutrients, thus affirming their beneficial effect on cardiovascular disease risk factors.[99] Because metformin has been shown to impair vitamin B_{12} status, practitioners should assess and monitor B_{12} levels if patients are taking this medication.[100]

Dosage

Recommended dose is 500 mcg/day.[101]

Precautions

None are noted at the dose recommended.

Vitamin C

Individuals with metabolic syndrome have been found to have significantly lower levels of vitamin C.[102] A deficiency of vitamin C is thought to be associated with a greater resistance to fat mass loss.[103] High doses of vitamin C have also been found to reverse the adverse effects of free fatty acids on vascular function.[104,105]

Dosage

Vitamin C 1000 to 2000 mg/day.[106]

Precautions

Take with food to reduce the risk of diarrhea.

Vitamin D

Vitamin D is an important fat-soluble vitamin that has been proven to increase the survival rate of patients with cardiovascular disease and type 2 DM. In a study of young adults, an inverse relationship among blood glucose, IR, and serum 25-hydroxy (OH) vitamin D was demonstrated.[107] Other research has confirmed that serum 25(OH) D levels positively correlate with insulin sensitivity.[108,109] Ford et al[110] also found a significant inverse relationship among abdominal obesity, elevated triglycerides, and hyperglycemia.

Dosage

Dose is 300 to 2000 units/day.[111] Dosing can also be guided by the season of the year and serum 25(OH) D levels (the preferred range is 30 to 60 ng/mL or 75 to 150 nmol/L).[112]

Precautions

Monitor serum calcium levels in patients taking thiazide diuretics and vitamin D supplements because this combination may cause hypercalcemia.[113]

Biotin

High-dose biotin is considered an important vitamin for preventing and treating IR and obesity.[114] When given in quantities 10 times greater than the physiologic range, it directly activates an enzyme that mimics the action of nitric oxide. One of the ways biotin improves glycemic control is by reducing excessive hepatic glucose output.[115]

Dosage

The dose is 3 mg three times daily.[114]

Precautions

None are known.

Chromium

The trace element chromium is an important nutrient that helps prevent IR and dyslipidemia associated with obesity.[116] Chromium also appears to be important for skeletal muscle IR.[115] This mineral has also been found to improve insulin sensitivity and increase glucose disposal in women with polycystic ovarian syndrome.[117]

Dosage

The dose is 200 to 1000 mcg/day.[117–119]

Precautions

Take half an hour before or 3 to 4 hours after thyroid or levothyroxine medication because chromium may bind to this medication and reduce absorption.[120]

Magnesium

Magnesium within the cell plays a vital role in regulating insulin action, insulin-mediated glucose uptake, and vascular tone.[121] Higher intakes of magnesium are associated with increased insulin sensitivity and a reduced risk of developing metabolic syndrome.[122,123] Conversely, low dietary intake of magnesium is associated with an increased risk of developing IR and type 2 DM.[124,125]

Dosage

A dose of 100 mg/day is recommended to reduce the risk of developing type 2 DM.[126] A dose of 2500 mg/day improves insulin sensitivity.[127] Dosing can also be guided by assessing red blood cell magnesium levels.

Precautions

High-dose magnesium may cause gastric irritation and diarrhea.[128]

Zinc

Although research on zinc has largely focused on type 2 DM, supplementation should be considered in patients with IR and metabolic syndrome, given the role of zinc in insulin production and metabolism. One of the mechanisms by which zinc exerts such valuable effects lies in its antioxidant capacity.[129] Two randomized controlled trials demonstrated a reduction in fasting glucose and insulin, as well as other markers of IR, in obese prepubescent children following zinc supplementation.[130,131]

Dosage

The dose is 20 mg/day.[131]

Precautions

None are noted at the dose recommended.

Alpha-Lipoic Acid

Alpha-lipoic acid (ALA) is a potent antioxidant that is considered important for the treatment of metabolic syndrome. The mechanisms by which ALA exerts its effects include protection against oxidative stress-induced IR, inhibition of hepatic gluconeogenesis, and increased peripheral glucose use.[132] ALA, either alone or in combination with the angiotensin receptor blocker irbesartan, has been shown to improve endothelial function and reduce IL-6 and PAF-1 in subjects with metabolic syndrome.[133]

Dosage

The dose is 100 mg three times daily before each meal.[133]

Precautions

None are reported.

Coenzyme Q10

Coenzyme Q10 (CoQ10) is required for adenosine triphosphate (ATP) synthesis and is therefore important for the conversion of carbohydrates to energy.[134] By enhancing the functioning of the mitochondrial enzyme glycerol-3-phosphate dehydrogenase, CoQ10 helps with glycemic control.[115] A study by Singh et al[135] demonstrated a reduction in systolic and diastolic blood pressure, fasting and 2-hour plasma insulin, and triglycerides. Markers of oxidation such as lipid peroxides, malondialdehyde, and diene conjugates were also lowered, thus indicating a decrease in oxidative stress.[135] Many patients with IR and metabolic syndrome are treated with statin drugs, and these medications have been found to lower plasma and tissue levels of CoQ10.[136]

Dosage

Give 120 mg/day (or 60 mg twice daily).[135]

Precautions

CoQ10 may decrease the anticoagulant effect of warfarin. Monitor clotting time regularly, particularly within the first 2 weeks of taking CoQ10.[137]

Acetyl-L-Carnitine

The amino acid carnitine plays an important role in energy metabolism, largely through its effects on fatty acid oxidation. A deficiency has been associated with various conditions, including obesity and type 2 DM.[138] When fatty acids are unable to enter the cell, triglycerides accumulate in the cytosol, an important factor in the pathogenesis of IR. Administering acetyl-L-carnitine to patients with type 2 DM and to healthy persons improves insulin-mediated glucose disposal.[139]

Dosage

The dose is 1 to 2 g/day away from food.[140]

Precautions

None are documented at the dose recommended.[140]

Omega-3 Fatty Acids

Long-term supplementation with omega-3 fatty acids has been shown to improve postprandial lipoprotein metabolism by decreasing triglycerides and increasing HDL-cholesterol.[2]

Dosage
The dose is 1 g/day of eicosapentaenoic acid and docosahexaenoic acid (EPA and DHA). For patients with elevated triglycerides, it is 2 to 4 g/day of EPA and DHA.[141]

Precautions
None are known at the dose recommended.

Botanicals

Ginseng (Panax ginseng)
The herb *Panax ginseng* has numerous medicinal effects, including antiinflammatory and antioxidant properties, and it has also been used in the treatment of type 2 DM. Ginseng is thought to control and prevent type 2 DM by increasing insulin sensitivity and enhancing insulin secretion.[142] Another proposed mechanism of action lies in the herb's ability to modulate glucose activity by increasing GLUT4 transporter systems.[143]

Dosage
Recommended dose is 100 to 200 mg/day (standardized to contain 4% ginsenosides).[144,145]

Precautions
Ginseng may decrease the effectiveness of warfarin.[146]

Green Tea (Camellia sinensis)
Green tea appears to have a beneficial effect on glucose tolerance and insulin sensitivity.[147] Animal studies suggested that green tea is able to reduce IR by enhancing glucose transport systems, namely GLUT4.[148] Green tea may also support body composition by stimulating thermogenesis and enhancing fat oxidation.[149]

Dosage
Green tea extract (270 mg/day of epigallocatechin gallate)[149]

Precautions
Green tea may decrease the effectiveness of warfarin.[150] Do not combine with ephedrine or other stimulants.[151]

Milk Thistle (Silybum marianum)
Milk thistle is considered an important herb in the treatment of hepatic disorders and also appears to play a beneficial role in glucose and lipid metabolism. Liver dysfunction impairs the efficiency of postprandial hepatic glucose storage and is thought to trigger hyperinsulinemia related to reduced liver clearance of insulin.[152]

Dosage
Give 420 to 600 mg/day (standardized to contain 70% to 80% silymarin).[153,154]

Precautions
Exercise caution in patients taking drugs metabolized by cytochrome P-450 isoenzymes CYP3A4 and CYP2C9 because the silibinin content of milk thistle may inhibit these hepatic isoenzymes.[155]

Pharmaceuticals

Although lifestyle modification is the preferred way of managing IR and metabolic syndrome, at times prescription drugs are necessary. The problem with such medications is that they do not correct the underlying nutrient deficiencies. Medications often merely "treat" the results of the disease; that is, they reduce high serum lipid or glucose levels or high blood pressure, but they do not treat the overall patient. Although no FDA-approved prescription drugs are available for IR, many of the medications used for type 2 DM have been researched for their use with metabolic syndrome. Some of these medications may not specifically address IR or may have unhealthy side effects (e.g., 3-hydroxy-3-methyl-glutaryl-coenzyme A [HMG-CoA] reductase inhibitors [statins] lower serum CoQ10; metformin reduces folic acid and vitamin B_{12} levels and may increase homocysteine levels). In addition, drugs do not correct diet and lifestyle issues. Pharmaceuticals can be an appropriate complementary option, when they are needed.

The most commonly used medications for type 2 DM are insulin sensitizers such as metformin, which reduce glucose output from the liver, and thiazolidinediones, which act as PPAR agonists and support glucose uptake in cells. Alpha-glucosidase inhibitors reduce the intestinal absorption of carbohydrates and thus lower postprandial hyperglycemia. Orlistat, an inhibitor of intestinal lipase that reduces the absorption of dietary fat and is usually used for treatment of obesity, has been shown to improve glucose in obese nondiabetic patients. Newer agents that therapeutically target glucagon-like polypeptide 1 (GLP-1) and gastric inhibitory polypeptide (GIP) are available. Injectable GLP-1 agonists (exenatide and liraglutide) aid glycemic control and often produce weight loss. Dipeptidyl peptidase (DPP-4) inhibitors (sitagliptin and saxagliptin) have not yet been studied in IR.[156]

Colesevelam hydrochloride, a bile acid sequestrant, is used for both hyperlipidemia and type 2 DM. A small study also showed it was helpful for impaired fasting glucose.[157] Commonly prescribed statins may worsen insulin sensitivity and can increase the risk of type 2 DM.[158]

Antihypertensive medications such as angiotensin-converting enzyme inhibitors or angiotensin receptor blockers may mildly reduce IR. The beta blocker nebivolol may actually help decrease IR by its ability to increase nitric oxide production. Most other beta blockers make IR worse. Furthermore, other medications, especially antipsychotic drugs, decrease insulin sensitivity.[156]

A quick-release formulation of bromocriptine mesylate (Cycloset) was approved by the FDA for treatment of type 2 DM. This drug is a dopamine agonist, which acts centrally to reduce resistance to insulin-mediated suppression of hepatic glucose output and tissue glucose disposal. Bromocriptine is also thought to improve glucose tolerance and IR and modulate neurotransmitter actions in the brain by reducing neuropeptide Y and norepinephrine levels.[159]

Some clinicians use one or a combination of prescription medications along with therapeutic lifestyle changes. As the patient improves, these medications can be eliminated.

Surgery

Of course the most dramatic, but at times successful, option is bariatric surgery.[156]

Prevention Prescription

- Maintain a healthy body weight. People with an increase in visceral (truncal) fat are at higher risk.
- Exercise 30 minutes/day most days of the week for patients with appropriate weight and 60 minutes/day most days of the week for those needing to lose weight.
- Manage stress and increase the relaxation (parasympathetic) response.
- Follow a low–glycemic load, Mediterranean-type diet.
- Take a high-quality multivitamin that includes minerals and B-group vitamins.

Therapeutic Review

Laboratory Evaluation

- 2-Hour glucose and insulin tolerance test to measure glucose and insulin levels after fasting and 2 hours after a glucose load
- Serum lipid measurements (looking for increased triglyceride level, decrease in high-density lipoprotein cholesterol level, and normal or slightly increased low-density lipoprotein cholesterol level)
- Fasting glucose higher than 100 mg/dL
- High-sensitivity C-reactive protein, a marker for inflammation, and gamma-glutamyltranspeptidase, a marker of liver toxicity

Lifestyle

- Encourage an exercise routine that consists of moderate intensity workouts and resistance training. A1
- Encourage goals to achieve appropriate weight. A1
- Encourage the patient to stop using nicotine-containing products. B1

Nutrition

- Low-carbohydrate, Mediterranean-type diet with a focus on low–glycemic index foods A1
- High-fiber diet including soluble fiber such as psyllium, oats, and barley B1
- Decreased consumption of red meat and fried foods B1

Mind-Body Therapy

- Encourage lifestyle choices to reduce stress and anxiety. Recommend a relaxation technique fitted for the individual. B1
- *Note:* The preceding recommendations highly outweigh those that follow for the treatment of insulin resistance and metabolic syndrome.

Supplements

- High-quality multivitamin with minerals and B-group vitamins B1
- Omega-3 fatty acids (eicosapentaenoic acid and docosahexaenoic acid): 1 to 4 g per day to reduce inflammation, blood pressure, and triglyceride levels B1
- Chromium picolinate: 200 to 1000 mcg/day B2
- Vitamin C: 1000 to 2000 mg/day B2
- Vitamin D: 300 to 2000 units/day B1
- Alpha-lipoic acid: 100 to 300 mg/day B1
- Coenzyme Q10: 60 to 120 mg/day B2
- High-risk individuals may need to consider additional supplementation as outlined in the body of the text.

Botanicals

- American ginseng: 100 to 200 mg/day B2
- Milk thistle: 420 to 600 mg/day B2

Pharmaceuticals

- Metformin: 500 to 2500 mg each morning or twice daily A2
- Pioglitazone: 15 to 45 mg/day A2

KEY WEB RESOURCES

National Diabetes Information Clearinghouse (NDIC): http://diabetes.niddk.nih.gov/dm/pubs/insulinresistance	This NDIC link contains information on IR and prediabetes.
myhealthywaist.org: http://www.myhealthywaist.org	This Web site offers education and tools about the importance of reducing large waist lines.
Lipids Online: http://www.lipidsonline.org	This Web site provides educational resources on lipids and health.
Calorie calculator: http://www.mayoclinic.com/health/calorie-calculator/NU00598	This calorie-needs calculator is provided by the Mayo Clinic.
Fitday: http://www.fitday.com	This Web site provides online education, tools, and record keeping to help meet weight loss and exercise goals.

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Chapter 32

Type 2 Diabetes

Richard Nahas, MD

Pathophysiology and Epidemiology

We are in the midst of a worldwide diabetes epidemic. World Health Organization estimates of the number of people with type 2 diabetes mellitus (DM) worldwide were 30 million in 1985, 171 million in 2000, and 220 million in 2009.[1] This number represents approximately 5% of the global adult population and is predicted to continue increasing for the foreseeable future. A more rapid increase appears to be occurring in the developing world and is attributed to rising obesity rates, sedentary lifestyles, aging of the population, and improved survival of people with the disease.

The prevalence of diabetes is approximately twice as high in blacks[2] and up to five times higher among indigenous populations in Australia,[3] Canada,[4] and the United States.[5] This prevalence may reflect genetic differences, more rapid changes in nutrition and lifestyle patterns, increased prevalence of vitamin D deficiency (see later), or other unknown factors.

The insulin resistance seen in type 2 DM is just one consequence of a chronic systemic inflammatory response, but type 2 DM is still diagnosed and treated based on derangements in glucose metabolism. This complex process involves multiple transporters, receptors, enzymes, and messenger molecules, which are regulated by hormones, cytokines, and neurotransmitters in multiple tissues. Providing a complete overview of glucose metabolism and the derangements seen in type 2 DM is beyond the scope of this chapter, but some key aspects are relevant to integrative treatment and are reviewed.

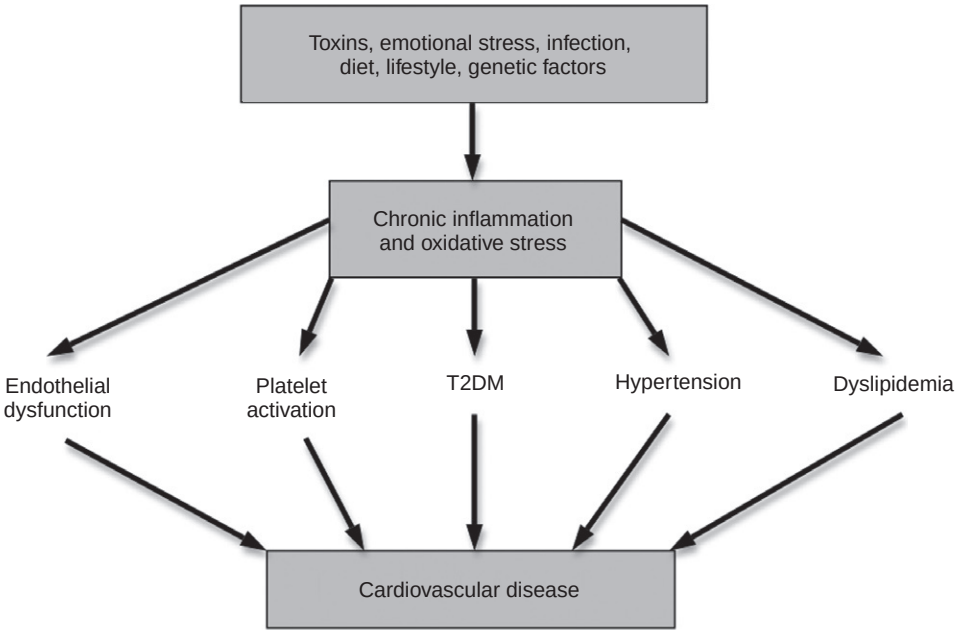
The process begins with carbohydrate intake, in the form of simple sugars or starches. This intake is based on feelings of hunger, satiety, cravings, and other signals from the brain, which are influenced by cholecystokinin, leptin, ghrelin, glucagon-like peptide, and other hormones. These brain signals are affected by many factors, including life stress, mood, thirst, circadian rhythms, physical activity, family eating patterns, and even social networks.[6] Overeating and other modern eating habits appear closely linked to the twin epidemics of obesity and type 2 DM, but they can be addressed only with an integrated approach to public health that considers social, economic, and educational policies.

Carbohydrates are long-chain molecules that are cleaved by pancreatic and brush border enzymes in the digestive tract, thus yielding glucose and other sugars. The amount of insulin released by beta cells in pancreatic islets is based on glucose entry into the bloodstream. Rapid sustained rises in serum glucose levels trigger greater insulin release, which has proinflammatory effects throughout the body. Changes in serum glucose and insulin levels after carbohydrate ingestion have been measured for hundreds of different foods, and these changes form the basis of the glycemic index and glycemic load (see Chapter 85, The Glycemic Index/Load).

The primary defect that is most widely associated with type 2 DM is insulin resistance. When insulin binds to the insulin receptor on the cell surface, a cascade of changes occurs to make glucose available for adenosine triphosphate (ATP) generation in mitochondria and shift the balance between glucose and free fatty acids as a fuel source for this process. The best-known action of insulin is to allow glucose entry into cells by triggering translocation of the glucose transporter 4 (GLUT4) from the cytoplasm to the cell membrane. Insulin also decreases protein breakdown and gluconeogenesis in the liver, increases fatty acid uptake and triglyceride synthesis in fat cells, regulates many cytokines and other hormones, activates numerous enzymes, and influences DNA transcription, vascular tone, and brain chemistry.

Extensive research has been undertaken to identify the causes of insulin resistance seen in type 2 DM. Several lines of evidence suggest that a more integrative approach to understanding this process is required (Fig. 32-1). As mentioned earlier, insulin resistance appears to be just one component of a complex systemic derangement in normal physiology that is referred to as chronic inflammation. C-reactive protein has emerged as a key marker of inflammation that is

FIGURE 32-1
Pathophysiology of type 2 diabetes mellitus and inflammatory disorders. T2DM, type 2 diabetes mellitus.



strongly correlated with type 2 DM.[7] Elevated levels of proinflammatory cytokines such as tumor necrosis factor-alpha, interleukin-1 (IL-1), IL-6, IL-8, and interferon-gamma promote a low-grade acute-phase response, including a procoagulant state, platelet activation, vascular adhesion, and other factors that result in endothelial dysfunction. Many of these important mediators are produced by adipocytes and macrophages in adipose tissue, and this may partly explain the link between obesity and type 2 DM.

