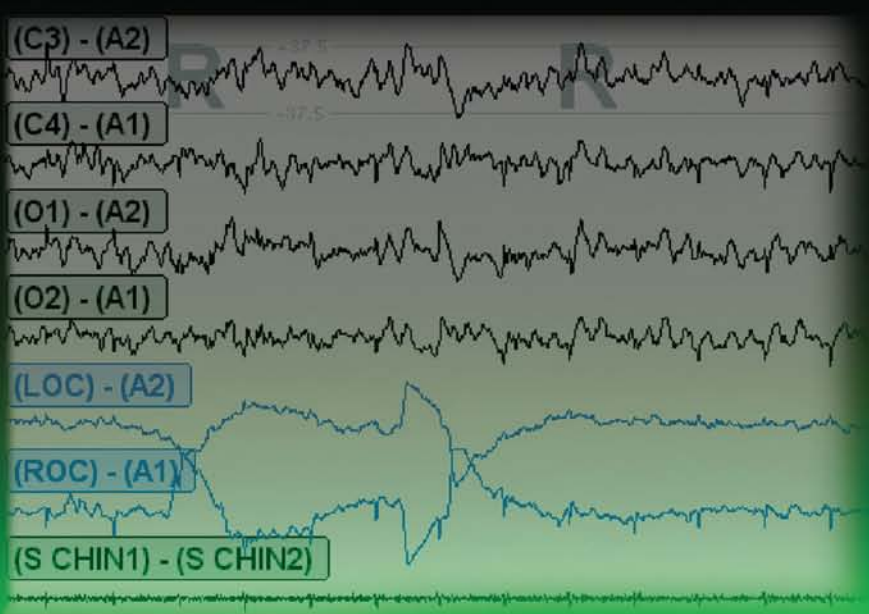
Clinician's Guide to Sleep Disorders



Edited by

Nathaniel F. Watson
Bradley V. Vaughn

Clinician's Guide to Sleep Disorders

NEUROLOGICAL DISEASE AND THERAPY

Advisory Board

1. Handbook of Parkinson's Disease, *edited by William C. Koller*
2. Medical Therapy of Acute Stroke, *edited by Mark Fisher*
3. Familial Alzheimer's Disease: Molecular Genetics and Clinical
   Perspectives, *edited by Gary D. Miner, Ralph W. Richter, John P. Blass, Jimmie L. Valentine, and Linda A. Winters-Miner*
4. Alzheimer's Disease: Treatment and Long-Term Management, *edited by Jeffrey L. Cummings and Bruce L. Miller*
5. Therapy of Parkinson's Disease, *edited by William C. Koller and George Paulson*
6. Handbook of Sleep Disorders, *edited by Michael J. Thorpy*
7. Epilepsy and Sudden Death, *edited by Claire M. Lathers and Paul L. Schraeder*
8. Handbook of Multiple Sclerosis, *edited by Stuart D. Cook*
9. Memory Disorders: Research and Clinical Practice, *edited by Takehiko Yanagihara and Ronald C. Petersen*
10. The Medical Treatment of Epilepsy, *edited by Stanley R. Resor, Jr., and Henn Kutt*
11. Cognitive Disorders: Pathophysiology and Treatment, *edited by Leon J. Thal, Walter H. Moos, and Elkan R. Gamzu*
12. Handbook of Amyotrophic Lateral Sclerosis, *edited by Richard Alan Smith*
13. Handbook of Parkinson's Disease: Second Edition, Revised and Expanded, *edited by William C. Koller*
14. Handbook of Pediatric Epilepsy, *edited by Jerome V. Murphy and Fereydoun Dehkharghani*
15. Handbook of Tourette's Syndrome and Related Tic and Behavioral Disorders, *edited by Roger Kurlan*
16. Handbook of Cerebellar Diseases, *edited by Richard Lechtenberg*
17. Handbook of Cerebrovascular Diseases, *edited by Harold P. Adams, Jr.*
18. Parkinsonian Syndromes, *edited by Matthew B. Stern and William C. Koller*
19. Handbook of Head and Spine Trauma, *edited by Jonathan Greenberg*
20. Brain Tumors: A Comprehensive Text, *edited by Robert A. Morantz and John W. Walsh*

21. Monoamine Oxidase Inhibitors in Neurological Diseases, *edited by Abraham Lieberman, C. Warren Olanow, Moussa B. H. Youdim, and Keith Tipton*
22. Handbook of Dementing Illnesses, *edited by John C. Morris*
23. Handbook of Myasthenia Gravis and Myasthenic Syndromes, *edited by Robert P. Lisak*
24. Handbook of Neurorehabilitation, *edited by David C. Good and James R. Couch, Jr.*
25. Therapy with Botulinum Toxin, *edited by Joseph Jankovic and Mark Hallett*
26. Principles of Neurotoxicology, *edited by Louis W. Chang*
27. Handbook of Neurovirology, *edited by Robert R. McKendall and William G. Stroop*
28. Handbook of Neuro-Urology, *edited by David N. Rushton*
29. Handbook of Neuroepidemiology, *edited by Philip B. Gorelick and Milton Alter*
30. Handbook of Tremor Disorders, *edited by Leslie J. Findley and William C. Koller*
31. Neuro-Ophthalmological Disorders: Diagnostic Work-Up and Management, *edited by Ronald J. Tusa and Steven A. Newman*
32. Handbook of Olfaction and Gustation, *edited by Richard L. Doty*
33. Handbook of Neurological Speech and Language Disorders, *edited by Howard S. Kirshner*
34. Therapy of Parkinson's Disease: Second Edition, Revised and Expanded, *edited by William C. Koller and George Paulson*
35. Evaluation and Management of Gait Disorders, *edited by Barney S. Spivack*
36. Handbook of Neurotoxicology, *edited by Louis W. Chang and Robert S. Dyer*
37. Neurological Complications of Cancer, *edited by Ronald G. Wiley*
38. Handbook of Autonomic Nervous System Dysfunction, *edited by Amos D. Korczyn*
39. Handbook of Dystonia, *edited by Joseph King Ching Tsui and Donald B. Calne*
40. Etiology of Parkinson's Disease, *edited by Jonas H. Ellenberg, William C. Koller and J. William Langston*
41. Practical Neurology of the Elderly, *edited by Jacob I. Sage and Margery H. Mark*

42. Handbook of Muscle Disease, *edited by Russell J. M. Lane*
43. Handbook of Multiple Sclerosis: Second Edition, Revised and Expanded, *edited by Stuart D. Cook*
44. Central Nervous System Infectious Diseases and Therapy, *edited by Karen L. Roos*
45. Subarachnoid Hemorrhage: Clinical Management, *edited by Takehiko Yanagihara, David G. Piepgras, and John L. D. Atkinson*
46. Neurology Practice Guidelines, *edited by Richard Lechtenberg and Henry S. Schutta*
47. Spinal Cord Diseases: Diagnosis and Treatment, *edited by Gordon L. Engler, Jonathan Cole, and W. Louis Merton*
48. Management of Acute Stroke, *edited by Ashfaq Shuaib and Larry B. Goldstein*
49. Sleep Disorders and Neurological Disease, *edited by Antonio Culebras*
50. Handbook of Ataxia Disorders, *edited by Thomas Klockgether*
51. The Autonomic Nervous System in Health and Disease, *David S. Goldstein*
52. Axonal Regeneration in the Central Nervous System, *edited by Nicholas A. Ingoglia and Marion Murray*
53. Handbook of Multiple Sclerosis: Third Edition, *edited by Stuart D. Cook*
54. Long-Term Effects of Stroke, *edited by Julien Bogousslavsky*
55. Handbook of the Autonomic Nervous System in Health and Disease, *edited by C. Liana Bolis, Julio Licinio, and Stefano Govoni*
56. Dopamine Receptors and Transporters: Function, Imaging, and Clinical Implication, Second Edition, *edited by Anita Sidhu, Marc Laruelle, and Philippe Vernier*
57. Handbook of Olfaction and Gustation: Second Edition, Revised and Expanded, *edited by Richard L. Doty*
58. Handbook of Stereotactic and Functional Neurosurgery, *edited by Michael Schulder*
59. Handbook of Parkinson's Disease: Third Edition, *edited by Rajesh Pahwa, Kelly E. Lyons, and William C. Koller*
60. Clinical Neurovirology, *edited by Avindra Nath and Joseph R. Berger*
61. Neuromuscular Junction Disorders: Diagnosis and Treatment, *Matthew N. Meriggioli, James F. Howard, Jr., and C. Michel Harper*