Insulin resistance is just one part of the *metabolic syndrome*. Environmental toxins, glycemic load, obesity, emotional factors, certain infections, and other sources of oxidative stress and chronic inflammation likely play a role in the epidemic of type 2 diabetes mellitus.

A key counterregulatory mediator that appears to down-regulate this cascade and protect against diabetes is adiponectin. This collagen-like molecule has pleiotropic effects in multiple tissues. It preserves beta cell function and stimulates insulin secretion in the pancreas, suppresses gluconeogenesis and enhances free fatty acid oxidation in the liver, and increases glucose uptake and fatty acid oxidation in skeletal muscle. Inflammation appears to lead to decreased transcription of this hormone in adipocytes themselves.

Insulin resistance and hyperglycemia appear to be largely responsible for the well-known microvascular complications of retinopathy, neuropathy, and nephropathy seen in type 2 DM. This is why intensive glycemic control slows the progression of microvascular complications. Unfortunately, several large trials demonstrated that intensive glycemic control does not prevent cardiovascular complications or mortality in type 2 DM.[8] These results call this intensive treatment approach into question. The reason may be that chronic inflammation is a more important therapeutic target than are the resulting insulin resistance and dysglycemia. Most patients with type 2 DM die of these cardiovascular complications,[9] so this is a potentially paradigm-shifting distinction.

An important principle of integrative physiology is that inflammation has many potential causes. One cause is infection. Type 2 DM is well known to be associated with periodontal disease, but this condition has always been assumed to be a vascular complication of the diabetic state. In fact, the relationship is more complex, with clear evidence from the National Health and Nutrition Examination Survey (NHANES) database that periodontal disease is a risk factor for subsequent diabetes.[10] Even more intriguing is evidence that surgical and medical treatment of periodontitis raises serum adiponectin levels[11] and improves long-term glycemic control.[12] The chronic inflammation seen in viral hepatitis also increases the risk of type 2 DM.[13] The fascinating possibility of a bidirectional relationship between inflammation and infection is suggested by the reduced risk of infection seen in users of antiinflammatory statin drugs.[14] Growing evidence suggests that autoimmune diabetes (type 1 DM) may be triggered by various infectious organisms; this evidence is unrelated but worthy of mention.

Environmental pollutants can also trigger inflammation, and their role in type 2 DM is receiving increasing attention. Chronic exposure to inorganic arsenic in drinking water has been associated with type 2 DM in several countries, and in a study of 788 adults from the U.S.-based NHANES study, the prevalence of type 2 DM was 3.58 times higher among those with urine arsenic levels in the 80th percentile than in the 20th percentile.[15] The same study population also had a striking association

between type 2 DM and levels of organochlorine pesticides, which was more pronounced in obese individuals.[16] This finding should come as no surprise when one considers that the complex signaling cascade triggered by insulin depends on many conformation-dependent enzymes with the potential to interact with these pollutants. Air pollution is also strongly associated with type 2 DM prevalence in U.S. cities, and the harmful cardiovascular effects of airborne particulate matter are greater in people with type 2 DM.[17] Smoking is another clear toxic source whose impact on type 2 DM risk and progression almost goes without saying. Smokers are at 44% increased risk of type 2 DM, and heavy smokers are at even greater risk.[18]

Emotional stress and inflammation are also closely linked. In the National Comorbidity Survey, childhood neglect was associated with a higher risk of type 2 DM, more so in women.[19] In a Dutch study of 2262 patients, those in the top quintile of self-reported stress were 60% more likely to have undiagnosed type 2 DM.[20] In the Copenhagen City Heart study, men with perceived stress at baseline were also more likely to develop subsequent type 2 DM (odds ratio [OR], 2.36; 95% confidence interval [CI], 1.22 to 4.59).[21] In a review of 13 prospective studies involving 6916 patients, depressed patients were 60% more likely to develop type 2 DM (95% CI, 1.37 to 1.88).[22] Emotional stress can affect insulin, cortisol, glucagon, and other hormones and several proinflammatory cytokines. The role of the renin-angiotensin system in the development and progression of type 2 DM (see the later discussion of angiotensin-converting enzyme [ACE] inhibitors) adds another potential mechanism linking emotional stress to this disease.

Although the increasing prevalence of type 2 DM clearly points to environmental and lifestyle factors, genetic factors may help identify those individuals most at risk. Earlier twin studies overestimated the genetic contribution to type 2 DM because they did not control for shared intrauterine factors. The sheer number of associations reported makes it unlikely that any one association will prove highly relevant to clinical care, but this research will certainly broaden our understanding of the complex set of factors that may contribute to this disease.

Integrative Therapy

Lifestyle Interventions

Most integrative practitioners would agree that type 2 DM treatment plans should include interventions that help patients improve their diet and get regular exercise. In the Action for HEAlth in Diabetes (AHEAD) trial, 5145 overweight adults with type 2 DM were randomized to an intensive lifestyle intervention or a minimal control intervention.[23] The objective was a 7% reduction in body weight, achieved by a diet containing less than 30% of total calories from fat (10% saturated fat), at least 15% of calories from protein, portion control supplemented with liquid meals, and 175 minutes of physical activity per week. Long-term follow-up was twice per month (one visit and one phone call), and regular group sessions were available. After 4 years, the intensive lifestyle group maintained a 6% weight loss and improved their fitness level, glycemic control (glycosylated hemoglobin [HbA1c] 0.3%), blood pressure, and lipid parameters. Further follow-up will reveal whether this program also improved cardiovascular outcomes.

This kind of comprehensive lifestyle intervention also appears to prevent type 2 DM. The Diabetes Prevention Program assigned 3234 adults with prediabetes (impaired fasting glucose or impaired glucose tolerance) to an intensive lifestyle intervention, metformin, or minimal intervention control.[24] Weight loss was also the goal in this trial; the diet was similar, and the target for physical activity was 150 minutes per week. After 2.8 years of median follow-up, the lifestyle group was 58% less likely than the control group to have type 2 DM. A 10-year follow-up study reported that the lifestyle group was 34% less likely to have type 2 DM; it was 18% less likely in the metformin group.[25]

Exercise

Exercise undoubtedly improves many disease outcomes, and type 2 DM is no exception. The reduction in HbA1c that was reported in a meta-analysis was 0.6%.[26] The question is not whether diabetic patients should exercise, but rather how much—and how to convince people to do it (see Chapter 99, Motivational Interviewing Techniques). One of the main target tissues for insulin is skeletal muscle, so resistance training would be expected to improve glycemic control. Systematic reviews suggest that little difference exists between resistance training and aerobic exercise in terms of HbA1c and glycemic control.[27] Even tai chi helps. This was reported in a 6-month trial involving 99 patients with type 2 DM that included only patients who completed at least 80% of the twice-weekly sessions.[28] Compliance is an issue with any form of exercise, and this may explain why two other tai chi trials reported no benefit.[29,30]

How much exercise is enough? More appears to be better. A dose–response effect has been reported in perhaps the most important outcome measure of all, which is death from any cause.[31] The only real risk that must be considered by diabetic patients just beginning to exercise is hypoglycemia. Close observation is important at the start of any exercise program, and medication doses will likely need to be lowered. Patients should be advised to keep simple sugars within reach during and after exercise (see Chapter 88, Writing an Exercise Prescription).

Behavior Change

Most clinicians have a clear understanding of the importance of diet and lifestyle in the management of type 2 DM and other metabolic signs of chronic inflammation. The difficulty is not in knowing what changes need to be made; making those changes is the hard part. Overall, the evidence on behavior change and lifestyle modification is not encouraging, but this should not deter motivated practitioners or their patients.

One tool I use is to ask patients to record their blood glucose after every single meal for an initial 2- to 3-week period. This powerful educational tool shows them how carbohydrate loads and exercise habits affect glucose levels. Other practitioners have pearls they use to motivate and educate patients. Referring patients to dietitians, personal trainers, psychologists, educators, mindfulness practices, videos, books, Internet-based reminders, and other resources in your community may be appropriate.

Do not make the mistake of assuming that your patients cannot or will not change. Although change is definitely the patients' responsibility, providing thoughtful support and encouragement is ours. A stage-based approach is usually more effective, as described in the Stages of Change model developed by Prochaska et al.[32] An additional tool that is often neglected by busy clinicians is to try and be a role model for patients. Advice about exercise and proper nutrition is much more convincing when it comes from a person who is active and healthy.

Nutrition

Carbohydrates, Glycemic Index, and Glycemic Load

Lifestyle programs may achieve better results in the future as they shift their focus to low-glycemic diets. In a Cochrane Review of 11 trials involving 402 patients with type 2 DM, low–glycemic index diets reduced HbA1c by 0.5%. They also reduced the incidence of hypoglycemic events as compared with the diets mentioned earlier,[33] and they are eventually expected to be incorporated into diabetes education programs worldwide. Systematic reviews suggest that low-glycemic diets also prevent cardiovascular disease[34] and certain cancers.[35]

Low-carbohydrate diets take the principle of glycemic load reduction one step further. They were once considered an unproven fad, but growing evidence suggests that they may be superior to low-fat high-carbohydrate diets in important ways. A systematic review of 19 trials involving 336 patients with type 2 DM found that people who ate low-carbohydrate diets had better glycemic control and lipid profiles than did those who followed a low-fat approach.[36] The Mediterranean diet, which emphasizes whole grains, vegetables, plant protein, and seafood with moderate wine consumption, has also been associated with better health outcomes. This diet may be modified for patients with type 2 DM by moderately decreasing high-glycemic fruits and grains (see Chapter 86, The Antiinflammatory [Omega-3] Diet).

Sugar-sweetened beverages (SSBs) increase the risk of type 2 DM and likely worsen the disease. Whether these drinks are sweetened with sucrose, high-fructose corn syrup, or fruit juice concentrates, they subject drinkers to high glycemic loads that promote beta cell dysfunction and inflammation. In a systematic review of 11 prospective cohort studies involving 310,819 individuals, those in the highest quartile of consumption of sugar-sweetened beverages (one to two drinks per day) had a 26% increased risk of developing type 2 DM.[37] Most researchers do not consider fruit juice to be a sugar-sweetened beverage, but no evidence indicates that it is safer. Fructose may, in fact, be more harmful than glucose because it is metabolized to lipids by the liver. This process increases uric acid levels, which are associated with type 2 DM,[38] and also raises blood pressure.[39]

Specific Foods

Overall nutritional principles can affect the risk and progression of type 2 DM (Fig. 32-2), but so can certain individual foods. Research on functional foods for the treatment of type 2 DM can guide the clinician willing to provide detailed advice to patients who are motivated to make healthy food choices.

Increased protein intake has been associated with an elevated risk of type 2 DM, but this risk appears to be attributed only to animal protein.[40] Vegetable protein does not appear to confer additional risk and may, in fact, improve glycemic control, lipid parameters, and markers of inflammation. This finding has been reported in studies examining intake of chickpeas, beans, lentils and other pulses,[41] soy,[42] and walnuts[43] and other nuts.[44] A growing body of research supports the beneficial effects of vegetarian and vegan diets for patients with type 2 DM.[45] In addition to vegetable protein, whole grains are also rich in minerals and antioxidants. In a large prospective cohort study, fiber from whole grains improved glycemic control in patients with type 2 DM.[46]

Most patients are happy to hear that coffee drinking is a healthy habit. The beans contain chlorogenic acids and other phenolic compounds that reduce oxidative stress and inflammation. Coffee consumption appears to prevent diabetes,[47] and it is associated with improved lipid parameters[48] and a reduced risk of total and cardiovascular mortality in patients with established type 2 DM.[49] Caffeine appears to increase postprandial hyperglycemia,[50] so the prudent course may be to advise patients to drink coffee that is decaffeinated (using steam, not methylene chloride or other chemical processes) or to drink it between meals.

Higher serum carotenoid levels, which reflect dietary intake of carotenoid-rich fruits and vegetables, were associated with markedly lower type 2 DM risk in an Australian study.[51] Although overall fruit and vegetable intake is not a strong predictor of risk,[52] a systematic review suggested that potent benefits are derived from leafy green vegetables.[53]

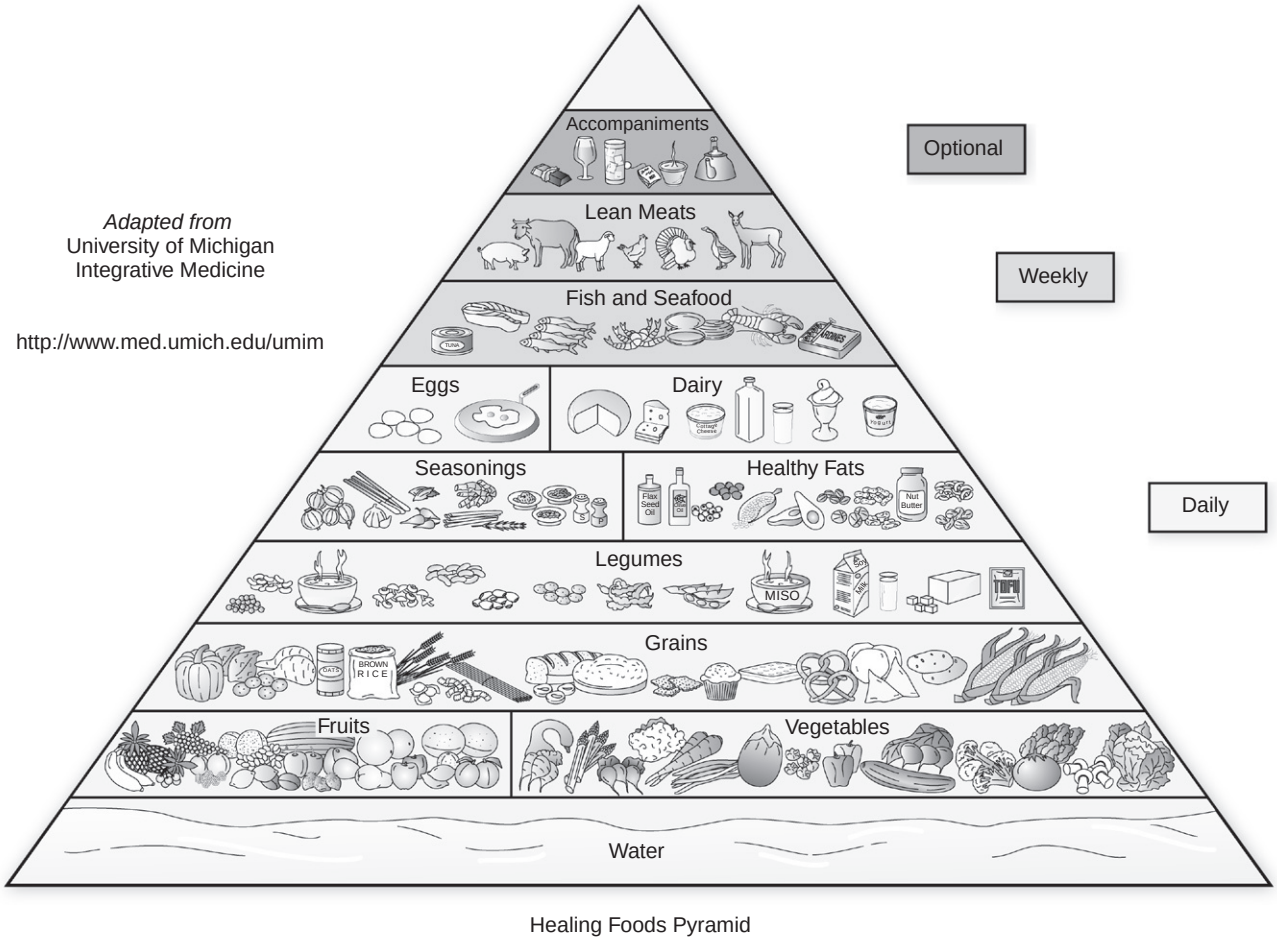
Moderate alcohol consumption prevents type 2 DM.[54] Guidelines have been cautious about recommending alcohol, for fear of the risk of abuse. This possibility should be kept in mind, but the effects of alcohol on insulin sensitivity and type 2 DM risk are too good to ignore. In a large Dutch cohort of 35,625 adults followed for more than 10 years, moderate drinkers were about half as likely to develop type 2 DM as nondrinkers, even if they were already following other healthy lifestyle habits.[55] The strongest benefit was noted in persons who were not obese, whose risk was reduced by almost two thirds.[55]

People with type 2 DM should probably not eat eggs. A combined analysis of the Physicians' Health Study I and the Women's Health Study found that those who ate more than four eggs per week had a 50% increased risk of developing type 2 DM.[56] Earlier reports noted that people with type 2 DM who ate even a single egg per week had twice the risk of cardiovascular disease as compared with those who did not eat eggs.[57] The consistent trend is for greater risk of egg consumption in men than in women.

Fish intake may increase the risk of type 2 DM. This potentially paradigm-shifting association has been reported in some population studies but not in others,[58] and although omega-3 fatty acids have been implicated, the mercury and polychlorinated biphenyl toxins in modern seafood may also play a role. Providing definite recommendations about fish intake is premature, particularly considering the overall cardiovascular benefits associated with it. The hope is that the issue will be clarified by future research.

Chia *(Salvia hispanica)* is a Mesoamerican and Andean whole grain that was used as a food and medicine by the

FIGURE 32-2
University of Michigan integrative medicine healing foods pyramid. (From Regents of the University of Michigan. Developed by Monica Myklebust, MD, and Jenna Wunder, MPH, RD, 2008.)



Aztecs for centuries. It has potent antioxidant effects and is the richest source of alpha-linoleic acid in nature. In a 12-week clinical trial, 20 patients with well-controlled type 2 DM who ate 37 g daily enjoyed reduced blood pressure, lower C-reactive protein, and lower HbA1c than did a control group who ate wheat bran.[59]

Onions *(Allium cepa)* and onion extracts demonstrated marked glucose-lowering effects in several animal studies. This finding was confirmed in an unblinded trial in a mixed diabetic population.[60] Although the exact mechanism is unclear, the well-known anticancer properties of onions should make them part of a healthy diabetic diet.

Foods found to be beneficial in type 2 diabetes mellitus include plant protein, whole grains, coffee, carotenoid-rich fruits and vegetables, green leafy vegetables, alcohol in moderation, chia, and onions. Foods found to be associated with increased risk include animal protein, particularly from eggs.

Management, Self-Care, and Education

Several guidelines for prevention and management of type 2 DM provide a good approach to treating these patients and should be consulted by integrative practitioners. These guidelines universally stress the importance of regular visits guided by a diabetic flow chart and the benefit of a diabetic health care team if available. A surveillance schedule should include regular HbA1c measurements, blood pressure and lipid checks, baseline electrocardiograms or exercise stress testing, urine albumin-to-creatinine ratios and serum creatinine levels, monofilament testing for neuropathy, foot inspections, funduscopy by an ophthalmologist, screening for sexual function, depression and anxiety, and immunizations as appropriate.

Self-monitoring of blood glucose is a practice that is widely taught and recommended as an important self-management practice for people with type 2 DM. This expensive habit (approximately $800 per year) is being called into question because good evidence indicates that it has minimal impact on glycemic control, medication changes, or

lifestyle habits and is not cost effective by any measure. In a systematic review of 30 randomized controlled trials (RCTs), patients who regularly practice self-monitoring of blood glucose had only slightly better glycemic control (0.21% lower HbA1c), a nonsignificant difference that does not improve clinical outcomes.[61]

Diabetes education is also considered a cornerstone of chronic type 2 DM management, but the evidence of its benefit is also surprisingly scant. A Cochrane Review identified nine RCTs that compared one-on-one education with usual care (six trials) or group classes (three trials). All were low-quality studies, and the only consistent benefit was seen among patients with the worst baseline glycemic control (HbA1c higher than 8%).[62] This result may be partly related to the emphasis placed by most education programs on low-fat diets, which are now known to be inferior to other nutritional approaches. The lack of a systematic approach to knowledge translation of health care research has been an important obstacle for many integrative medicine interventions.

Mind-Body Therapy

Many different mind-body therapies are available to interested patients and clinicians. I find it more appropriate to provide patients with options that seem appropriate for their individual situation and use leading questions to help them make a final choice about which therapy to pursue (see Chapter 93, Relaxation Techniques).

Emotional trauma, current psychological stress, mood disorders, and other factors play critical roles in the development and progression of type 2 DM. The many mechanisms briefly mentioned earlier are the subject of intensive research in the burgeoning field of psychoneuroimmunology. Interventions that reduce stress, promote mindfulness, and strengthen the mind-body connection are even more important to address with patients whose health outcomes are intimately related to their daily choices about how they live their lives. Nonetheless, the evidence to support the use of specific mind-body therapies is relatively limited.

Cognitive-Behavioral Therapy

Cognitive-behavioral therapy helps patients gain insight into the habits and patterns that affect their thoughts and actions and the ways in which these thoughts and actions affect their health and their lives. A sizeable body of research has established the benefits of cognitive-behavioral therapy on glycemic control and self-care. In a systematic review of 25 trials in type 2 DM, 12 trials involving 522 patients used glycemic control as an outcome measure. In those trials, participants who received 6 to 16 group or individual counseling sessions had 0.76% reduction in HbA1c as compared with those receiving various control interventions.[63]

Biofeedback

Biofeedback training can strengthen the mind-body connection by helping patients learn to control specific bodily functions, including muscle tension, skin temperature, sweating, breathing, heart rate, and even regional brain waves. In a published study, researchers randomized 39 patients with well-controlled type 2 DM to receive 10 weekly individual sessions of skin temperature and electromyograph biofeedback or 3 group education sessions. Glycemic control improved, and HbA1c decreased by 0.8%.[64] This finding may seem surprising, but biofeedback trials have reported changes in plasma cortisol, peripheral vasoconstriction, and other markers of sympathetic nervous system activity.

Sleep

Abnormal sleeping habits increase the risk of type 2 DM. In a systematic review of 13 prospective cohort samples involving 107,756 men and women from around the world, this outcome was seen in people whose average night's sleep was less than 6 hours (relative risk [RR], 1.28) or more than 8 hours (RR, 1.48), as well as in those people who had trouble falling asleep (RR, 1.57) or staying asleep (RR, 1.84).[65] One study found that daytime napping was also associated with an increased risk of type 2 DM.[66] Obstructive sleep apnea is a more serious sleep disorder that increases the risk of many diseases, including type 2 DM.[67] Better sleep is an important independent target for mind-body medicine interventions.

Supplements

Table 32-1 describes the glycemic effects and cardiovascular benefits of different treatments for type 2 DM.

Vitamin D

For more than 1 million years, *Homo sapiens* lived outdoors. Modern lifestyles severely restrict sun exposure, a drastic change in the human environment that has been ignored until recently. Vitamin D synthesis in the skin is triggered by exposure to ultraviolet (UV) light. This stimulus damages DNA, so it should not be surprising to learn that vitamin D activates DNA and cellular repair systems. By binding to nuclear vitamin D receptors, vitamin D actually regulates many aspects of physiology. Investigators now know that vitamin D does more than make bones.

Low serum 25-hydroxyvitamin D (25-OHD) levels are associated with a growing list of serious chronic diseases, including cardiovascular disorders, neurologic diseases, allergic and autoimmune problems, several cancers, and all-cause mortality. Whether this is a cause-and-effect relationship or whether low vitamin D is simply a marker of chronic inflammation, oxidative stress, or some other physiologic disturbance is unclear. Nonetheless, vitamin D trials have reported improvements in chronic pain, blood pressure, pregnancy outcomes, and autoimmune disease risk.

Vitamin D deficiency increases mortality risk in type 2 DM,[68] but the evidence that treating this deficiency improves outcomes in type 2 DM should be considered preliminary.[69] One small study reported that improvements in vitamin D status were associated with reductions in HbA1c in patients with type 1 DM.[70] Large single doses given to patients with type 2 DM significantly reduced blood pressure in a reported trial,[71] and another trial reported improvements in endothelial function.[72] In a study of 24 patients with type 2 DM who were given low doses of vitamin D (400 and 1200 units) for 4 months to treat deficiency, none of their glucose or metabolic parameters improved, but their 25-OHD levels were still low at the end of the study period.[73]

Guidelines for vitamin D supplementation vary widely, and at this time they should be considered in process. I advise patients to supplement in a manner that mimics sunlight exposure. Patients are told to take 10,000 to 15,000 units

TABLE 32-1. Glycemic Effects and Cardiovascular Benefits of Different Treatments for Type 2 Diabetes Mellitus

THERAPY	EFFECTS	CARDIOVASCULAR BENEFITS
Arsenic exposure avoidance	Arsenic exposure increased risk 358% in population studies	—
Emotional stress avoidance	Emotional stress increased risk 60% to 236% in population studies	CV and all-cause mortality
Egg avoidance	Egg consumption increased risk 50% in two population studies	CV disease
Coffee	Reduced risk 40% in meta-analysis	Lipids, CV mortality
Leafy green vegetables	Reduced risk 14% in meta-analysis	BP, lipids, all-cause mortality
Moderate alcohol consumption	Reduced risk 50% in meta-analysis	Lipids, CV and all-cause mortality
Avoidance of sugar-sweetened beverages	Sugar-sweetened beverages increased risk 26% in meta-analysis	—
Treatment of periodontal disease	Periodontal disease increased risk 150% to 225% in population studies	MI and stroke risk
Lifestyle intervention	HbA1c decreased 0.3% in meta-analysis	BP, lipids
Regular exercise	HbA1c decreased 0.6% in meta-analysis	BP, lipids, CV and all-cause mortality
Low-glycemic diet	HbA1c decreased 0.5% in meta-analysis	Lipids, CV disease
Beans and pulses	HbA1c decreased 0.5% in meta-analysis	BP, lipids
Chia	—	BP, C-reactive protein
Cognitive-behavioral therapy	HbA1c decreased 0.78% in meta-analysis	—
Biofeedback	HbA1c decreased 0.8% in one trial	—
Treatment of vitamin D deficiency	May decrease type 2 DM risk	Endothelial function
Chromium	HbA1c decreased 0.6% in meta-analysis	—
Alpha-lipoic acid	Decreased diabetic neuropathy	? Liver, CV disease
Omega-3 fatty acids	—	Lipids, platelets, CV disease
Magnesium	HbA1c decreased 0.3% in meta-analysis Reduces type 2 DM risk 16%	Lipids, endothelial function
L-Carnitine	? Insulin sensitivity	Lipids, lipoprotein(a)
Benfotiamine		Endothelial function
Vitamin K_2	? Stimulates beta cells	CV disease
Avoidance of selenium	Selenium may increase risk 55%	—
Avoidance of high-dose vitamin B_6, vitamin B_{12}, folate	These vitamins may increase nephropathy	Increased CV disease
Berberine	HbA1c decreased 0.9% in one trial	—
Cinnamon	HbA1c decreased 0.5% in one trial	—
Ginseng	Improved glucose parameters	—
Fenugreek	HbA1c decreased 1.4% in one trial	—
Ivy gourd	HbA1c decreased 0.6% in one trial	—
Momordica charantia	Improved glucose parameters in four trials	—
Prickly pear cactus stem	Improved glucose parameters in one trial	—
Pycnogenol	HbA1c decreased 0.8% in one trial	—
Metformin	HbA1c decreased 1.0%	CV and all-cause mortality
Sitagliptin	HbA1c decreased 1.25%	—
Sulfonylurea	HbA1c decreased 1.0%	May increase risk
Pioglitazone	HbA1c decreased 1.25%	—
Bariatric surgery	Curative in 78% of patients	? CV and all-cause mortality
Insulin	Dose-dependent	—

BP, blood pressure; CV, cardiovascular; DM, diabetes mellitus; HbA1c, glycosylated hemoglobin; MI, myocardial infarction.

at a time, one to three times per week, until their 25-OHD levels are at the middle of the normal range. Although this range appears to vary from person to person, a reasonable maintenance dose may be 1000 to 4000 units daily. Toxicity is rare unless daily doses of more than 20,000 units are taken for several months. Large, long-term studies will certainly be forthcoming and will help clarify this very important potentially modifiable risk factor.

Dosage

The dose is 1000 to 4000 units daily or 10,000 to 15,000 units one to three times a week. Monitor serum 25-OHD levels to keep them between 30 and 80 ng/mL.

Precautions

Side effects are rare, but hypercalcemia with subsequent calcification of blood vessels with prolonged use of high doses has been observed.

Chromium

This trace element has several effects on carbohydrate and lipid metabolism. A complex containing trivalent chromium is known as glucose tolerance factor. Evidence suggests that it acts to reduce tissue lipid content and that chromium responders are more likely to be more obese, more insulin-resistant, and have poorer glycemic control regardless of baseline chromium status.[74]

A meta-analysis of 41 trials that evaluated the glycemic effects of various formulations found 14 trials involving patients with type 2DM.[75] The evidence is difficult to interpret because of low study quality and differences in formulation and dose, but the best results were reported in trials that used chromium picolinate or brewer's yeast at doses of at least 200 mcg daily. In these trials, the mean reduction in HbA1c was 0.6% compared with placebo.

Dosage

A dose of 200 to 1000 mcg daily is recommended.

Precautions

Chromium has no known side effects.

Alpha-Lipoic Acid

Also known as thioctic acid, alpha-lipoic acid (ALA) is a potent lipophilic antioxidant that is found in most eukaryotic cells. It also acts as a cofactor for several mitochondrial and cytosolic enzymes, with the R+ enantiomer being the active form. In addition to its antioxidant activity, it can also regenerate other antioxidants by reducing them; this list includes vitamins C and E, coenzyme Q10, and glutathione. ALA also chelates mercury, arsenic, iron, and other metals that act as free radicals. It is present in trace amounts in organ meats and some vegetables, but these amounts are negligible as compared with usual therapeutic doses.

ALA has been used to treat several diseases in Europe and Japan since the 1950s. A large body of preclinical research supports the potential benefit of ALA in liver disorders, cardiovascular disease, cancer prevention, and neuropsychiatric disorders and for heavy metal and general detoxification.

Good evidence indicates that ALA reduces painful diabetic neuropathy. First used parenterally, ALA in oral form was effective in a multicenter trial involving 181 patients with type 2 DM who received varying doses for 5 weeks. All doses provided overall 50% symptom reduction, with the lowest dose (600 mg daily) causing the fewest side effects.[76] This finding may be related to reduced lipid peroxidation in neuronal cell membranes or improved endothelial function and microvascular blood flow.[77] ALA also may improve insulin sensitivity through enhanced GLUT4 translocation and glucose uptake in muscle and fat cells.[78] This last effect was seen in intravenous ALA trials and is not yet firmly established with the oral form, but it provides further support for the use of ALA in patients with type 2DM.

Most published trials have used regular ALA (an R-S racemic mixture). R-Lipoic acid is marketed as a superior product because it is the endogenously produced form, but little evidence supports this claim. A sustained-release form is also marketed as superior based on the short half-life of regular ALA, but whether peak levels or total levels are most important is unclear, and evidence of safety and efficacy is similarly lacking. At this time, regular ALA is the recommended form.

Dosage

The best dose for neuropathy is 600 mg daily, but a dose of 50 to 100 mg is sufficient for antioxidant purposes. Absorption is best on an empty stomach.

Precautions

The most common side effect is nausea, but insomnia, fatigue, diarrhea, and rashes have also been reported.

Omega-3 Fatty Acids

Fish and other marine species are the main sources of eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA) in the human diet. Alpha-linoleic acid is an omega-3 precursor found in walnuts, flax, and other grains. Although they do not affect glycemic control, these fats have antiinflammatory, antithrombotic, and antiarrhythmic effects that appear to prevent and treat cardiovascular disease. For this reason, they offer important benefits to patients with type 2 DM.

A Cochrane Systematic Review of 23 trials involving 1075 patients who used omega-3 fatty acids at an average dose of 3.5 g daily reported improved lipid parameters and platelet function.[79] Small trials have also reported improvements in endothelial function; in one study, impaired flow-mediated dilatation improved significantly after subjects consumed 2 g of omega-3 fatty acids.[80]

Dosage

Most cardiovascular benefits of omega-3 fats occur at doses of 1000 mg (EPA and DHA) daily, but higher doses are often used.

Precautions

Fishy repeats and mild gastrointestinal upset are the only side effects. Although bleeding in aspirin or warfarin users is often cited as a reason for caution, the literature contains no reports of this effect.

Magnesium

Magnesium affects insulin secretion and action, and it also influences lipid parameters and endothelial function. A systematic review identified 9 trials that evaluated magnesium

supplementation for 4 to 16 weeks in 370 patients with type 2 DM and noted improvements in fasting glucose and high-density lipoprotein cholesterol. In the five trials of sufficient duration to evaluate HbA1c, a nonsignificant reduction of 0.31% (95% CI, −0.81 to 0.19) was reported.[81] A separate review of magnesium for the prevention of type 2 DM found seven cohort studies and reported an overall benefit; an average daily dose of 100 mg decreased risk by approximately 16%.[82] How accurately routine tests reflect total body stores is unclear.

Dosage

Usual starting doses are approximately 100 mg daily and can be increased as desired or to bowel tolerance. Magnesium is available as oral liquid or tablets, transdermal lotion, or Epsom salts, as well as in parenteral formulations.

Precautions

Gastrointestinal intolerance, mainly diarrhea, is the most common side effect. Chelated magnesium (magnesium glycinate) causes less diarrhea than do other forms of magnesium.

Antioxidants

People who eat diets that are rich in antioxidants have a greatly reduced type 2 DM risk, but commonly used antioxidant supplements do not appear to have the same preventive effect. In 8171 women who were followed for 9.2 years in the Women's Antioxidant Cardiovascular Study, only mild benefit was suggested by a nonsignificant trend with vitamin C, whereas vitamin E increased risk and beta-carotene offered no benefit.[83] The Prevention of Progression of Arterial Disease and Diabetes (POPADAD) trial found no significant benefit in 1276 Scottish adults who took a low-dose mixed antioxidant supplement or placebo for 8 years.[84]

The benefits of antioxidant-rich foods are probably more attributable to the dozens of phytomedicines they contain that we are only beginning to understand. Although antioxidants and multivitamins are commonly prescribed by integrative practitioners as "insurance against deficiency," this practice may not be safe. High doses of vitamins have been shown to interfere with absorption and use of lesser-known but potentially more powerful antioxidants in food; high-profile examples include tocopherols and carotenoids.

Whole food supplements may be a reasonable alternative approach. In one study, an antioxidant supplement derived from pomegranate, green tea, and ascorbic acid improved lipid parameters and markers of oxidative stress in a placebo-controlled trial involving 114 patients with type 2 DM in Turkey.[85]

Vitamin E

Vitamin E is one of the most commonly used specific antioxidants, but no real evidence indicates that it helps patients with type 2 DM. Negative results reported in large cardiovascular and cancer trials have been the subject of media reports, controversy, and debate among integrative medicine practitioners. Alpha-tocopherol supplementation did not decrease the risk of type 2 DM in the large Alpha-Tocopherol Beta-Carotene (ATBC) cancer trial.[86] One small trial actually reported prooxidant effects shortly after ingestion of a single 1200-unit dose.[87]

Although several tocopherols and tocotrienols have vitamin E–like activity, most vitamin E supplements only contain alpha-tocopherol. Some investigators believe that negative results in vitamin E trials can be explained by the decreased absorption of the other, more potent molecules in this family whose absorption is inhibited by alpha-tocopherol supplementation.[88] In fact, one study comparing the effects of alpha- and gamma-tocopherol on markers of oxidative stress and inflammation in patients with type 2 DM found no differences between the two.[89] Single trials reported that gamma-tocopherol increased blood pressure[90] and did not change platelet function.[91]

Greater benefit from alpha-tocopherol has been demonstrated in people who are homozygous for a haptoglobin gene variant that is present in 3% to 4% of the population and increases oxidative stress. In an Israeli double-blind study involving 1434 people with type 2 DM who were homozygous for haptoglobin-2, alpha-tocopherol actually reduced the risk of a combined cardiovascular end point by more than 50%.[92] This is an example of how genetics may improve treatment outcomes in future personalized medicine.

Vitamin E supplements containing mixed tocopherols and trienols are increasingly available, but we cannot provide clear dosing guidelines for their use for type 2 DM. Vitamin E has no known side effects.

L-Carnitine

L-Carnitine shuttles fatty acids into mitochondria. It has been proposed as a potential therapy for type 2 DM based on the known intracellular lipid accumulation that occurs in the disease. A pilot study found no improvements in glycemic control after 4 weeks of L-carnitine use in 12 patients with type 2 DM,[93] but several trials reported that it improved lipid parameters and significantly reduced lipoprotein (a), an important independent inherited cardiac risk factor for which few effective therapies exist.[94]

Dosage

The usual dose is 500 to 1000 mg three times daily.

Benfotiamine

Postprandial endothelial dysfunction has been proposed as the link between metabolic syndrome and atherosclerosis. This state is linked to oxidative stress, hyperglycemia, hypertriglyceridemia, and altered nitric oxide function. It is attributed to glucose-protein complexes in food, named advanced glycation end products (AGEs). These complexes are formed at high temperatures and activate AGE-specific receptors, which activate monocytes and endothelial cells and ultimately promote inflammation. Benfotiamine is a synthetic analogue of thiamine that is much more bioavailable. It activates transketolase, an enzyme that helps clear AGEs, thus improving postprandial endothelial function.

In a pilot study, 350 mg of benfotiamine after meals completely eliminated the vascular measures of postprandial endothelial dysfunction in 13 patients with type 2 DM.[95] This important finding has not been replicated since it was reported in 2006, but corroborating evidence seems like a high priority. Several trials suggested that benfotiamine improves diabetic neuropathy,[96,97] a finding that is not surprising considering the neurologic symptoms seen in thiamine

deficiency. One trial found no improvement in some markers of diabetic nephropathy,[98] but another reported improvements in microalbuminuria.[99]

Dosage
The 350-mg dose used in the pilot study is higher than that found in most formulations.

Precautions
This early evidence is very promising, but it is probably premature to recommend widespread use of this synthetic thiamine analogue because long-term safety results are not available.

Vitamin K
This fat-soluble vitamin exists as phylloquinone (K_1) in plants and menaquinone (K_2) in animals and in a fermented soybean product named natto. Vitamin K_2 is considered more biologically active and is a cofactor for carboxylation of proteins. It helps make osteocalcin, which strengthens bones by forming a protein scaffold on which it is laid. It also makes matrix Gla protein, which prevents vascular calcification by repairing smooth muscle and endothelium. Vitamin K_2 is receiving growing attention as a target for treatment of diverse disorders in addition to its established role in coagulation factors biosynthesis.

Early studies suggest that vitamin K_2 also stimulates beta cell proliferation and enhances insulin sensitivity. Vitamin K deficiency, as suggested by low levels of carboxylated osteocalcin, is also associated with type 2 DM risk.[100] Recommending vitamin K_2 for glycemic control is premature, but its endothelial and cardiovascular benefits may make it an appealing addition to an integrative type 2 treatment plan.

Dosage
The starting dose of vitamin K_2 is usually 100 mcg daily, but higher doses have been commonly used.