62. Drug-Induced Movement Disorders, *edited by Kapil D. Sethi*
63. Therapy of Parkinson's Disease: Third Edition, Revised and Expanded, *edited by Rajesh Pahwa, Kelly E. Lyons, and William C. Koller*
64. Epilepsy: Scientific Foundations of Clinical Practice, *edited by Jong M. Rho, Raman Sankar, and José E. Cavazos*
65. Handbook of Tourette's Syndrome and Related Tic and Behavioral Disorders: Second Edition, *edited by Roger Kurlan*
66. Handbook of Cerebrovascular Diseases: Second Edition, Revised and Expanded, *edited by Harold P. Adams, Jr.*
67. Emerging Neurological Infections, *edited by Christopher Power and Richard T. Johnson*
68. Treatment of Pediatric Neurologic Disorders, *edited by Harvey S. Singer, Eric H. Kossoff, Adam L. Hartman, and Thomas O. Crawford*
69. Synaptic Plasticity : Basic Mechanisms to Clinical Applications, *edited by Michel Baudry, Xiaoning Bi, and Steven S. Schreiber*
70. Handbook of Essential Tremor and Other Tremor Disorders, *edited by Kelly E. Lyons and Rajesh Pahwa*
71. Handbook of Peripheral Neuropathy, *edited by Mark B. Bromberg and A. Gordon Smith*
72. Carotid Artery Stenosis: Current and Emerging Treatments, *edited by Seemant Chaturvedi and Peter M. Rothwell*
73. Gait Disorders: Evaluation and Management, *edited by Jeffrey M. Hausdorff and Neil B. Alexander*
74. Surgical Management of Movement Disorders (HBK), *edited by Gordon H. Baltuch and Matthew B. Stern*
75. Neurogenetics: Scientific and Clinical Advances, *edited by David R. Lynch*
76. Epilepsy Surgery: Principles and Controversies, *edited by John W. Miller and Daniel L. Silbergeld*
77. Clinician's Guide to Sleep Disorders, *edited by Nathaniel F. Watson and Bradley V. Vaughn*
78. Amyotrophic Lateral Sclerosis, *edited by Hiroshi Mitsumoto, Serge Przedborski and Paul H. Gordon*

Clinician's Guide to Sleep Disorders

edited by

Nathaniel F. Watson, M.D.
University of Washington School of Medicine
Seattle, Washington, U.S.A.

Bradley V. Vaughn, M.D.
The University of North Carolina School of Medicine
Chapel Hill, North Carolina, U.S.A.

Taylor & Francis
Taylor & Francis Group
New York London

Published in 2006 by
Taylor & Francis Group
270 Madison Avenue
New York, NY 10016

Printed in the United States of America on acid-free paper
10 9 8 7 6 5 4 3 2 1

International Standard Book Number-10: 0-8247-2930-7 (Hardcover)
International Standard Book Number-13: 978-0-8247-2930-1 (Hardcover)
Library of Congress Card Number 2005044632

Library of Congress Cataloging-in-Publication Data

Clinician's guide to sleep disorders / edited by Nathaniel F. Watson, Bradley Vaughn.
p. ; cm. -- (Neurological disease and therapy ; v. 77)
Includes bibliographical references and index.
ISBN-13: 978-0-8247-2930-1 (alk. paper)
ISBN-10: 0-8247-2930-7 (alk. paper)
1. Sleep disorders. I. Watson, Nathaniel F. II. Vaughn, Bradley. III. Series.
[DNLM: 1. Sleep Disorders. WM 188 C6426 2006]

RC547.C555 2006
616.8'498--dc22 2005044632

informa
Taylor & Francis Group
is the Academic Division of Informa plc.

Visit the Taylor & Francis Web site at
http://www.taylorandfrancis.com

Preface

The prominence of sleep and sleep disorders medicine has increased significantly in recent years. This greater awareness necessitates an improved knowledge of sleep disorders by all physicians, particularly primary care providers. Although sleep specialists are available to care for these patients, the high prevalence of sleep disorders dictates that non-specialists be adept at managing these disorders as well. This book was written with these practitioners in mind.

Many excellent comprehensive sleep texts currently exist. However, their thorough nature limits their practical usefulness in a busy clinic. We sought to create a text covering the breadth of clinical sleep medicine using a symptom-based approach that could be referenced "on the fly" in clinical practice. As such, we created chapter headings that are descriptive of symptoms rather than specific disorders. We further listed symptoms at the beginning of each chapter, along with the responsible disorders. We relied heavily on tables and figures to make the book friendly and a quick reference, and generally limited discussion of disease pathophysiology to those elements necessary to help patients understand their afflictions. Our goal was a readable book, whether from cover to cover or table to table. We strove to leave out nothing necessary, while keeping in nothing superfluous. We hope this book facilitates primary care providers and non-sleep specialists as they care for patients with sleep complaints.

The first two chapters, one reviewing the general approach to patients with sleep complaints and the other covering diagnostic tests, provide the foundation for the diagnosis of all sleep disorders discussed in this book. Chapters 3 through 9 address specific sleep disorders and common sleep related issues. These chapters provide practical information regarding the diagnostic evaluation and therapeutic management of patients with these disorders. Chapters 10 and 11 consider special groups of patients with unique sleep related challenges, while Chapter 12 speculates regarding future directions in the field of sleep medicine. We believe these chapters will provide

busy clinicians with the framework to successfully identify and manage patients with sleep disorders.

We carefully followed the current International Classification of Sleep Disorders diagnostic headings and criteria in an effort to facilitate a common language between sleep specialists and non-sleep specialists alike. Some topics are addressed in more than one chapter, more a function of the diverse nature of sleep disorders than undisciplined writing. When appropriate, the reader is directed to the primary chapter for the topic of interest.

Each of the contributing authors was chosen based on their authoritative and unique understanding of their particular topic. The energy and enthusiasm they brought to their work is clearly evident in their respective chapters. Without them, this book would not have been possible and we sincerely thank them for their efforts. We encourage our readers to share with us their experiences and thoughts regarding this book. Only in this manner will we be able to continue to move forward the field of sleep disorders medicine.

In closing, we would like to thank Jinnie Kim, Dana Bigelow, and the editorial staff at Taylor & Francis for their unwavering commitment and enthusiasm for this book. We would also like to thank our families, for without their support and encouragement this work would not have been possible. As such, we dedicate this book to them: Phyllis, Benjamin, Karen, Heather, Courtney, and Jennifer.

Nathaniel F. Watson
Bradley V. Vaughn

Contents

Contributors

Maha Alattar Department of Neurology, University of North Carolina–Chapel Hill, Chapel Hill, North Carolina, U.S.A.

Richard P. Allen Department of Neurology, Johns Hopkins University School of Medicine, Johns Hopkins Center for RLS, Baltimore, Maryland, U.S.A.

Oneil S. Bains Section of Sleep Medicine, Virginia Mason Medical Center, Seattle, Washington, U.S.A.

O'Neill F. D'Cruz Departments of Neurology and Pediatrics, University of North Carolina–Chapel Hill, Chapel Hill, North Carolina, U.S.A.

William J. DePaso Sleep Disorders Center at Virginia Mason Medical Center, Seattle, Washington, U.S.A.

Madeleine M. Grigg-Damberger Department of Neurology, University of New Mexico School of Medicine and Pediatric Sleep Medicine Services, University Hospital Sleep Disorders Center, Albuquerque, New Mexico, U.S.A.

Vishesh K. Kapur Department of Medicine and University of Washington Sleep Disorders Center at Harborview, University of Washington, Seattle, Washington, U.S.A.

Mark Quigg Department of Neurology, University of Virginia, Charlottesville, Virginia, U.S.A.

Bradley V. Vaughn Department of Neurology, The University of North Carolina School of Medicine, Chapel Hill, North Carolina, U.S.A.

Nathaniel F. Watson Department of Neurology, University of Washington School of Medicine, Seattle, Washington, U.S.A.

Edward M. Weaver Sleep Disorders Center and Department of Otolaryngology, Head and Neck Surgery, University of Washington and Veterans Affairs Puget Sound Healthcare System, Seattle, Washington, U.S.A.

1

Approach to the Patient with a Sleep Complaint

Vishesh K. Kapur

Department of Medicine and University of Washington
Sleep Disorders Center at Harborview, University of Washington,
Seattle, Washington, U.S.A.