Precautions
Patients taking warfarin will need close monitoring and dose adjustment after starting vitamin K_2, but this ultimately reduces the fluctuations in international normalized ratio results seen in vitamin K_2–deficient patients.[101] Vitamin K has no other known side effects.

Risks of Specific Supplements
Although evidence indicates that selenium has insulin-like actions and may delay microvascular complications, integrative practitioners should know that selenium is associated with increased risk of type 2 DM. In the Nutritional Prevention of Cancer trial, 1202 people with localized melanoma were randomized to receive selenium or placebo for cancer prevention. After 7.7 years of follow-up, selenium users developed type 2 DM more often (hazard risk, 1.55; 95% CI, 1.03 to 2.33), with the greatest risk in people with the highest baseline selenium levels (hazard risk, 2.70; 95% CI, 1.30 to 5.61).[102] Selenium supplementation should be considered only in patients with low baseline selenium levels. The maximum daily dose is 200 mcg. The way in which inorganic and organic forms differ in their effect on type 2 DM risk is unclear.

Practitioners should also exercise caution when using B vitamins in patients with nephropathy. In the Canadian Diabetic Intervention with Vitamins to Improve Nephropathy (DIVINe) trial, 238 patients with type 1 DM and type 2 DM were given a tablet containing folic acid 2.5 mg, vitamin B_6 25 mg, and vitamin B_{12} 1 mg daily or placebo for almost 3 years to treat elevated homocysteine. Although the treatment group had lower plasma homocysteine levels, they had worse kidney function and more cardiovascular events.[103] The investigators postulated that this finding may be explained by cell proliferation induced by folic acid, increased methylation from folic acid and vitamin B_{12}, or nitric oxide–related mechanisms. Earlier reports noted poorer cardiovascular outcomes associated with B vitamins, and one hopes that further study will clarify this issue.

Botanicals

Berberine (Berberis vulgaris)
The barberry plant has been used medicinally for centuries to treat dozens of symptoms, most commonly gastrointestinal and biliary disorders. It contains many physiologically active alkaloids, but the one that has received the most attention is berberine.[104] This compound has antimicrobial, anticonvulsant, and antihypertensive properties. A hypoglycemic effect was first incidentally noted in China in the 1980s, when diabetic patients were given berberine to treat diarrhea, and studies suggest that it may regulate insulin receptor transcription.[105] In a placebo-controlled trial in 116 patients with type 2 DM who were given 1 g of berberine or placebo daily for 3 months, HbA1c decreased from 7.5% to 6.6%.[106] An earlier small trial reported similar impressive benefits.[107] More research on berberine in type 2 DM will undoubtedly be forthcoming.

Dosage
Root or berry extracts at doses of 200 to 500 mg three times daily are commonly used.

Precautions
Berberine can cause uterine contractions, so it should be avoided in pregnancy, but otherwise few side effects have been reported.

Cinnamon
Cinnamon is a culinary spice made from the bark of *Cinnamonum* sp. trees. The aqueous extract appears to improve insulin receptor function by multiple mechanisms, and it also increases glycogen synthase activity.

In a published review, we found three trials evaluating cinnamon in patients with type 2 DM.[108] One was a short-term study that reported changes in fasting glucose,[109,] and the two studies that measured HbA1c found no improvement but were of low quality.[110 111] Since then, another trial compared *Cinnamonum aromaticum* (cassia cinnamon) 500 mg twice daily with usual care in 109 patients with type 2 DM for 90 days. The reported average reduction in HbA1c was 0.83% in the cinnamon group and 0.37% in those receiving usual care, a difference that reached statistical significance.[112]

As mentioned earlier, the aqueous extract appears to contain the most active ingredients. Patients may wish to take

cinnamon as a hot water infusion. Cinnulin PF is a standardized extract that is widely promoted, but no evidence indicates that it is superior.

Dosage
The optimal dose is unclear, but 1-g doses are commonly prescribed (1 teaspoon of cinnamon = 4.75 g). Most over-the-counter cinnamon is a combination of cassia cinnamon and Ceylon cinnamon.

Precautions
Stomatitis and perioral dermatitis have been reported in some patients.

Ginseng
Several plant species are known as ginseng, including *Panax ginseng*, *Panax japonicus*, *Eleutherococcus senticosus,* and *Panax quinquefolius.* They are named after panacea, the Greek goddess of healing, based on their long use as a cure-all for boosting immune function, energy, stamina, and well-being. Ginseng species contain triterpenoid glycosides named ginsenosides that regulate hepatic glucose uptake, glycogen synthesis, and insulin release. Several animal and human trials have demonstrated acute hypoglycemic effects, with no clear difference among tree species. A few small trials have reported improved measures of postprandial insulin and glucose release, but no HbA1c reductions have been reported.[113]

Dosage
Panax ginseng can be used at doses of 1 to 2 g of crude root or powder or 100 to 400 mg of extract standardized to 4% ginsenosides. It can also be used as a hydroalcoholic tincture, hot infusion, or cold decoction.[114]

Precautions
The most common side effect is insomnia, so do not take close to bedtime.

Fenugreek (Trigonella foenum graecum)
Fenugreek is a legume used extensively in India, North Africa, and the Mediterranean. The defatted seeds have been used to treat diabetes for centuries in Ayurvedic and other healing systems. One ingredient, 4-hydroxyisoleucine, increases pancreatic insulin secretion and inhibits glucosidase, and research has demonstrated effects on satiety, gastric emptying, and insulin receptor function. Fenugreek may also have lipid-lowering effects.

In our published review, we identified three small low-quality trials that reported improvements in plasma glucose with fenugreek in patients with type 2 DM.[108] Since then, promising results from a Chinese trial have been reported. Researchers evaluated a fenugreek extract in 69 patients with type 2 DM who had baseline HbA1c of 8.0%. Patients who took 2 g after each meal (equivalent to 32 g crude seeds) for 12 weeks had lower fasting and postchallenge glucose levels and an impressive 1.46% reduction in HbA1c as compared with 0.4% in patients using placebo.[115]

Confirmation of these findings is urgently needed, but this widely used food and medicine certainly deserves attention by integrative practitioners. Optimal dosing, preparation, and use also remain unclear; many different approaches are used in various traditions. One small trial reported improvements when seed powder was added to hot water but not when it was added to yogurt.[116] In addition to the use of fenugreek in food, dry seeds (1 teaspoon) are chewed with meals in many cultures to improve digestion.

Dosage
Until further evidence provides clear guidance, practitioners may use crude powder or extracts at doses equivalent to 20 to 30 g of crude seeds. This dose can be titrated to meal size and individual results.

Precautions
Fenugreek can cause gastrointestinal intolerance with diarrhea, dyspepsia, abdominal distention, and flatulence.

Ivy Gourd (Coccinia indica)
Ivy gourd, a perennial herb in the cucumber family, comes from India but spreads easily and is now distributed worldwide. It is an important Ayurvedic diabetes medicine with additional choleretic, laxative, antiinflammatory, and demulcent properties. The leaves appear to have insulinomimetic effects on lipoprotein lipase, glucose-6-phosphatase, and other glycolytic enzymes.

Results of the first human trial were published in 1980, and the investigators reported glucose-lowering effects.[117] In a more recent trial in 60 patients with well-controlled type 2 DM, 1 g per day of an alcoholic extract for 90 days significantly lowered HbA1c from 6.7% to 6.1%.[118] This dose was equivalent to approximately 15 g of dried leaves and was selected based on traditional practitioners' use of a "handful" of leaves in their patients. Clearly, this is yet another promising botanical medicine worthy of further study.

Dosage
Dried leaves or extracts at doses equivalent to 15 g can be used with meals.

Precautions
Ivy gourd has no known side effects or risks.

Prickly Pear Cactus (Opuntia streptocantha)
The prickly pear cactus was used to treat gastritis and ulcers for centuries by pre-Columbian indigenous peoples in Mexico. The raw stems (cladodes) are liquefied or broiled and consumed with meals to reduce hyperglycemia; in Spanish they are called nopales. In a study of 35 patients with type 2 DM, glucose was measured after three typical breakfasts were eaten with and without nopales. Postprandial rises in glucose were significantly lower after meals with nopales.[119] The glucose-lowering effects of nopales were attributed to its fiber and pectin content, but extracts had the same activity even after filtering out fiber and pectin. Novel compounds are being studied for their possible role.[120] Although no studies have investigated the effects of long-term use on HbA1c, this food medicine is cheap, readily available, and commonly used in the southwestern United States and Mexico.

Dosage
Doses of 85 g or more appear to reduce glucose parameters.

Pycnogenol (Pinus maritima)

Pycnogenol is a standardized extract of French maritime pine bark. It contains procyanidins, catechins, and other compounds with potent antioxidant activity. Cardiovascular benefits have been noted in small trials, but improvements in lipids, blood pressure, and platelet function have been inconsistent. In 48 patients with type 2 DM who used 125 mg of pycnogenol daily or placebo for 12 weeks, those in the treatment group had a 0.8% reduction in HbA1c, along with blood pressure and low-density lipoprotein (LDL) cholesterol reductions.[121] An earlier trial reported similar HbA1c reductions in 77 patients with type 2 DM, but a significant placebo reduction of 0.53% made this finding nonsignificant.[122]

Dosage

Optimal benefits have been reported with doses of 100 to 200 mg.

Pharmaceuticals

The standard approach to treating type 2 DM is focused on improving glycemic control, as reflected by serum levels of HbA1c. This approach is based on the assumption that all reductions in HbA1c are of equal benefit, regardless of how they are achieved. Newer evidence contradicts this assumption. More recent systematic reviews clearly indicate that different drugs have very different effects on real-world clinical measures of morbidity and mortality, independent of their ability to lower blood glucose. Growing recognition of this important gap in our understanding of type 2 DM treatment can create confusion for patients and caregivers, but bridging this gap will be crucial to providing more effective integrative treatment in the future.

Metformin

Metformin is a biguanide that is structurally similar to guanidines originally discovered in extracts of *Galega officinalis* (French lilac). Metformin has been in use since the 1950s, thus making it one of the oldest oral hypoglycemic drugs, but it may be the best. Although its exact mechanism of action is unclear, it improves insulin sensitivity and reduces hepatic gluconeogenesis. It is the only drug that has been shown to reduce cardiovascular mortality (OR, 0.74; 95% CI, 0.62 to 0.89) in systematic reviews,[123] and as such it should be considered first-line treatment for diabetes.

Dosage

The typical dose range is 500 to 1000 mg twice daily.

Precautions

Apart from mild occasional nausea and diarrhea, the only drawback of metformin use is impaired vitamin B_{12} absorption in the terminal ileum, which can lead to vitamin B_{12} deficiency.[124] Metformin can also cause lactic acidosis in patients with renal insufficiency or alcoholism.

> Improving glycemic control does not always improve cardiovascular outcomes. Metformin is the only hypoglycemic drug with proven cardiovascular and mortality benefits.

Sulfonylureas

Sulfonylureas increase insulin secretion by pancreatic beta cells by binding to membrane channels. These drugs have also been used for several decades, but they do not appear to improve cardiovascular outcomes. One problem is that they cause weight gain. They also cause more frequent hypoglycemic episodes, which can lead to arrhythmias and cardiac ischemia.[125] A systematic review found that glyburide was almost twice as likely as other sulfonylureas to cause hypoglycemia, but cardiovascular outcomes were the same for all drugs in the class.[126] Patients using sulfonylureas and metformin in combination are also at greater risk of cardiovascular mortality than are patients using metformin alone.[127]

Dosage

The usual dose of glyburide is 2.5 to 10 mg twice daily.

Precautions

Hypoglycemia and weight gain.

Thiazolidinediones

Thiazolidinediones increase insulin sensitivity by activating peroxisome proliferator-activated receptor gamma, a nuclear receptor with salutary effects on fatty acid balance, adipocyte differentiation, adiponectin, and other factors involved in glucose and lipid metabolism. The use of rosiglitazone has decreased dramatically since it was found to increase the risk of heart attacks by more than 40% in patients with type 2 DM, possibly because of drug-related LDL rise or congestive heart failure. Pioglitazone (Actos) is the only drug in this class that clinicians can use. Its impact on cardiovascular outcomes is still unclear, but a systematic review did find that it improved glycemic control by 0.58% HbA1c when it was added to metformin.[128]

Dosage

The dose of pioglitazone is 15 to 30 mg once daily.

Precautions

The average weight gain is 7 lb, and mild edema is commonly noted. Another problem with long-term use is osteoporosis; in a meta-analysis of 10 trials involving 13,715 participants, fracture risk was more than doubled (OR, 2.23; 95% CI, 1.65 to 3.01).[129] Pioglitazone can increase cardiac disease risk.

Incretins: Sitagliptin

Incretins are hormones produced in the small intestine during a meal that enter the vasculature and trigger insulin release by pancreatic beta cells. The two incretins are glucagon-like peptide (GLP-1) and gastric inhibitory peptide (GIP). A newer class of drugs inhibits dipeptidyl peptidase-4 (DPP-4), an enzyme that degrades GLP-1 and GIP, thus leading to increased insulin and decreased glucagon levels. The most widely studied drugs in this class are sitagliptin (Januvia) and, to a lesser extent, vildagliptin.

Dosage

The recommended dose of sitagliptin is 100 mg once daily.

Precautions

The only side effects noted in trials have been nasopharyngitis and headache, but because DPP-4 degrades dozens of other enzymes and the drugs have not been evaluated in long-term trials, questions about safety remain. The impact of these drugs on cardiovascular events and mortality also is unclear, but meta-analyses suggest HbA1c reductions of 0.7%.[130]

Exenatide

Exenatide (Byetta) is a GLP-1 analogue that is administered as a weekly injection. In comparison trials with insulin and other oral hypoglycemics, it reduced HbA1c by approximately 1.0% without causing hypoglycemia or weight gain.[131] More research on long-term use and clinical outcomes will likely follow for this promising drug, but this drug is limited by having to be injected.

Dosage

The dose is 5 mcg twice daily for 1 month and is then increased to 10 mcg twice daily as needed.

Precautions

Reported side effects include diarrhea, nausea, and vomiting. Cases of pancreatitis have also been reported. No cardiovascular outcomes are available.

Alpha-Glucosidase Inhibitors

Alpha-glucosidase inhibitors prevent enzymatic cleavage of oligosaccharides into glucose and other simple sugars. They improve glycemic control by reducing glucose absorption when they are taken with meals. Systematic reviews have reported HbA1c reductions of approximately 0.8%,[132] but no clear cardiovascular benefits have been seen.

Dosage

A dose of 25 to 100 mg three times daily can be used, but no additional benefit is seen with doses greater than 50 mg.

Precautions

The most unpopular side effect is flatulence, but these drugs can also elevate liver enzymes.

Insulin

Although insulin administration can be lifesaving, insulin is a proinflammatory hormone. Every effort should be made to optimize glycemic control, but it is probably best to use the lowest possible doses of exogenous insulin to achieve this goal. Insulin-dependent patients with type 2 DM can often greatly reduce their dose requirements by following an integrative treatment protocol, as described in this chapter.

One important mechanism of risk is stimulation of insulin-like growth factor-I (IGF-I) and other growth hormones. IGF-I levels predict cancer risk, and the first suggestion that insulin users may be at increased risk of cancer was published in 1967.[133] For reasons that are unclear, people with type 2 DM have a 20% increased risk of breast cancer[134] and a 30% increased risk of colon cancer.[135] Some studies suggest that glargine, a long-acting insulin analogue, may be more carcinogenic by stimulating IGF-I much more than other types of insulin. The hope is that the International Study of Insulin and Cancer, funded by Sanofi-Aventis (the makers of glargine) will clarify this issue.

Many insulin protocols, regimens, and analogues are available; their use is beyond the scope of this chapter. Practitioners should be aware that although these regimens may allow patients to take their insulin in a more convenient or practical manner, no evidence indicates that any one approach is superior to another. Short-acting insulin analogues are commonly used, but meta-analyses suggest that they do not provide any advantage over regular human insulin.[136] Similarly, no evidence indicates that the long-acting insulin analogues glargine and detemir are superior to regular insulin.[137] Continuous infusion pumps are a newer technology that may be superior, but their benefit has been demonstrated only in type 1 DM.[138]

Other Drugs That Improve Outcomes

Angiotensin-Converting Enzyme Inhibitors

ACE inhibitors prevent and treat diabetes. This startling fact makes it clear that integration between seemingly disparate physiologic systems can have a powerful impact on health and disease. Exactly how the renin-angiotensin system influences glucose metabolism is unclear, but multiple lines of suggestive evidence exist. Angiotensin II is known to mediate vasoconstriction and hypoperfusion of skeletal muscle and pancreatic islets. It also appears to affect insulin signaling and glucose transport in ways that are still unknown. In a systematic review of 13 trials involving 93,451 patients with hypertension, the use of these drugs reduced the risk of incident type 2 DM by an impressive 26%.[139] Many ACE inhibitors are available; the most widely studied is ramipril, at a recommended dose of 2.5 to 10 mg once daily.

Statins

Statins are universally recommended for patients with type 2 DM, but their effect on this disease now seems complicated. As a drug class, 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors are known for their ability to improve lipid parameters. The clear cardiovascular benefits of these drugs are actually more strongly associated with antiinflammatory effects, however. The absolute risk reduction seen with these drugs is very compelling in people who have already had a cardiovascular event, but it is unimpressive in those who have not. patients with type 2 DM fall somewhere in between; the higher baseline vascular risk in diabetes makes statin therapy much more appropriate.[140] Red yeast rice is a natural source of several statin compounds, and it may be considered a reasonable alternative for patients who cannot tolerate or do not want to use a statin drug.

Unfortunately, newer evidence suggests that some statins increase type 2 DM risk. In a meta-analysis of 13 trials involving 91,140 adults, the overall increase in type 2 DM risk was 9% (95% CI, 1.02 to 1.17).[141] Subgroup analysis revealed that different statins have very different effects. Simvastatin, atorvastatin, and rosuvastatin increase the risk of type 2 DM, whereas pravastatin reduces the risk.[142] This finding suggests that pravastatin may be a better choice in patients with type 2 DM until this issue becomes clearer. Recommended dose is 20 to 80 mg once daily.

Aspirin

Low-dose aspirin has long been advocated for cardiovascular prevention, but it appears to offer little benefit in patients with type 2 DM. This conclusion was noted in a joint position paper published by the American Heart Association, the American College of Cardiology, and the American Diabetes Association and was based on a meta-analysis of nine RCTs. A nonsignificant benefit and the risk of major gastrointestinal bleeding make aspirin recommended only for men older than 50 years and women older than 60 years who have at least one cardiac risk factor.[143]

Mechanical Therapies

Bariatric Surgery

Various surgical procedures induce weight loss by resecting, tightening, shrinking, or bypassing the stomach and upper digestive tract. These forms of so-called bariatric surgery lead to profound weight loss, and they may be the most important advance in the treatment of type 2 DM in decades. Although surgery is not the most philosophically appealing solution to the worldwide epidemic of type 2 DM and other metabolic diseases related to obesity, it is increasingly recognized by governments and insurers worldwide.

In a review of 103 clinical trial treatment arms involving 3188 patients with type 2 DM, 78% had complete resolution of clinical and laboratory manifestations of diabetes after surgery; 87% of patients improved significantly and reported an average weight loss of 38.5 kg.[144] Long-term reductions in all-cause morbidity and mortality are increasingly reported.

Short-term complications include gastric dumping syndrome, hernias, wound infections, and pneumonia. The most important long-term consideration is nutrient malabsorption. Deficiencies of vitamins A, C, D, K, and B_{12} and folate and of iron, selenium, calcium, zinc, and copper should be expected.[145] All patients who have undergone bariatric surgery should take a daily multivitamin and multimineral supplement. Anemia, hyperparathyroidism, and peripheral neuropathy are common. Patients who have undergone bariatric surgery and who report vague symptoms should be evaluated for nutrient deficiency and reminded of the importance of supplementation.