Symptoms	***Differential Diagnoses***
Insomnia	*Psychiatric disorders*
	Psychophysiological insomnia
	Obstructive sleep apnea
	Inadequate sleep hygiene
	Idiopathic insomnia
	Restless legs syndrome
	Environmental sleep disorder
	Adjustment insomnia
	Delayed sleep phase disorder
	Medications
	Medical disorders
Hypersomnia	*Insufficient sleep syndrome*
	Obstructive sleep apnea
	Periodic limb movement disorder
	Medications
	Narcolepsy
	Idiopathic hypersomnia
	Mood disorders
Unusual sleep behaviors	*Confusional arousals*
	Sleepwalking
	Sleep terrors
	Rhythmic movement disorder
	REM sleep behavior disorder
	Sleep-related epilepsy
	Periodic limb movement disorder
Disturbances in the timing of sleep	*Jet lag disorder*
	Shift work sleep disorder
	Irregular sleep–wake rhythm disorder
	Delayed sleep phase disorder
	Advance sleep phase disorder
	Non-24 hr sleep–wake disorder

INTRODUCTION

Sleep occupies one-third of our lives and significantly influences the other two-thirds. Sleep is not just the absence of wakefulness but rather an essential life process with its own distinct physiology. Descriptions of sleep can be found through the ages. The Upanishads, an ancient Indian philosophy text (circa 1000 B.C.), considered that dreaming and deep dreamless sleep comprised two of the four states of being (1). Sleep phenomena are described in many Western works as well (2). Greek mythology includes Hypnos, the god of sleep, and the hero Endymion, who after a kiss from the moon sleeps forever and remains eternally youthful. In Shakespeare's *Macbeth*, Lady Macbeth suffers from nightmares and sleepwalking after helping Macbeth kill the king of Scotland. Charles Dickens' *Pickwick Papers* described the sleepy fat boy Joe, who likely had obesity-hypoventilation syndrome, a disorder associated with obstructive sleep apnea.

Though sleep has been acknowledged in literary, artistic, and religious works through the ages, modern medicine has underestimated its influence on human functioning. In the last 50 years, much has been learned about sleep physiology, pathophysiology, and its impact on humans. This includes recognition of the high prevalence of sleep disorders such as obstructive sleep apnea, insomnia, and restless legs syndrome, and the effect of these disorders on health and society. A better understanding of sleep has led to the development of sleep disorders medicine, an active and growing field consisting of scientists and clinical specialists focusing on sleep and its disorders.

Understanding sleep medicine is important for the general practitioner, as sleep-related complaints such as insomnia and sleepiness are ubiquitous in society (Table 1). One-third of adults have frequent symptoms of insomnia, 9% to 15% of whom suffer daytime consequences (3). Excessive sleepiness is present in more than 10% of adults (9). Restless legs syndrome and obstructive sleep apnea affect 3% and 10% of the population, respectively, making

Table 1 Prevalence of Sleep Disorders in Adults

Disorder/complaint	Prevalence (%)	Methods of definition
Insomnia	9–15	Symptoms and daytime dysfunction (3)
Obstructive sleep apnea	3	AHI >5 and hypersomnia (4)
Narcolepsy	0.026	International classification of sleep disorders criteria using interview and polysomnography (5)
Restless legs syndrome	10	International restless legs study group criteria (6)
Sleepwalking	2	Telephone interview (7)
REM sleep behavior disorder	0.5	Telephone interview (8)

Abbreviation: REM, rapid eye movement.

them some of the most common disorders known to man (4,6). The ubiquitous nature of sleep problems makes it essential for the primary care provider to understand the fundamentals of sleep physiology and clinical sleep medicine. This will not only facilitate management of these problems in clinic, but also help dictate when to refer the patient to a sleep specialist.

SLEEP PHYSIOLOGY

Sleep physiology includes sleep states (sleep stages and the ultradian rhythm), factors influencing alertness, sleep timing, and duration (circadian rhythm, homeostasis, and individual sleep need), and organ system variability (e.g., autonomic nervous system). From a behavioral standpoint, sleep is a reversible immobile unconscious state characterized by closed eyes and reduced responsiveness to external stimuli. This definition of sleep persisted for centuries until a physiological description was possible following the advent of electroencephalography (EEG) by Hans Berger in 1928 (10). This technique demonstrated differences in brain electrical activity occurring at sleep onset that persisted throughout sleep. Using EEG and electrooculography (EOG, electrical activity generated by eye movements), Nathaniel Kleitman and Eugene Aserinsky discovered rapid eye movement (REM) sleep in 1951. This state was physiologically distinct from the rest of sleep, termed nonrapid eye movement (NREM) sleep (10). In 1957, Kleitman and William Dement performed continuous nighttime EEG and EOG recordings of sleep, demonstrating a predictable alternating pattern of NREM and REM sleep called the ultradian rhythm (10).