Metformin, angiotensin-converting enzyme inhibitors, statin drugs, and bariatric surgery appear to offer proven benefits in type 2 diabetes mellitus, but other hypoglycemic drugs do not.

Prevention Prescription

- Manage psychological stress and treat emotional trauma or mood disorders if present.
- Obtain 6 to 8 hours of restful sleep per night.
- Eat a low-glycemic Mediterranean diet that includes whole grains, vegetable protein, vegetables and some fruit, coffee, and moderate alcohol.
- Avoid sugar-sweetened beverages, animal protein, and eggs.
- Practice daily exercise, aerobic or resistance.
- Manage weight and treat obesity.
- Avoid air pollution by maintaining safe distance from high-traffic roads at work or home.
- Maintain proper oral hygiene and treat periodontitis if present.
- Treat hypertension with ramipril (2.5 to 10 mg daily) or another angiotensin-converting enzyme inhibitor.
- Treat prediabetes with aggressive lifestyle intervention and consider metformin, 500 to 1000 mg twice daily.
- Treat vitamin D deficiency if present.
- Take omega-3 fatty acids at 1 to 2 g daily.
- Take magnesium at 100 to 300 mg daily.
- Avoid selenium supplementation if serum levels are adequate.

Therapeutic Review

Lifestyle

- Consider referral to a comprehensive lifestyle program if available. A1
- Strive to inspire patients with your own lifestyle choices. C1

Exercise

- Encourage daily aerobic, resistance, or mindfulness-based (e.g., tai chi) exercise. A1
- Provide behavioral support tailored to patients' stage of readiness to change. B1

Diet

- Low-glycemic diet and moderate carbohydrate reduction A1
- Avoidance of sugar-sweetened beverages and juices, animal protein, and eggs B1
- Consumption of more lentils, beans, pulses and soy, chia and other whole grains, onions and leafy green vegetables, and walnuts and other nuts A1
- Moderate coffee and wine consumption A1

Mind-Body Therapy

- Ask about and treat disordered sleep, stress, anxiety, and depression. 
- Discuss stress reduction options and facilitate the chosen modality. 
- Refer patients to a psychologist you are comfortable with as needed. 

Supplements

- Vitamin D: 1000 to 4000 units daily unless deficient 
- Alpha-lipoic acid: 50 to 100 mg daily 
- Chromium: 200 to 1000 mcg daily 
- Benfotiamine: 350 mg with meals 
- Omega-3 fatty acids: 1 to 4 g daily 
- L-Carnitine: 500 to 1000 mg three times daily 
- Magnesium: 200 to 500 mg daily 
- Vitamin K: 100 mcg daily (caution with warfarin) 

Botanicals

- Berberine *(Berberis vulgaris):* 200 to 500 mg three times daily 
- Ivy gourd *(Coccinia indica):* 15 g powdered dried leaves or equivalent extract) 
- Fenugreek *(Trigonella foenum-graecum):* 30 g seed powder or equivalent extract with meals 
- Cinnamon: 1 to 5 g ground bark with meals or equivalent extract 
- *Panax ginseng:* 1 to 2 g ground root or 100 to 400 mg extract 
- Prickly pear cactus *(Opuntia streptocantha):* 85 g broiled or liquefied stems with a meal 
- Pycnogenol *(Pinus maritima):* 100 to 200 mg daily 

Pharmaceuticals

- Metformin: 500 to 1000 mg twice daily 
- Ramipril: 5 to 10 mg daily (or another angiotensin-converting enzyme inhibitor) 
- Pravastatin: 20 to 80 mg daily (or other statin or red yeast rice) 
- Other drug classes as needed to achieve a glycosylated hemoglobin level lower than 7.0%, including thiazolidinediones, sulfonylureas, incretins, and insulin

Surgery

- Bariatric surgery for morbidly obese patients 

KEY WEB RESOURCES

Glycemic Index Foundation (an international glycemic index database): http://www.glycemicindex.com.

California Academy of Family Physicians list of diabetes flow sheets: http://www.familydocs.org/new-directions-diabetes-care/tools-and-resources/flow-sheets-forms-signs-and-charts.php.

National Center for Alternative and Complementary Medicine, National Institutes of Health diabetes Web site: http://nccam.nih.gov/health/diabetes.

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Chapter 33

Hypothyroidism

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Pathophysiology

Hypothyroidism is the insufficient synthesis of thyroid hormone, necessary for metabolic processes throughout the body. Worldwide, iodine deficiency is the most common cause of *primary hypothyroidism,* the most common type of hypothyroidism. In iodine-sufficient countries, autoimmune destruction of the gland (Hashimoto disease) is the leading cause of primary hypothyroidism. The second leading cause of primary hypothyroidism is iatrogenic, including surgery, radioactive iodide, medications (i.e., lithium, amiodarone), overconsumption of goitrogens, and external-beam radiation. Primary hypothyroidism accounts for approximately 95% of cases compared with less than 5% from secondary and tertiary types.

Secondary hypothyroidism results from decreased thyroid-stimulating hormone (TSH) secretion from pituitary tumors (adenomas most commonly), pituitary surgery, or other pituitary disease, such as Sheehan syndrome. *Hypothalamic or tertiary hypothyroidism* results in decreased thyrotropin-releasing hormone secretion related to infiltrative processes such as sarcoidosis, infection, or congenital defect. *Transient hypothyroidism* may occur after abrupt withdrawal of long-term thyroid hormone therapy or from silent or subacute thyroiditis.

Clinical Presentation

Common symptoms of hypothyroidism include fatigue, dry skin, cold intolerance, hair loss, concentration problems, constipation, weight gain, carpal tunnel symptoms, dyspnea, hoarseness, and menorrhagia. Physical signs include dry and coarse skin, brittle nails, cool extremities, thinning of the lateral eyebrows and hair, myxedema, delayed tendon reflexes, and diminished hearing.[1] In addition to these physical findings, basal metabolic rate may be estimated using axillary temperature measurements and assessment of Achilles tendon reflexes. A series of morning basal body temperatures less than 97.4 °F and delayed Achilles tendon reflexes may add to the clinical diagnosis.[2]

Laboratory Studies

The laboratory evaluation of hypothyroidism remains a controversial topic in the medical community. The minimal evaluation should include TSH, free triiodothyronine (T_3), free thyroxine (T_4), and thyroid peroxidase antibodies (TPO Abs). Additional testing may include measuring nutritional cofactors and related hormone pathways such as urinary iodine levels and adrenal gland function, although these tests are not commonly performed in conventional endocrinology (with respect to hypothyroidism). Some clinicians also check reverse T_3, which is a much less active form of T_3 hormone.

TSH secretion varies in a circadian pattern, with highest levels between 10 PM and 4 AM and the lowest levels between 10 AM and 6 PM.[3] Hence testing at a consistent time of day is best for serial comparisons, preferably during the morning before caffeine consumption.

The normal TSH reference range is wide, from 0.45 to 4.5 milliunits/L. Some investigators suggested lowering the upper limit of serum TSH concentration to 2.5 milliunits/L.[4–6] Every individual has an endogenously set TSH value that determines that person's optimum level with respect to thyroid function. Significant variation of TSH measurements in a symptomatic but euthyroid patient deserves further investigation of cofactors and treatment, depending on symptoms.

Primary Hypothyroidism

In primary hypothyroidism, serum TSH is elevated with decreased serum free T_4. The thyroid secretes mostly T_4 and 10% to 20% T_3. Approximately 80% to 90% of circulating T_3, the most active thyroid hormone, is derived from peripheral deiodination of T_4. Serum free T_3 levels are normal in approximately 25% of hypothyroid patients. This reflects the body's adaptive responses to hypothyroidism through increased peripheral conversion of T_4 to the active T_3. Thus, serum free T_3 measurements should not be used in isolation to confirm or exclude the diagnosis of

hypothyroidism. Serum T_3 levels are frequently lower in euthyroid patients with nonthyroidal disease and during food restriction. These lower free serum T_3 levels occur because of a decreased peripheral conversion of T_4 to T_3.[7,8] Measuring serum free T_3 levels, however, may help with titrating thyroid hormone dosages, particularly in patients taking combination T_4 and T_3 medication. One must evaluate and treat for other causes of hypothyroid-like symptoms, including adrenal insufficiency, hypogonadism, anemia, and depression, which may be comorbid conditions in a single patient.

Serum triiodothyronine (T_3) is generally not used to confirm the diagnosis of hypothyroidism. It may be useful for guiding thyroid hormone dose titration in patients taking a combination of thyroxine (T_4) and T_3 medication.

Secondary and Tertiary Hypothyroidism

Patients may present with symptoms consistent with primary hypothyroidism but with evidence of pituitary hormone imbalance. TSH levels may vary from low, normal, or even slightly elevated values, whereas the free T_4 level is low. Generally, serum TSH concentrations are low in patients with pituitary disease and normal or high in patients with hypothalamic disease. Clinical correlation and magnetic resonance imaging of the hypothalamus and pituitary are necessary for proper diagnosis.

Subclinical Hypothyroidism

In subclinical hypothyroidism, TSH is elevated but free T_4 is in the normal range. The thyroid gland is stimulated to work harder while still keeping up with the body's metabolic needs. The prevalence of subclinical hypothyroidism is variable, with 8% of women and 3% of men affected, increasing to 15% to 18% in women older than 60 years of age.[9] Annually, 2% to 5% of patients with subclinical hypothyroidism will progress to overt hypothyroidism.[4]

In subclinical hypothyroidism, the clinical decision to prescribe thyroid hormone is based mainly on the presence of symptoms and laboratory results. If a patient is symptomatic, checking TPO Ab may help identify an autoimmune cause (Hashimoto disease) and the risk of progression to overt hypothyroidism. If the TPO Ab test result is positive and the patient is symptomatic, then treatment with low-dose thyroid hormone may be indicated. If the patient has significant symptoms with a borderline TSH level but negative TPO Ab, a low dose of thyroid hormone may still be warranted for several months' trial.

Possible consequences of untreated subclinical hypothyroidism are coronary atherosclerosis, elevated low-density lipoproteins (LDLs), and progression to overt hypothyroidism.[10] Statin-induced myopathy may be associated with mild thyroid insufficiency, so thyroid hormone may be useful for high-risk cardiovascular patients starting statin medication, particularly if their TSH concentration is elevated.[11,12]

The risks of cardiac arrhythmias (atrial fibrillation) and osteoporosis must be weighed against the benefits of receiving thyroid hormone therapy.[4]

Other abnormal laboratory findings in hypothyroidism may include increased creatine phosphokinase, elevated cholesterol and triglycerides, and normocytic or macrocytic anemia.

Integrative Therapy

Tenets of an integrative, functional medicine approach to improving thyroid health include the following[13]:

- Reduce chronic stress from physical, emotional, nutritional, and environmental sources that can promote an overactive immune system, particularly in patients with positive antithyroid antibodies.
- Provide nutrients that are needed for adequate thyroxine (T_4) manufacture, proper T_4 to triiodothyronine (T_3) conversion, and optimal T_3 binding activity to intracellular receptors.
- Exercise and follow a heart-healthy nutrition program to increase energy and maintain weight (or at least stop gaining weight).
- Use appropriate testing, monitoring, and medications as needed to treat hypothyroidism.

Exercise

Along with a heart-healthy, antiinflammatory nutrition plan, exercise is absolutely critical for hypothyroid patients to maintain healthy weight (or stop gaining weight), elevate mood, modify cardiac risk, and increase bone density, especially when they have a decreased metabolic rate (see Chapter 88, Writing an Exercise Prescription).

Nutrition

Foods to Avoid or Limit

Brassica Vegetables

Patients should avoid eating very large amounts of *Brassica* vegetables (e.g., cabbage, turnips, Brussels sprouts, rutabagas, broccoli, cauliflower, bok choy). Millet, peaches, peanuts, pine nuts, strawberries, spinach, and cassava root have small levels of goitrogens as well. These foods are rich in dietary sulfhydryl and thiocyanate compounds that can adversely affect the iodination of thyroglobulin if they are consumed in high amounts.[13,14] An observational study of 37 healthy subjects looked at a high daily soybean intake of 30 g or more over 1 to 3 months. The subjects had within normal range increases in TSH levels and more hypothyroid-like symptoms that normalized 1 month after soybean cessation.[15] When eating a reasonable amount of soy and *Brassica* vegetables (less than 30 g per day), steaming or cooking these foods briefly may help reduce their goitrogenic effect while preserving their nutrient content.[16,17]

Steaming or cooking *Brassica* vegetables and soy briefly may help reduce their goitrogenic effect while preserving their nutrient content.

Soy

Isoflavones are iodinated by TPO, which may be the mechanism for their competitive interference with thyroid hormone production.[14] Genistein, the major soy isoflavone, can be goitrogenic as seen in iodine-deficient neonates exclusively fed soy formula. Soy isoflavones can also aggravate hypothyroidism in iodine-deficient adults.[18] Adequate supplementation of at least 150 mcg of iodine and 200 mcg of selenium may counteract this risk. For adults receiving thyroid hormone replacement therapy who eat soy or take soy supplements, the thyroid hormone may require more frequent dosage surveillance and higher dosing. Ideally, soy foods (in limited amount) and thyroid medication should be taken several hours apart.[19]

A small double-blind randomized placebo-controlled study of iodine-replete healthy postmenopausal women showed that soy supplementation did not significantly affect TSH or serum T_4 or T_3 levels compared with placebo. The supplement used was Novasoy by Archer Daniels Midland (ADM) that contained 40% isoflavones (50 mg isoflavones per capsule), at three capsules a day for 6 months.[20] More research is necessary to determine the effect of soy and goiter development in healthy iodine-sufficient individuals.

Supplements

Several minerals and trace elements are essential for proper thyroid function and metabolism.

Iodine: Too much or too little can cause hypothyroidism; too much can also cause hyperthyroidism.

Iodine Deficiency

Underconsumption of iodine deprives the thyroid gland of manufacturing active thyroid hormones through the organification of iodine. Repleting with iodine is the treatment of choice for iodine deficiency, and it is achieved with varying success in areas of the world by the iodination of refined salt. Iodine lost from salt is estimated to be 20% from production site to table, with another 20% lost during cooking.[21] Thus, iodine should also come from sources such as fresh ocean fish, seaweed, and unrefined sea salt. (Tables 33-1, 33-1e, and 33-2). Short-term iodine repletion with supplements is discussed later for appropriate patients. A minimum of 150 mcg of iodine should be consumed on a daily basis for adults (200 mcg for pregnant women and 290 mcg for lactating women).[22]

Table 33-1e, which compares seaweed iodine by genus, location, and study, can be found online at expertconsult .com.

Iodine Testing

If a patient is suspected to have iodine deficiency caused by dietary restrictions (e.g., seafood avoidance, low salt consumption), iron deficiency, medication use, or heavy metal toxicity, iodine testing may be useful. Because public health programs to iodize salt have occurred worldwide,

TABLE 33-1. Iodine Content of Selected Foods

FOOD	CONTENT (mcg)
Salt, iodized, 1 teaspoon	400
Bread made with iodate dough conditioner and continuous mix process, one slice	142
Bread, made with regular process, one slice (most widely available)	35
Haddock, 3 oz	104–145
Shrimp, 3 oz	21–37
Egg, one	18–26
Cottage cheese 2%, ½ cup	26–71
Cheddar cheese, 1 oz	5–23
Ground beef, 3 oz	8

Adapted from U.S. Department of Agriculture. *Composition of Foods.* USDA handbook no. 8 series. Washington, DC: Agricultural Research Service; 1976–1986.

TABLE 33-2. Commonly Used Seaweed Preparations*

TYPE OF SEAWEED	COMMON USE	AMOUNT TO MEET MINIMUM IODINE DOSE OF 150 mcg/day	AMOUNT TO MEET MAXIMUM IODINE DOSE OF 1100 mcg/day
Nori	Sushi wrapper, rice balls	9 g/day	69 g/day
Wakame	Miso soup	2 g/day	17 g/day
Dulse	Seaweed chips, soups, sauces	2 g/day	15 g/day
Kelp/kombu	Hot pot dishes, soups	9 mg/day	710 mg/day

Adapted from Teas J, Pine S, Critchley A, et al. Variability of iodine content in common commercially available seaweeds. *Thyroid.* 2004;14:839.
*Minimum and maximum daily iodine amounts are based on U.S/Japanese source values.

TABLE 33-1e. Comparison of Seaweed Iodine by Genus, Geographic Location, and Study

SEAWEED ORIGIN AND TYPE	UNITED STATES, CANADA, NAMIBIA, TASMANIA, JAPAN (mcg/g)	UNITED KINGDOM (mcg/g)	CHINA (mcg/g)	FRANCE (mcg/g)	BRITISH COLUMBIA, CANADA (mcg/g)
Arame	586	714	—	—	600
Dulse	72	44	—	—	—
Hijiki	629	391	—	—	436
Kelp granules, tablets (salt substitute)	8165	67	—	—	815
Kelp/kombu	1542	2650	3040	5307	2110
Nori	16	43	36	—	17
Wakame	66	161	1571	—	60
Alaria	—	—	—	—	151

Adapted from Teas J, Pine S, Critchley A, et al. Variability of iodine content in common commercially available seaweeds. *Thyroid*. 2004;14:839.

one may assume that most individuals are iodine replete in targeted countries. However, cases of iodine deficiency have been identified in the United States, a country that has largely eradicated iodine deficiency. The *24-hour urine iodine test* (unprovoked) is the standard test for checking iodine status.[23]

Some clinicians use the *iodine loading test,* a provoked measure of body iodine stores. The test consists of consuming 50 mg of an iodine/iodide combination followed by a 24-hour urine collection. An iodine loading test result is normal if 90% or more iodine was excreted in the urine. If the test resulted in a 75% excretion rate, this would imply that the body needs more iodine.[24,25] If an iodine deficiency is noted from this test, some clinicians have used kelp tablets or iodine/iodide replacement (Lugol's solution or Iodoral). However, the risk of iodine toxicity, transient hyperthyroidism, and hypothyroidism increases with this approach. Iodine supplementation should be recommended for short term only, with iodine sources coming from food thereafter.

The *iodine skin patch test* is unreliable and should not be used in isolation for determining iodine status. The test consists of painting a 3 × 3 inch square of iodine tincture on the inner forearm or abdomen at bedtime. A normal body iodine level is supposedly diagnosed if the orange color of the patch takes longer than 24 hours to disappear. If the patch disappears in 10 hours or less, it implies a significant iodine deficiency. However, the iodine skin patch test fails to take into account the differences in an individual's skin moisture, ambient temperature, and atmospheric pressure, all of which may affect iodine evaporation rate and patch color intensity.

The 24-hour unprovoked urine iodine test is the standard test for checking iodine status.

Iodine Excess

The tolerable upper intake level (UL) for adults is 1100 mcg/day (1.1 mg/day).[26] The UL is the highest level of a daily intake that is likely to pose no risk of adverse health effects to almost all individuals in the general population. Chronic overexposure to iodine reduces organic binding of iodine by the thyroid gland. A daily iodine intake of 10 times (more than 1500 mcg/day) the minimum daily adult requirement may cause iodine goiter in some people, especially in individuals with underlying thyroid abnormalities such as Hashimoto disease.[27–29] Difficulty arises in determining the cumulative daily dose of iodine one is exposed to in food (i.e., kelp, seaweed, food preservatives) and in iodine-containing substances (i.e., medications, contaminated drinking water, topical antiseptics).

Some practitioners believe in using iodine doses much higher than the UL to overcome measured deficiencies for hypothyroidism and even other conditions such as breast cancer.[25] The evidence base on this practice needs larger randomized controlled studies than the current literature offers.

The recommended iodine replacement dose far exceeds the UL, but the UL is not meant to apply to individuals who are treated with the nutrient under medical supervision or to individuals with predisposing conditions that modify their sensitivity to the nutrient.[26] Hence patients with a documented iodine deficiency who are closely monitored should receive dietary or medical iodine replacement. The best dosage and duration of oral iodine replacement vary with the individual patient. A dosing regimen is suggested in the following section. Multiple factors such as a low-salt/low-seafood diet, high goitrogen consumption, and exposure to chlorine, bromine, fluoride, perchlorate, and certain medications, as well as heavy metal toxicity, can negatively influence the iodination steps necessary for thyroid hormone production.[13]

The clinician must use caution in repleting high doses of iodine in a person with a low-iodine state because this can temporarily trigger iodine-induced hyperthyroidism (Jod-Basedow phenomenon) or iodine-induced hypothyroidism (Wolff-Chaikoff effect).

Patients who are taking iodine supplements or kelp tablets should be counseled to report side effects that are consistent with either a worsened hypothyroid state or, conversely, a hyperthyroid state.

Dosage: Dietary Iodine for the General Population

Adult men: 150 mcg up to 1100 mcg
Adult women: 150 mcg up to 1100 mcg
Pregnant women: 220 mcg up to 1100 mcg
Lactating women: 290 mcg up to 1100 mcg[22,26]
The iodized salt equivalent is up to 2.75 teaspoons per day (based on 400 mcg of iodine per 1 teaspoon).

Caution

Do not recommend iodized salt for individuals with congestive heart failure, hypertension, or salt sensitivity. Recommend fish or seaweed for natural iodine supply in these patients.

Dosage: Iodine Tablets or Drops for Documented Iodine Deficiency

For adults with iodine deficiency documented by a 24-hour urinary iodine test, monitor closely for iodine toxicity if oral iodine/iodide is prescribed, and use the supplement for the short term only. Iodine should then be replaced by food sources, and substances that deplete iodine stores should be avoided when possible. See Table 33-1 for selected foods high in iodine.

Lugol solution: two drops contain 5 mg iodine and 7.5 mg iodide as potassium iodide. The dose is two drops orally daily for 1 to 3 months, and then retest.

Iodoral tablet: Each 12.5-mg tablet contains a combination of 5 mg iodine and 7.5 mg iodide as potassium iodide.[30] The dose is one half to one tablet orally daily for 1 to 3 months, and then retest.

Precautions

Monitor for signs of iodine toxicity: brassy taste in the mouth, increased salivation, gastrointestinal upset, and acne. Chlorophyll tablets may ease the metallic taste side effect.[25]

Selenium

Selenium is an essential trace element required for the deiodination of T_4 to active T_3 hormone.[31,32] At least 55 mcg per day of selenium is recommended for adults. A handful of Brazil nuts (six to eight raw nuts) contains approximately 543 mcg of selenium, the highest natural food source of this mineral. See Table 33-3 for foods containing high levels of selenium.[33]

Dosage

Adult men: 55 mcg up to 400 mcg
Adult women: 55 mcg up to 400 mcg
Pregnant women: 60 mcg up to 400 mcg
Lactating women: 70 mcg up to 400 mcg[22,26]

Precautions

The UL for adults is 400 mcg per day, based on the risk of selenosis.[34,35] Excessive intake of selenium (selenosis) can cause discoloration of the skin, deformation and loss of nails, reversible baldness, excessive tooth decay and discoloration, garlic breath odor, weakness, lack of mental alertness, and listlessness.[36]

Vitamin A

Vitamin A is a fat-soluble vitamin obtained directly from animal sources (preformed vitamin A known as retinol) or synthesized from beta-carotene from plant sources. Beta-carotene is a provitamin A precursor that is converted to retinol in the gut.

In persons with vitamin A and iodine deficiency from malnutrition, hypothyroidism risk can be reduced with vitamin A supplementation.[31,37] Vitamin A is involved in T_4 manufacture and in intracellular receptor formation for T_3.[38] In the United States, vitamin A deficiency is most often associated with excess alcohol intake and strict dietary restrictions. Vegetarians who avoid dairy and eggs should be able to meet their vitamin A requirements through beta-carotene by eating at least five servings of fruits and vegetables daily. At least 3 to 6 mg of beta-carotene daily (equivalent to 833 to 1667 units of vitamin A) may maintain blood levels in the range associated with a lower risk of chronic diseases. The highest yielding sources of carotenoids are carrots, cantaloupes, sweet potatoes, and spinach. Most U.S. residents consume enough retinol in milk, margarine, eggs, meat, liver, and fortified ready-to-eat cereals.[39]

TABLE 33-3. Selenium Content of Selected Foods

FOOD	CONTENT (mcg)
Brazil nuts, unblanched, dried, 1 oz (six to eight nuts)	543
Halibut, Atlantic or Pacific, half fillet (159 g weight)	88
Pearled barley, raw, 1 cup	75
Wheat flour, whole grain, 1 cup	74
Lobster, 3 oz	62
Sardines, Atlantic 3 oz	45
Couscous, 1 cup	43

Adapted from U.S. Department of Agriculture (USDA), Agricultural Research Service. USDA National Nutrient Database for Standard Reference. Release 23. Nutrient Data Laboratory. <http://www.ars.usda.gov/ba/bhnrc/ndl>; Accessed 12.08.11.

Dosage: Vitamin A (Preformed)

One microgram retinol is equivalent to 3.33 units vitamin A (on a label) and equivalent to 12 mg beta-carotene (from food).
Adult men: 900 mcg (approximately 3000 units) up to 3000 mcg (approximately 10,000 units) preformed vitamin A
Adult women: 700 mcg (approximately 2300 units) up to 3000 mcg (approximately 10,000 units) preformed vitamin A
Pregnant women: 770 mcg (approximately 2500 units) up to 3000 mcg (approximately 10,000 units) preformed vitamin A
Lactating women: 1300 mcg (approximately 4300 units) up to 3000 mcg (approximately 10,000 units) preformed vitamin A[22,26]

Precautions

Too much preformed vitamin A can lead to toxic symptoms, namely birth defects, liver abnormalities, reduced bone mineral density, and central nervous system disorders. No published UL is available for carotenoids.[26]

Zinc

Abnormal zinc metabolism has been linked to hypothyroidism.[31,40,41] Zinc participates in more than 300 enzymatic reactions, along with multiple functions in transport, immunity, metabolism, and cell structure. Zinc is involved in conversion of T_4 to T_3 through the deiodinase enzyme. Zinc is also necessary to synthesize retinol-binding protein, which transports vitamin A to body tissues, an important factor in T_3 binding to intracellular receptors in the body. Severe zinc deficiency often accompanies vitamin A deficiency in malnutrition or severe dietary restriction. For most of the U.S. population, most zinc in the diet comes from meat, fish, poultry, fortified breakfast cereals, dairy, oysters, liver, dried beans, ginger, soy, and nuts. Good protein intake correlates with zinc intake.[42] The UL for zinc is 40 mg/day for adults.[26]

Dosage

Adult men: 11 mg up to 40 mg
Adult women: 8 mg up to 40 mg
Pregnant women: 11 mg up to 40 mg
Lactating women: 12 mg up to 40 mg[22,26]

Precautions

Doses greater than 40 mg/day can lead to copper deficiency and gastrointestinal irritation.

Iron

Iron deficiency impairs thyroid hormone synthesis by reducing the activity of TPO. In a deficient state, iron supplementation improves the efficacy of iodine

supplementation.[31] Animal sources provide the most potent iron content, with liver, seafood, organ meats, and poultry in descending order of potency. Vegetarian sources of iron are most potent in dried beans, iron-fortified cereal and bread, blackstrap molasses, spinach, peas, and dried apricots. Concomitant intake of vitamin C–rich food or vitamin C as a supplement enhances the gastrointestinal absorption of iron. Laboratory evaluation should include serum ferritin, which reflects the body's iron storage pool. Ferritin is the carrier protein for iron.[42] The UL for iron is 45 mg/day for adults.[26]

Dosage

Adult men and postmenopausal women: 8 mg up to 45 mg/day
Adult premenopausal women: 18 mg up to 45 mg/day
Pregnant women: 27 mg up to 45 mg/day
Lactating women: 9 mg up to 45 mg/day[22,26]

Precautions

Long-term overdose of iron can create abnormal iron accumulation in the liver. Hemochromatosis may result, causing tissue damage. Iron overload can also favor oxidation of LDL cholesterol and the generation of free radicals that may also damage body tissues.[42]

Soy, calcium, and iron supplements should be consumed at least 2 to 3 hours separately from thyroid medication because they may interfere with their bioavailability. Thyroid medication is typically most effective when taken on an empty stomach in the morning, at least 30 minutes before eating breakfast for maximum absorption.

Botanicals

Seaweed

Seaweed is a rich source of naturally occurring iodine and is a good source for meeting daily iodine requirements. Seaweed may aggravate thyroid conditions if too much is ingested, however, as is seen in Asian populations that regularly consume seaweed.

Seaweed iodine content varies by many factors, and this poses a challenge in terms of determining safe consumption levels. The part of seaweed used, cooking method, genus, geographic location, climate, and stage of growth all play a role in seaweed's iodine content. Iodine content is lowest in certain types of seaweed, such as nori and dulse. Iodine is also lowest in seaweed harvested dried on the beach or free-floating in bunches. Iodine level can be reduced by boiling seaweed for 15 minutes and discarding the water. Iodine content is highest if the seaweed is harvested from young plants, stored in watertight and airtight containers, and eaten roasted rather than boiled.[43]

Exercise caution in patients taking blood thinners who consume bladderwrack, an edible brown kelp, which may have some anticoagulant activity.[44] Depending on local pollution levels, edible seaweeds may contain heavy metals such as arsenic and cadmium. Hence selection of high-quality kelp and seaweed from reputable harvesters is ideal to reduce the risk of toxic ingestion.[45] Table 33-1e [online at expertconsult.com] compares differences in seaweed iodine content based on genus and location, and Table 33-2 outlines commonly used seaweed preparations and iodine content based on U.S and Japanese source values.[43]

Guggulu (Commiphora mukul)

Some animal studies showed that the Ayurvedic herb guggulu, a gum resin of the *Commiphora mukul* tree, may stimulate thyroid function. It seems to increase T_3 synthesis by increasing conversion of T_4 to T_3.[46–48] Asian studies showed that guggulu may also improve the hyperlipidemia that often accompanies hypothyroidism.[49]

A double-blind randomized controlled trial in the United States, however, showed that hyperlipidemic patients ingesting a standard Western diet who took a standardized dose of guggulu experienced a rise in LDL cholesterol levels compared with placebo. TSH levels were not significantly different after treatment with guggulu.[50] The differences in medical traditions of Ayurvedic and Western medicine and diet must be considered with respect to these differing results. More research is necessary to study the effects of guggulu in the context of an Ayurvedic treatment plan as opposed to its incorporation as a single ingredient in a conventional Western medicine regimen. Take great care in recommending Asian-source Ayurvedic herbs because some brands commonly found in the United States were found to have significant levels of lead, mercury, and arsenic.[51]

Pharmaceuticals

Synthetic Hormone Replacement: T_4 Alone Versus Combination T_4 Plus T_3

The use of combination T_4 (levothyroxine) plus T_3 (liothyronine) therapy versus T_4 alone has been controversial.[52–56] The conventional medicine treatment of choice for hormone replacement in hypothyroidism remains T_4 alone.[57]

Proponents of combination therapy have advised the use of sustained-release T_3 plus T_4, or the use of porcine thyroid (e.g., Armour, Nature-Throid, Westhroid), which contains natural T_3 and T_4 plus other iodinated compounds. Another good option is to use compounded T_3 and T_4 from a reliable compounding pharmacy. The best candidates for this kind of combination therapy typically have had unsatisfactory results from T_4 therapy alone despite proper dosage titration and TSH monitoring.[2,55,56]

Desiccated Porcine Thyroid Replacement

Porcine thyroid hormone (e.g., Armour, Nature-Throid, Westhroid) is an older medication used in hypothyroidism considered by some in the medical community to be obsolete and by others as equally efficacious or superior to synthetic hormones. Desiccated porcine thyroid contains approximately 20% T_3 and 80% T_4, as well as other iodinated compounds, diiodotyrosine (T_2) and monoiodotyrosine (T_1), which may play a role in providing additional relief of symptoms. As with its synthetic T_4

TABLE 33-4. Adult Thyroid Hormone Dosage Recommendations

THYROID HORMONE	GENERIC (TRADE NAME)	STARTING ORAL DOSE	AVERAGE DAILY DOSE AND TITRATION
Synthetic T_4 alone	T4 levothyroxine (Synthroid, Unithroid, Levoxyl) Note: Stick with one formulation (generic or name brand) throughout the course of treatment because of dose variability	100 mcg daily[a] or 25–50 mcg daily in older or sensitive patients	200–300 mcg daily[a] Titrate every 6 weeks until symptoms improved and TFTs normalize Follow TFTs every 6 months or sooner if symptoms arise[a]
Synthetic T_4 + T_3 separate tablets or compounded together by a reliable compounding pharmacy	T_4 levothyroxine + T_3 liothyronine (Cytomel)	100 mcg T_4 + 25 mcg T_3 daily[a] or 25–50 mcg T_4 + 12.5 mcg T_3 daily in older or sensitive patients	Titrate T_4 as above Titrate T_3 by 12.5–25 mcg/day every 1–2 weeks to a maximum of 100 mcg/day;[a] sustained-release T_3 may be more effective[b]
Synthetic T_4 + T_3 combination tablet (Liotrix)	Liotrix (Thyrolar) Liotrix is a uniform mixture of synthetic T_4 and T_3 in 4:1 ratio by weight	1 tablet = 50/12.5 mcg of T_4 and T_3 Various proportions available Start with 1–2 tablets daily[a]	Use if simplification of dosing is necessary; no therapeutic advantage over using T_4 + T_3 as separate doses[a]
T_4 and T_3 desiccated porcine thyroid gland	Armour, Nature-Throid, or Westhroid 1 grain = 60 mg = 38 mcg T_4 + 9 mcg T_3	Start with ¼–½ grain = 15–30 mg daily[c]	60–120 mg (1–2 grains) daily Titrate by 15 mg (¼ grain) orally every 2–3 weeks[c]

T_3, triiodothyronine; T_4, levothyroxine; TFTs, thyroid function tests (thyroid-stimulating hormone, free T_4, free T_3).
[a]Data from Lexi-Comp Online.[58]
[b]Data from Blanchard[55] and Henneman et al.[56]
[c]Data from Gaby[2] and Armour Thyroid Web site.[59] For converting synthetic T_4 and T_3 to desiccated porcine thyroid, see http://www.armourthyroid.com.

and T_3 counterparts, close monitoring of symptoms and a regimen of thyroid function tests are important when taking care of a patient prescribed porcine thyroid replacement. Recommended thyroid hormone dosages are shown in Table 33-4.[2,55,56,58,59]

1 grain (60 mg) desiccated porcine thyroid = 100 mcg thyroxine (T_4) and 25 mcg triiodothyronine (T_3).

Other Endocrine Factors to Consider When Treating Hypothyroidism

The thyroid gland does not work in isolation and requires inputs from a complex web of chemical messages, notably from the brain, gut, gonads, and adrenal glands. Balancing the interplay of hormones (and reducing the stressors that diminish their function) is important in the holistic treatment of thyroid disease. Chapter 47 (Effective Treatment of Chronic Fatigue Syndrome, Fatigue, Fibromyalgia, and Muscle/Myofascial Pain: A Comprehensive Medicine Approach) specifically addresses the evaluation and treatment for adrenal gland insufficiency, which plays an important role in thyroid dysfunction.

Therapies to Consider

Traditional Chinese Medicine

In the traditional Chinese medicine (TCM) system, the diagnosis and treatment of individuals with a conventional medicine diagnosis of hypothyroidism depend on the history, tongue, and pulse diagnosis. Hypothyroidism is generally considered to be a deficiency of spleen or kidney "yang" energy, especially if the disorder is characterized by cold sensation, lack of appetite, fatigue, and weight gain. Weight gain is evidence of "dampness," which is a complication of spleen or kidney yang deficiency. The spleen and kidney are considered too weak to transform excess dampness, thus causing accumulation of fat and swelling. The clinician should appreciate that these findings are classic and may not adequately describe an individual's complete TCM diagnosis.[60]

Herbal treatment in hypothyroidism aims to strengthen qi and yang deficiency. Qi and yang tonics may include codonopsis, astragalus, epimedium, curculigo, cinnamon bark, and cuscata, to name a few.[61]

TCM therapies include acupuncture, herbs, moxibustion, nutrition, massage, and movement. The therapeutic effect of these therapies on hypothyroidism may result from promotion of T_4 deiodination with production of more active T_3.[62–65] Research in this area is necessary to understand the mechanisms of action of TCM in the treatment of thyroid disease more fully.

Yoga

Hatha Yoga is a component of the philosophical doctrine of Yoga. Hatha Yoga is the physical training that prepares the body for a spiritual path through poses (asanas), breathing exercises, and asceticism (self-denial and active self-restraint). The body is prepared with this physical practice so that the mind can meditate without obstacles. Asanas are special positions of the body that may strengthen, purify, and balance the endocrine, nervous, and circulatory systems. Although asanas are rarely prescribed to treat specific illnesses, they may have healing properties.

The shoulder-stand asana (Sarvāngāsana) may help stimulate the thyroid and parathyroid glands because these glands receive increased blood flow from the firm chin lock of the pose.[66] In this pose, the body is positioned more

or less perpendicular to the floor, with the head and neck tucked under, the chest brought forward to touch the chin, and the hands strongly supporting the back (Figs. 33-1 and 33-2). Frequent practice with a skilled instructor and strengthening of the neck, back, and core muscles allow the body gradually to straighten and become more perpendicular to the floor. Contraindications to this pose include spinal osteoarthritis, cervical disk disease, neck injury, hypertension, glaucoma, stroke, and vertebrobasilar syndrome. Inversion poses such as the shoulder stand should be avoided in women who are menstruating and after the first trimester of pregnancy.[67,68]

FIGURE 33-1
Modified Sarvāngāsana. (Courtesy of Ms. Polly Liontis, RYT.)

FIGURE 33-2
Sarvāngāsana. (Courtesy of Ms. Polly Liontis, RYT.)

Prevention Prescription

- Consume a diet with adequate amounts of iodine, selenium, iron, vitamin A, and zinc.
- Do not consume excessive amounts of iodine for long periods of time.
- Avoid substances that block thyroid hormone synthesis, such as chlorine, bromine, perchlorate, and certain medications, as well as radiation to the head and neck area when possible.

Therapeutic Review

Exercise

- Maintain a regular aerobic and weight-bearing exercise routine. A1

Nutrition

- Eat a heart-healthy, antiinflammatory diet to maintain proper body weight and reduce cardiovascular risk. A1
- Limit goitrogenic foods and avoid substances that interfere with thyroid activity.
- Limit vegetables from the *Brassica* family (cabbage, turnips, Brussels sprouts, rutabagas, broccoli, cauliflower, bok choy), millet, peaches, peanuts, pine nuts, strawberries, spinach, and cassava root. Cook vegetables briefly to reduce goitrogenic substances and consume at least 2 to 3 hours separately from thyroid medication. A1
- Avoid the following medications and toxins, if possible: lithium, thionamides, amiodarone, interferon-alpha, interleukin-2, cholestyramine, perchlorate, expectorants, aluminum hydroxide, raloxifene, heavy metals, chlorine, fluoride, and bromine. A2

Continued

- Avoid topical antiseptics (Betadine) and radiocontrast dyes when possible. A2

Supplements

- Vitamins and minerals (preferably consumed in food)
  - Iodine*: 150 to 1100 mcg/day A2
  - Iron: 8 to 45 mg/day A2
  - Selenium: 55 to 400 mcg/day A2
  - Vitamin A†: 2300 to 10,000 units/day A2
  - Zinc: 8 to 40 mg/day A2

Botanicals

- Seaweed: Total iodine content should not exceed 1100 mcg/day for the general population unless on targeted megadose therapy. See Table 33-2 for assistance in determining allowable grams per day, depending on the variety of seaweed. B2
- Guggulu: Consider using it in the context of an Ayurvedic treatment regimen and not as an isolated treatment for hypothyroidism or hyperlipidemia. Take care to avoid heavy metal toxicity in certain Asian formulations. C2

Pharmaceuticals

- Levothyroxine alone (T_4): gold standard of therapy A2
- Synthetic combination T_3 plus T_4: considered if T_4 alone fails to control symptoms adequately; may use compounded formulations B2
- Desiccated porcine thyroid: considered if synthetic T_3 plus T_4 fails to control symptoms adequately or based on patient preference or physician experience B2

Traditional Chinese Medicine

- Qi and yang tonics include codonopsis, astragalus, epimedium, curculigo, cinnamon bark, and cuscata. A traditional Chinese medicine practitioner with a strong background and certification in Chinese herbalism should prescribe these combinations. C2

Mind-Body Therapy

- Advise yoga therapy with an emphasis on thyroid-enhancing poses such as the shoulder stand (Sarvāngāsana) if the patient has no contraindications.
- Yoga practice may be helpful even without challenging poses such as the shoulder stand, for the purposes of stress reduction, meditation, enhanced flexibility, and strength. C1

* Consider testing for iodine deficiency. Use Lugol solution or Iodoral tablet for documented deficiency for a limited time when the patient is unable to increase iodine through diet or is unable to reduce exposure to iodine-depleting medications or substances. C2

† Most people in the United States receive an adequate supply of preformed vitamin A (retinol) in milk, liver, margarine, and fortified cereals. Beta-carotene from plants is an excellent source of vitamin A.

KEY WEB RESOURCES

MedlinePlus information on thyroid diseases. http://www.nlm.nih.gov/medlineplus/thyroiddiseases.html.	This Web site from the U.S. National Library of Medicine of the National Institutes of Health provides patient information for the conventional diagnosis and treatment of thyroid disease.
American Thyroid Association. http://www.thyroid.org.	This Web site provides patients and physicians with guidelines for the conventional diagnosis and treatment of thyroid disease.
About.com information on thyroid disease. http://www.thyroid.about.com.	This patient advocate Web site provides a forum for patients to discuss integrative therapies for managing thyroid disease through novel testing, nutrition, supplements, and alternative thyroid medication use.

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Chapter 34

Hormone Replacement in Men

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Pathophysiology

Testosterone Production

Conversion of cholesterol and steroid hormones occurs in only three organs: the adrenal cortex, the testis in men, and the ovary in women. Whereas most endocrine texts discuss adrenal, ovarian, testicular, placental, and other steroidogenic processes in a gland-specific fashion, steroidogenesis is better understood as a single process that is repeated in each gland with cell type–specific variations on a single theme.[1] The relative activity of the steroidogenic enzymes in each of the three organs determines the major secreted product. This is not absolute, however, and other organs are capable of secreting small amounts. In pathologic situations such as a defect in steroidogenesis or a steroid-secreting tumor, a very abnormal pattern of steroid secretion may be observed.[2]

Testosterone is made primarily by the testes. Testosterone production depends on intact hypothalamus, pituitary gland, and testicular Leydig cells.[3] These Leydig cells make up less than 10% of the testicular volume and produce 95% of circulating testosterone.[4] A small amount of testosterone is also produced in the adrenal glands and other tissues such as the fat cells by conversion from adrenal androgens such as dehydroepiandrosterone (DHEA) and androstenedione into testosterone.[5]

Testosterone is produced from the conversion of cholesterol, a 27-carbon molecule, by using enzymes that are cytochrome P-450 proteins requiring oxygen and reduced nicotinamide-adenine dinucleotide phosphate (NADPH). The biosynthetic pathway is largely made up of cleavage of carbon-carbon bonds and hydroxylation reactions.[1] The first and rate-limiting step in steroidogenesis is the conversion of cholesterol to pregnenolone, a 21-carbon molecule, by a single enzyme, P450scc (CYP11A1), but this enzymatically complex step is subject to multiple regulatory mechanisms.[6] Chronic quantitative regulation is principally at the level of transcription of the CYP11A1 gene encoding P450scc, which is the enzymatically rate-limiting step. Acute regulation is mediated by the steroidogenic acute regulatory protein (StAR), which facilitates the rapid influx of cholesterol into mitochondria, where P450scc resides.[1] Cholesterol is converted to pregnenolone, which produces other possible precursors such as progesterone, 17-alpha hydroxy-progesterone, androstenedione, 17-alpha hydroxy-pregnenolone, DHEA, and androstenediol. These reactions can be seen in Figure 34-1.

The anterior hypothalamus secretes gonadotropin-releasing hormone in a pulsatile fashion. This hormone then stimulates the pituitary to secrete luteinizing hormone (LH) in a pulsatile fashion as well. Investigators have established that steroidogenesis in Leydig cells is mainly regulated by LH, through the interaction with its receptors coupled to the adenylate cyclase–cyclic adenosine monophosphate signaling pathway.[6] The LH stimulates the Leydig cells in the testes to produce testosterone, a 19-carbon corticosteroid. Testosterone can then be aromatized in adipose tissue to estradiol, an 18-carbon corticosteroid. Testosterone can also be converted, by 5-alpha-reductase, to dihydrotestosterone (DHT).

Dihydrotestosterone

DHT, one of the two important androgens in boys and men, is synthesized in the prostate, testes, hair follicles, and adrenal glands. In men, approximately 5% of testosterone undergoes 5-alpha reduction to form the more potent androgen DHT. DHT has three times greater affinity for androgen receptors than does testosterone.[7] During embryogenesis, DHT has an essential role in the formation of the male external genitalia, and in the adult, DHT acts as the primary androgen in the prostate and hair follicles.

DHT is generated by reduction of testosterone by the enzyme 5-alpha-reductase (Fig. 34-2). Two isoenzymes of 5-alpha-reductase have been discovered. Type 1 is present in most tissues of the body where 5-alpha-reductase is expressed and is dominant in sebaceous glands. Type 2 5-alpha-reductase is dominant in genital tissues, including

FIGURE 34-1
The steroidogenic pathways. DHEA, dehydroepiandrosterone; DHT, dihydrotestosterone.

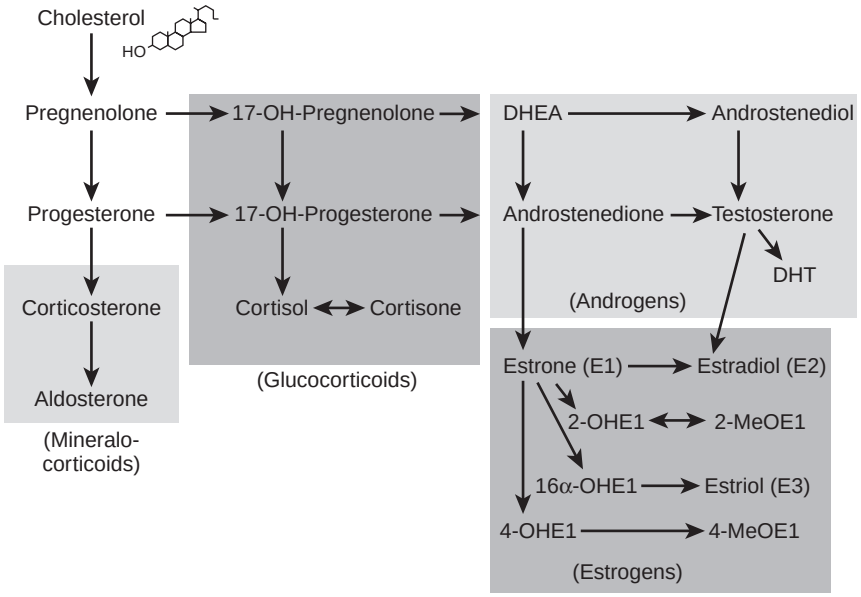
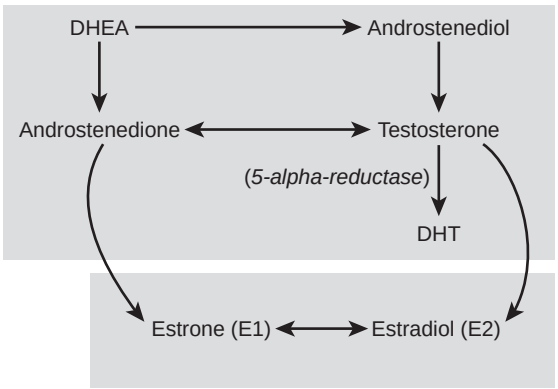


FIGURE 34-2
Androgens. DHEA, dehydroepiandrosterone; DHT, dihydrotestosterone.



the prostate.[8] Because DHT is the primary prostatic androgen, it may have a significant role in prostate disease pathogenesis.[9] In reality, the prostate has only one function, which is to secrete seminal fluid to support the sperm, assisting in reproduction. This process requires an extremely high concentration of androgens in the tissues. This allows DHT, with its greater affinity for testosterone receptors, to enhance the tissue response to androgens in the prostate.

Benign prostatic hypertrophy (BPH) seems to be related to long-term exposure of the prostate to DHT and possibly to estrogens.[10] Serum DHT levels are not elevated in humans with BPH; they remain at a normal level with aging despite a decrease in plasma testosterone.[8] Investigators hypothesized that DHT may provide an amplification mechanism for testosterone that could be a beneficial effect in men with low

BOX 34-1. 5-Alpha-Reductase Inhibitors

Finasteride
Dutasteride
Zinc
Progesterone
Saw palmetto
L-Lysine
Epigallocatechin gallate (ECGC)
Linolenic acid

circulating testosterone. Since then, the essential role of DHT in the development of BPH has been recognized; treatment has focused on blocking the 5-alpha-reductase enzymes (Box 34-1).[11,12]

The normal level of DHT in the blood is approximately one tenth that of testosterone, but the affinity of DHT for androgen receptors is three times greater. Amory et al[13] looked at the effects of reduction of serum DHT on bone mineral density, serum lipoproteins, hemoglobin, prostate-specific antigen (PSA), and sexual function in healthy young men. By blocking 5-alpha-reductase using dutasteride and finasteride, these investigators significantly suppressed circulating DHT levels. They found that this therapy did not affect bone mineral density, markers of the metabolism, serum lipoproteins, or hemoglobin. Serum PSA and self-assessed sexual function decreased during treatment with both 5-alpha-reductase inhibitors but returned to baseline during follow-up.[13] Therefore, sexual function has some relationship with the circulating serum level of DHT, and aggressively lowering that level, even without lowering testosterone, may potentially affect libido and sexual arousal.

Dehydroepiandrosterone

DHEA is not a hormone. It is a very important prohormone secreted in large amounts by the adrenals in humans and other primates, but not in lower species. DHEA is secreted in larger quantities than cortisol and is second in blood concentration only to cholesterol.[14] Humans are unique in that their adrenal glands can secrete large amounts of DHEA and its sulfate (DHEA-S), which are converted to androstenedione and then into androgens and estrogens and peripheral tissues. This gives the tissues autonomous intracrine control, so they can adjust the formation and metabolism of active sex steroids according to local requirements. Investigators have estimated that 30% to 50% of total androgens in men are synthesized in peripheral intracrine tissues from an adrenal precursors.[15]

> Intracrinology, a term coined in 1988, describes local formation, action, and inactivation of the sex steroids from the inactive sex steroid precursor dehydroepiandrosterone.[16]

When human development is completed and adulthood is reached, DHEA and DHEA-S levels start to decline from age 25 years. By 70 to 80 years of age, peak DHEA-S concentrations are only 10% to 20% of those in young adults.[14,17] The marked reduction in the production of DHEA-S by the adrenals during aging results in the dramatic fall in the availability of active sex steroids in peripheral target tissues. This change is thought to be associated with age-related illnesses such as insulin resistance, obesity, osteoporosis, cardiovascular disease, loss of muscle mass, cancer, and other diseases.[15] Genazzani et al[17] discussed the findings that DHEA appears to be beneficial in hypoandrogenic men, as well as in postmenopausal and aging women.

DHEA administration has been shown to reduce accumulation of abdominal visceral fat and protect against insulin resistance. Villareal et al[18] showed that DHEA therapy, when compared with placebo in a randomized double-blind placebo-controlled trial, resulted in a significant decrease in visceral and subcutaneous fat, as well as in a significant increase in insulin sensitivity. A possible explanation for the findings is that DHEA is an activator of peroxisome proliferator-activated receptor-alpha (PPAR-alpha). Activation of PPAR-alpha induces transcriptional up-regulation of fatty acid transport proteins that facilitate fatty acid entry into cells and the enzymes involved in the beta oxidation of fatty acids. This process favors increased fat oxidation and reduced fat deposition.[18] Hernández-Morante et al[19] took this one step further and focused on gender-specific fat distribution. They found that serum DHEA-S was inversely and specifically associated with visceral fat area, as assessed by computed tomography in men and with waist-to-hip ratio (WHR) in women. Therefore, DHEA-S promotes lipolysis preferably in subcutaneous fat in women and in visceral fat in men.[19]

The activation of PPAR-alpha also gives DHEA-S a role in inhibition of vascular inflammation in human aortic endothelial cells. Altman et al[20] found that DHEA-S can reduce inflammation in vascular endothelial cells by a mechanism involving the PPAR-alpha receptor that inhibits transcription factors involved in endothelial cell inflammation. In addition, treatment of endothelial cells with DHEA-S dramatically inhibited the tumor necrosis factor-alpha–induced activation of necrosis factor (NF)-kappa beta-alpha, an inflammatory transcription factor. These results signified the ability of DHEA-S to inhibit the inflammatory process and showed potential direct effects on vascular inflammation.[20] DHEA was also shown to increase endothelial cell proliferation and enhance large and small vessel endothelial cell function.[21,22]

Because visceral fat, inflammation, and endothelial cell function are all related to cardiovascular disease, correlation of DHEA levels with the risk of cardiovascular disease makes sense. In fact, this association was seen in several studies. In 2003, Thijs et al[23] looked at a total of 12 studies and calculated the pool relative risk associated with levels of DHEA-S. These investigators found a 13% increase in fatal coronary heart disease with a 2 micromol/L decrease in DHEA-S.[23] Barrett-Connor et al[24] studied the relationship of baseline circulating DHEA-S levels with subsequent 12-year mortality from any cause, from cardiovascular disease, and from ischemic heart disease in a cohort of men aged 50 to 79 years at the start of the study. The mean DHEA-S levels decreased with age and were significantly lower in men with a history of heart disease. In addition, these investigators found that an increase in DHEA-S was associated with a reduction in overall mortality from any cause and an even greater reduction in mortality from cardiovascular disease. These investigators concluded that DHEA-S concentration is independently and inversely related to death from any cause and death from cardiovascular disease in men older than 50 years.[24] These results were confirmed in 2010 by Ohlsson et al[25] after studying a cohort of 2644 men, age 69 to 81 years, with a mean follow-up of 4.5 years. These investigators concluded that low serum levels of DHEA-S predict death from all causes, from cardiovascular disease, and from ischemic heart disease in older men.[25] What we do not know at this time, however, is whether supplementing with DHEA reduces risk or is safe with regard to other risks, such as prostate cancer.

Estrogen

Testosterone can be converted into estradiol by an aromatase enzyme. Androstenedione can also be converted into estrone, which can then be converted into estradiol through a reversible reaction. Androgen-to-estrogen conversion, however, is irreversible. Because aromatase enzymes are seen in fat cells, obesity is associated with increased conversion of testosterone to estradiol. Aromatase levels are known to rise with age.[26] This increase often causes a relative imbalance of estrogen and testosterone in men as they grow older. In addition to having a decreased output of testosterone with age, the age-related increase of aromatase causes older men to convert what testosterone they do produce into estrogen.

Other possible mechanisms for increasing aromatization to estradiol include liver dysfunction, zinc deficiency, and excessive alcohol consumption.[27] Excess estrogen or an elevated estrogen-to-testosterone ratio can cause gynecomastia, breast tenderness, BPH (from estrogenic stimulation of the prostate stromal tissue), and impotence (from blockage of DHT receptors by estradiol).[28]

However, estrogen plays several very important roles in men. These roles were elucidated when a few men who lacked aromatase or estrogen receptors were studied. Investigators found that these men had problems including osteopenia, abnormal lipid profiles, hyperinsulinemia, and glucose intolerance.[29,30] When appropriately balanced with testosterone, estrogen also appears to have a role in libido and sexual desire in men. In a study by Carani et al,[31] a man who lacked aromatase enzyme was followed during the course of testosterone therapy, estradiol therapy, and combination therapy with estradiol and testosterone. His libido significantly improved only with combination therapy.[31]

To help maintain an optimal balance of estradiol and testosterone naturally, the patient should appropriately manage his weight, with a focus on limiting central adiposity. In addition, he should limit alcohol, caffeinated beverages, and tightly fitting undergarments because these stimulate conversion of testosterone to estradiol. If lifestyle changes are not enough, the use of aromatase inhibitors may be necessary (Box 34-2).

Testosterone Decline

The daily average production of testosterone in healthy young men is 7 mg. Testosterone levels peak for men in their 20s. After the age of 40 years, a 0.2% to 2% annual decline is observed in morning total testosterone.[32] Half the healthy men between the ages of 50 and 70 years have a bioavailable testosterone level lower than the lowest level seen in healthy men who are 20 to 40 years of age.[33] At the age of 75 years, the mean total testosterone level in the morning is approximately 66% of the mean level at age 20 to 30 years. However, the mean free testosterone and bioactive testosterone (free testosterone plus albumin-bound testosterone) levels are only 40% of the mean levels in younger men.[34] Testosterone levels decline because of decreased production secondary to reduced Leydig cell activity and decreasing LH, as well as increased binding of available testosterone by sex hormone–binding globulin.[35]

Testosterone has a circadian rhythm. Testosterone levels are approximately 20% higher in the morning than in the evening. Investigators noted that the circadian rhythm in serum testosterone levels found in normal young men is markedly attenuated or absent in healthy older men. The early morning rising testosterone levels characteristic of young men is not present in the older men.[36] Research suggests that the decline in nocturnal testosterone secretion appears to involve a combination of testicular and pituitary hypogonadism.[32]

In 2006, Travison et al[37] observed that recent years had seen a substantial and yet unrecognized age-independent population level decrease of testosterone in men in the United States. These investigators reported that a population level decline was greater in magnitude than the cross-sectional decline in testosterone typically associated with age. They hypothesized that the observed age-matched decline resulted from an undocumented historical or contemporary or environmental influence that had not yet been identified.[37] Obesity, stress, medication use, metabolic syndrome, and environmental toxins such as bisphenol A (BPA) and phthalates are known to contribute to low testosterone.[38–43] Therefore, patients should be monitored for signs and symptoms of low testosterone. Helping them understand that things they can do in everyday life may to help maintain optimal testosterone levels is even more important. Besides aging alone, lifestyle and different comorbidities are associated with the decline in total testosterone level. This finding suggests that the age-related decline in total testosterone may be at least partly prevented through the management of potentially modifiable risk factors and health-related behavior.[11]

BOX 34-2. Aromatase Inhibitors

Anastrozole (Arimidex)
Letrozole (Femara)
Quercetin
Chrysin*
Resveratrol/grape seed extract
Zinc
Progesterone

*Many studies show limited usefulness.

Obesity, stress, metabolic syndrome, and environmental toxins (bisphenol A, phthalates) can lead to low testosterone levels. Exercise, avoiding weight gain, and not smoking can reduce the rate of decline of testosterone.

Mortality

Several studies have linked androgen deficiency to increased mortality in men.[44] In 2007, Maggio et al[45] looked at the mortality rate of men over the course of 6 years in the InCHIANTI study compared with their levels of testosterone, DHEA-S, and insulin-like growth factor-I (as an indicator of growth hormone level). These investigators stated: "Multisystem disorders that are widely prevalent in aging, such as the metabolic syndrome, frailty syndrome, and chronic heart failure, are more significantly associated with multiple hormonal dysregulation rather than a single hormonal derangement. Studies have found that the risk of death increases progressively with the number of dysregulated hormones and becomes 2.5 times higher when 3 hormones are dysregulated compared with no dysregulation."[45] Laughlin et al,[46] in the Rancho Bernardo study, followed 794 men for up to 20 years (average, 11.8 years) and found that men with total testosterone and bioavailable testosterone levels in the lowest quartile were 40% more likely to die of all causes than were men with testosterone levels in the highest quartile.

Symptoms Associated With Low Testosterone

Approximately 30% of men 60 years old and older are estimated to have low testosterone,[47] which is often accompanied by undesirable signs and symptoms such as low bone and muscle mass, increased fat mass (especially central adiposity), low energy, low libido, and impaired physical, sexual, and cognitive function. That these complaints have clinical consequences is supported by prospective cohort studies showing that men with low testosterone are at increased risk of falls[48]; hip fracture, if estradiol is also low[49]; anemia[50]; type 2 diabetes[51]; depressive illness[52]; and, in some studies, Alzheimer disease.[53,54] Table 34-1 is a review of evidence regarding testosterone and specific conditions.[26,44,47,51,54–73]

TABLE 34-1. Evidence of Androgen-Deficient Effects on Specific Conditions

CONDITION	EVIDENCE
Obesity	BMI is inversely associated with free testosterone. This may be related to the increased conversion of testosterone to estrogen by aromatase that occurs in visceral fat.[26]
Metabolic syndrome	Low TT may predict the onset of diabetes and has been associated with increased risk.[55–57] High TT is associated with less risk.[51] Low TT is associated with insulin resistance and risk of metabolic syndrome.[44,58] A meta-analysis of 20 studies found that testosterone therapy resulted in a reduction in FBS, TG, and waist circumference and a rise in HDL.[58]
Heart disease	TT is lower in men with CVD.[44] Low TT is associated with visceral obesity, insulin resistance, low HDL, and high TG and LDL.[59] Low TT is associated with an increased risk of aortic atherosclerosis independent of BMI, lipids, smoking, and ETOH intake.[54,60] Low TT is associated with hyperlipidemia including TC, LDL, and TG.[61,62] Low TT is associated with higher mortality in men with CAD.[63]
Alzheimer disease	Androgens and estrogens have a neuroprotective effect and have been associated with less beta amyloid plaque and enhanced neuron survival in AD.[64] AD patients treated with testosterone improved over the course of a year.[65] High TT levels have been associated with better performance in memory, executive function, and spatial ability.[66,67]
Depression	Some studies suggest low TT in depressed men.[68,69] Men with low TT often present with depressive symptoms.[70] In men with refractory depression, those treated with testosterone gel versus placebo had greater improvement in Hamilton depression scores, a finding suggesting potential benefit in augmenting therapy in this population.[71] This gel appears less beneficial as monotherapy.[72]
Osteoporosis	Low TT is found in 20% of men with symptomatic vertebral fractures and in 50% of older men with hip fractures.[73] Testosterone therapy along with calcium, vitamin D, weight-bearing exercises, smoking cessation, falls prevention, and limited ETOH intake, should be considered in men with osteoporosis.[47]

AD, Alzheimer disease; BMI, body mass index; CAD, coronary artery disease; CVD, cardiovascular disease; ETOH, ethyl alcohol; FBS, fasting blood sugar; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglycerides; TT, total testosterone.

BOX 34-3. Physical Signs of Testosterone Deficiency

Dry eyes
Reduced muscle tone
Depressed attitude
Poor concentration and memory
Decreased axillary and pubic hair
Pale skin
Anemia
Increased fat deposits in breast, abdomen, and hips
Nervousness and irritability

BOX 34-4. Signs and Symptoms of Low Testosterone

Decreased muscle mass and strength
Decreased sex drive
Reduced frequency and firmness of erections; reduced ejaculate volume
Hot flushes
Excessive emotions and sensitivity to difficulty
Unnecessary worry, anxiety, and fear
Depression
Loss of self-confidence
Joint pains
Persistent fatigue that increases with activity

From Hertoghe T. *The Hormone Handbook*. Walton-on-Thames, UK: International Medical Publications; 2006:219.

Diagnosis of Testosterone Deficiency

The diagnosis of testosterone deficiency rests on physical signs, symptoms, and laboratory values demonstrating symptomatic, inadequate testosterone levels. Men with acquired hypogonadism, as seen after trauma or orchiectomy, note certain well-documented changes in body composition, mood, strength, libido, and erectile function. Because testosterone levels naturally decrease with aging, it can be difficult to define which older men are actually androgen deficient and should have testosterone therapy. Therefore, each individual patient should be treated based on specific signs and symptoms (Boxes 34-3 and 34-4) combined with laboratory assessment showing low testosterone levels.

Laboratory Testing for Testosterone Deficiency

Testosterone can be evaluated by several testing modalities. These include tests of serum, urine, saliva, and capillary blood spot. However, most published studies on testosterone use serum levels. That being said, follow-up testing should be done with consideration for the therapeutic modality being used. For example, serum levels are excellent

ways to measure testosterone therapy that uses injections, pellets, transdermal gels, and oral micronized testosterone. However, transdermal creams do not readily equilibrate in the serum for several weeks and thus may be more difficult to evaluate. Saliva and urine tests are better for evaluating transdermal creams.

Serum testing is best for measuring testosterone therapy given by injection, pellets, transdermal gels, and oral micronized oral formulations. Saliva and urine tests are better modalities for evaluating transdermal creams.

Testing should be done at the same time of the day each time, preferably first thing in the morning. For optimal results, the patient should avoid sexual intercourse, vigorous exercise, or intense emotional stress for 24 to 72 hours before testing. In addition to testing testosterone levels, evaluation of other hormones should be done as well, especially before starting testosterone therapy. Because metabolic syndrome and cardiovascular disease are so closely tied to testosterone deficiency, evaluations of insulin sensitivity and cardiovascular risk factors are important. The function of the hypothalamic-pituitary-adrenal (HPA) axis is also closely tied to testosterone level and to the success of therapy. Therefore, I recommend a four-point cortisol level to evaluate diurnal cortisol rhythms in the health of the HPA axis (Box 34-5).

BOX 34-5. Recommended Baseline Laboratory Testing for Testosterone Deficiency (Serum)

Total and free testosterone
Sex hormone–binding globulin (SHBG)
Dihydrotestosterone
Dehydroepiandrosterone (DHEA)
Ultrasensitive estradiol
Luteinizing hormone and follicle-stimulating hormone (LH and FSH)
Prolactin (prolactinoma can suppress testosterone levels)
Prostate-specific antigen (PSA)
Complete blood cell count (CBC)
Chemistry panel with liver functions tests (LFTs)
Lipid panel
Fasting insulin
Fasting glucose
Hemoglobin A1c
Cardiovascular C-reactive protein
Homocysteine
Vitamin D
Zinc level
Salivary diurnal cortisol

Integrative Therapy

Supplements

Zinc

Zinc is an important cofactor in many metabolic reactions within the body. In addition, zinc has been implicated in testicular development, sperm maturation, and testosterone synthesis. Therefore, zinc deficiency may affect testosterone production and male fertility.[74] Hartoma et al[75,76] were able to demonstrate a significant positive correlation between serum zinc and serum testosterone in men 36 to 60 years old.

In rats, cadmium toxicity was used to induce testicular disease that resulted in significant decreases in plasma testosterone level, sperm count, and motility. The addition of zinc and selenium to the cadmium caused reductions in the serum and testicular cadmium concentrations and offered more efficient protection against testicular damage.[77] Another article by He et al[78] showed that supplementation with zinc and selenium are "favorably related to androgen deficiency and sperm production." Netter et al[79] looked at men with idiopathic infertility of more than 5 years' duration. These investigators found that when serum testosterone was low, administration of oral zinc increased testosterone, DHT, and sperm count. In the group whose testosterone level was within normal limits, administration of oral zinc did not increase testosterone or sperm count. However, DHT increased significantly.[79]

The relationships among chronic renal disease, zinc deficiency, low libido, and testosterone levels have been studied for decades. In 1977, Antoniou et al[80] looked at impotent men who were undergoing hemodialysis and who had low plasma zinc levels, low libido, and low plasma testosterone. These investigators compared administration of zinc with that of placebo and found that, "dialytic administration of zinc strikingly improved potency in all patients and raised the plasma testosterone to normal in those with low testosterone. Zinc deficiency is a reversible cause of gonadal dysfunction."[80] In 2010, Vecchio et al[81] also studied sexual dysfunction in patients with chronic kidney disease. These investigators found that "oral zinc improved the end of treatment testosterone levels."[81]

Dosage

Usual dose is 15 to 30 mg daily.

Precautions

Zinc should not be given with other minerals because of inhibition of absorption (particularly copper).

Botanicals

Saw Palmetto

Saw palmetto *(Serenoa repens)* is a weak inhibitor of 5-alpha-reductase. Therefore, it could reduce the conversion of testosterone to DHT. It may also have a role in reducing the number of estrogen and DHT receptors. Sinescu et al[82] showed that long-term treatment with 320 mg *Serenoa repens* proved to be efficient in reducing urinary obstruction and improving symptoms and quality of life in patients with BPH.

Wilt et al[83] stated that the evidence suggests that *Serenoa repens* improves urologic symptoms and flow measures.

Compared with finasteride, *Serenoa repens* produced similar improvements in urinary tract symptoms and urinary flow and was associated with fewer adverse treatment events. Further research is needed using standardized preparations of *Serenoa repens* to determine its long-term effectiveness and ability to prevent complications of BPH despite recent research showing limited benefit.[83]

Bonvissuto et al[84] studied the antiinflammatory effects of *Serenoa repens,* lycopene, and selenium on prostate inflammation in rats. These investigators showed that, in comparison with single agents, the combination of *Serenoa repens,* lycopene, and selenium in vivo reduced prostate inflammation induced in rats by bladder outlet obstruction.[84]

Dosage

The dose is 160 mg twice daily or 320 mg daily.

Precautions

Side effects are mainly gastrointestinal, including nausea, vomiting, constipation, and diarrhea. Saw palmetto can also cause dizziness.

Chrysin

Chrysin is a naturally occurring flavone that can be chemically extracted from the blue passion flower *(Passiflora caerulea).* It is also reported in *Oroxylum indicum* or Indian trumpet flower. Flavones, or flavonoids, have been used as drugs and food supplements and are reported to have antioxidant, antibacterial, antiinflammatory, and antiviral properties.[85,86] Chrysin (5,7-dihydroxyflavone) was once believed to be an effective aromatase inhibitor, inhibiting the conversion of testosterone to estradiol and decreasing the levels of estrogen in the body. Several in vitro studies supported the aromatase inhibitory activity of chrysin. In the 1980s, Kellis et al[87,88] found that chrysin had significant aromatase-inhibitory activity when it was tested with placental microsomes. Afterward, several other studies drew similar conclusions.[89–94]

However, the growing consensus is that chrysin has limited effect on estrogen levels in either animals or humans. Unfortunately, follow-up studies have determined that cell membranes effectively block chrysin from entering the cells and having any effect at all on estrogen levels in biologic organisms.[90,95,96] In vivo studies involving biologic organisms lend support to the observation that chrysin has no effect on estrogen levels, but it may have other detrimental effects on the body, particularly on thyroid function.[97]

Lifestyle Overview

Lifestyle plays a critical role in the balance of male hormones. The hypogonadal axis is very closely tied to diet, amount and quality of sleep, level of stress, and toxin exposure. Therefore, whether or not hormone therapy is to be instituted, lifestyle factors need to be evaluated and corrected.

Toxin Exposure

Increasing numbers of reports suggest that chemical and physical agents in the environment affect testosterone levels and male fertility. The different potential toxin exposures include pesticides, food additives and preservatives, organophosphates, polychlorinated biphenyls (PCBs), electromagnetic radiation, heavy metal toxicity, phthalates, and BPA. The additives in our food and processed foods, such as refined sugar and high-fructose corn syrup, create a strain in the detoxification system as we try to handle foods our body was never intended to use. In addition, many of these additives, such as hydrogenated fats, high-fructose corn syrup, artificial sweeteners, flavor enhancers, and preservatives, do not contain beneficial nutrients. Therefore, we are eating foods that may add calories without providing nutrition, thus creating hormone imbalance.

Phthalates

Phthalates are esters of phthalic acid and are mainly used as plasticizers. Billions of pounds of phthalates had been produced worldwide. Phthalates were introduced in the 1920s and are currently used for enteric coatings, viscosity control agents, lubricants, and binders.[98] We come in contact with phthalates every day in our shampoos, colognes, detergents, cleaning materials, paints, food packaging, and many other places. In 2008, the United States Research Council[41] recommended investigating the cumulative effect of phthalates and other antiandrogens. The Council stressed that the effect of phthalates should be examined together with other antiandrogens, which otherwise may have been excluded, because their structures were different. Various effects on the development of the reproductive system can be observed in boys and men at much lower doses than previously observed after exposure to various phthalates. Phthalate syndrome has been described and includes infertility, decreased sperm count, cryptorchidism, hypospadias, and other reproductive tract malformations.[41]

Bisphenol A

BPA has been used in commerce since the 1960s and is primarily used to make plastics. It is currently used in polycarbonate bottles (clear, flexible plastic) such as water bottles. It is also found in baby bottles, dental sealants, sports equipment, eyeglasses, CDs and DVDs, and in the lining of aluminum cans.[99] BPA is a known endocrine disrupter and can mimic estrogens.[100] Early development appears to be the time of greatest sensitivity to its effects. In 2007, a consensus statement by 38 experts on BPA concluded that the average levels in people are higher than those that cause harm to animals in laboratory experiments.[101] BPA and phthalates appear to be related to obesity. In 2008, Elobeid et al[102] concluded that obesity may be increased as a function of BPA exposure. In 2009, Rubin et al[103] stated that in a review of available studies, perinatal BPA exposure acts to exert persistent effects on body weight and adiposity. The relationship is strong enough that another review in 2009 concluded that eliminating exposures to BPA and improving nutrition during development offered the potential for reducing obesity and associated diseases.[104]

BPA is also linked to prostate disease. A 2006 study in rats showed that neonatal BPA exposure at 10 mcg/kg levels increased prostate gland susceptibility to adult-onset precancerous lesions and hormonal carcinogenesis.[105] In 2007, Richter et al[106] did an in vitro study showing that BPA exposure is associated with permanently increased prostate size. The correlation was confirmed again in 2009, when

Prins et al[107] found that newborn rats exposed to a low dose of BPA (10 mcg/ kg) had increased prostate cancer susceptibility as adults.

Organophosphates and Polychlorinated Biphenyls

Organophosphates and PCBs are also creating problems. Several studies suggested that human semen quality has declined over the past decades, and some investigators associated this decline with occupational exposure to pesticides. In 2008, Recio-Vega et al[108] evaluated the effect on semen quality of organophosphate pesticides at three occupational exposure levels. The worst semen quality was found among subjects with the highest organophosphate exposure and the highest urinary organophosphate levels.[108] PCBs are a class of persistent organic pollutants that were widely used in the midtwentieth century. Although their production and use was banned in most countries several decades ago, the general population continues to be exposed because of the persistence and accumulation of PCBs. Regardless of study design or measurement method, the adverse association between PCB level and sperm motility may suggest a lack of exposure threshold for PCB-related effect on sperm motility. In addition, some studies also reported an adverse association between PCBs and circulating testosterone levels in men.[109,110]

Reducing Toxin Exposure

Although many of our foods come in packaging that contains BPA, we can still reduce our exposure. Plastic should not be heated, given that heating can trigger release of chemicals. This is true even for microwave-safe containers because, although they do not disintegrate, they may still leach toxins into the food. Plastic storage containers are also labeled depending on the type of resin used to make the container. The bottom of plastic containers usually has a triangle with a number that identifies the type of resin used. Containers marked with a number 2 (high-density polyethylene), number 4 (low-density polyethylene), or number 5 (polypropylene) are designed to be reused and do not leach chemicals. Bottles marked number 1 (polyethylene terephthalate) are for one-time use and should not be reused; however, they are safe for the one-time use. Containers marked number 3 (polyvinyl chloride), number 6 (polystyrene), and number 7 (polycarbonate) leach chemicals into the food and should be avoided. Polycarbonate plastics (number 7) leach the most BPA. Some plastics made from corn husks and other plants are a more environmentally safe, sustainable option. These are labeled number 7 PLA (polylactide biodegradable corn), and they should be used when available. Plastic wrap, freezer bags, and sandwich bags may or may not leach chemicals. It depends on the brand. The National Geographic Society produces the Green Guide (www.TheGreenGuide.com), which provides an updated list of specific safe brands of freezer bags and sandwich bags.

Plastics marked with a number 2, 4, 5, and 7 PLA are the safest to use. Those marked with a number 1 should be used only once, and those marked with a 3, 6, or 7 should not be used at all. Those marked as 7 PLA (made from corn husks) appear to be safe.

Mind-Body Therapy: Stress Reduction

The HPA axis, the mediator of cortisol, plays an essential role in hormone balance and general homeostasis. That acute distress activates the sympathetic nervous system and HPA axis is well documented. In addition, chronic stress, with its prolonged high cortisol levels and subsequent increases in visceral adipose tissue, can create a vicious circle. Visceral fat leads to increased inflammation and cytokine production, which creates increased demand for cortisol and increased visceral adipose tissue. Studies have shown that patients with central obesity have increased cortisol secretion. A high WHR is associated with low production of sex steroids, such as testosterone in men.[111] In addition, studies of the HPA axis and the hypothalamic-pituitary-testicular (HPT) axis have revealed a reciprocal relationship between these two endocrine pathways. Stress can have varying effects on testosterone secretion, and increased levels of glucocorticoids can abolish normal HPT rhythmicity.[112] Rivier[113] hypothesized that cytokine release by inflamed tissues, an event that may precede any symptoms, is responsible for activation of the HPA axis and, independently, for decreased activity of the HPT axis.

Long-term overactivation of the HPA axis results in low diurnal cortisol variation and blunted dexamethasone suppression, findings that indicate abnormal regulation of the HPA axis. This HPA axis abnormality has been reported to be a characteristic consequence of frequently repeated or chronic environmental stress challenges. Rosmond et al[114] studied men with normal cortisol variability as compared with those with low variability (abnormal HPA regulation). These investigators showed that in men with low diurnal cortisol variability, stress-related cortisol secretion showed a strong negative relationship with testosterone, insulin-like growth factor-I, high-density lipoprotein, and obesity factors (body mass index, WHR) and blood pressure.[114] The close association of HPA axis dysfunction may explain the previously reported powerful risk of abdominal obesity on low testosterone, cardiovascular disease, type 2 diabetes, and stroke.[115]

Sleep

A very strong relationship exists between sleep efficacy and testosterone production. In addition, increased concentrations in HPA axis hormones have been noted in sleep-deprived individuals. Changes in nocturnal testosterone are sleep related, with levels rising during sleep and falling on waking. Peak testosterone levels coincide with rapid eye movement (REM) sleep onset. The decreasing sleep efficacy in numbers of REM sleep episodes with altered REM sleep latency is associated with lower concentrations of circulating testosterone. This situation is normally seen in older men. In addition, sleep curtailment has been shown to lead to reduced levels of circulating androgens in healthy young men as well.[116] Penev[117] objectively measured differences in amount of nighttime sleep and showed that the amount of nighttime sleep was an independent predictor of the morning total testosterone levels of his subjects. Reduced sleep duration is also associated with an increased incidence of type 2 diabetes. Short sleep times of 5.5 hours per night were associated with weight gain, reduced oral glucose tolerance, and reduced insulin sensitivity[118] (see Chapter 8, Insomnia).