Sleep Is Nonhomogenous

Electrical recordings highlight the nonhomogenous nature of sleep. Sleep consists of two distinct states that are as different from each other as they are from wakefulness. The majority (80%) of sleep time is spent in NREM sleep consisting of four sleep stages. Stage 1 is a brief (5%) transition between wakefulness and deeper NREM sleep stages. Stage 2 sleep occupies a majority of sleep time (50–55%) with characteristic bursts of 12–16 Hz "sleep spindles" and distinctive high-amplitude 0.5–1 Hz "K-complexes." Stages 3 and 4 are termed slow-wave sleep (SWS) or "delta" sleep due to the presence of slow 0.5–4 Hz high-amplitude waves. Slow-wave sleep comprises about 20% of sleep time and represents the deepest stages of NREM sleep. During this stage, sleep is particularly restorative and the arousal threshold is high. REM sleep makes up 20% of sleep and comprises two phases. Tonic REM exhibits muscle hypotonia on electromyography (EMG) and a desynchronized EEG. Phasic REM is characterized by bursts of rapid eye movements and myoclonic twitches of facial and limb muscles. Like SWS, REM sleep is considered a restorative sleep stage and one or both are typically reduced when sleep

Table 2 Normative Values for Sleep Stage Percentages

Gender	Stage 1	Stage 2	Stages 3/4	Stage REM
Men (%)	4	58	15	21
Women (%)	4	52	22	21

Note: Median sleep stage percentages in community dwelling adults ≥40 years of age without sleep complaints.
Abbreviation: REM, rapid eye movement.
Source: From Ref. 11.

disruption is present. Table 2 provides normative values for the various sleep stages in adults over the age of 40 (11).

Rapid eye movement and NREM sleep differ not only in the nature of brain electrical activity (desynchronized in REM vs. synchronized in NREM), muscle tone (lower in REM), and eye movements (rapid vs. slow or absent) but also in the relative functions of the respiratory, cardiac, and autonomic nervous systems. During NREM sleep, there is an increase in parasympathetic and decrease in sympathetic outflow relative to quiet wakefulness (12). In REM sleep, parasympathetic tone also increases and sympathetic tone decreases even further. Autonomic instability during phasic REM results in surges of sympathetic activity (12).

Regarding the respiratory system, sleep onset is associated with loss of voluntary control of respiration, resulting in greater reliance on chemoregulation. Furthermore, the apneic threshold (the pCO_2 level below which resting ventilation is inhibited) increases and chemosensitivity is reduced. This reliance on chemoregulation and the increase in the apneic threshold predispose to central apneas in the setting of fluctuations of pCO_2, as seen at sleep onset or following cortical arousals. Other changes affecting respiration include a decrease in metabolism (decreased VCO_2 and VO_2) and increased upper airway resistance secondary to hypotonia of upper airway muscles, a condition that predisposes to obstructive sleep apnea. In comparison to wakefulness, minute ventilation decreases due to a change in tidal volume cause pCO_2 to rise and pO_2 to fall (13).

Variability in respiration is also observed in different sleep stages. In NREM sleep, breathing is regular and rhythmic, as opposed to REM sleep where tidal volume and rate vary. Respiratory muscle function is compromised during REM sleep due to atonia of accessory muscles (intercostals) and reduced tonic muscle activity of the diaphragm (13). As a result, hypoventilation is frequently seen during stage REM.

The Ultradian Rhythm

Continuous physiologic recordings of sleep demonstrate a cycling between NREM and REM sleep during the night. This "ultradian rhythm"

is represented graphically by the hypnogram showing the progression of sleep stages over time (Fig. 1). Typically, 4 to 6 cycles of NREM and REM sleep occur in 90–110-minute intervals during the night. The first REM episode occurs approximately 70 minutes after sleep onset and is usually the shortest of the night. REM episodes lengthen in subsequent cycles. In contrast, the longest period of SWS occurs in the first cycle and decreases with successive cycles. Disorders that occur in SWS, such as sleepwalking, happen more frequently in the first third of the night, while those that occur in REM sleep, such as REM sleep behavior disorder, occur later in the night.

The Circadian Rhythm

The sleep–wake cycle occurring over a 24-hour period is a circadian rhythm. The central pacemakers of this rhythm are the suprachiasmatic nuclei, two small paired nuclei located directly above the optic chiasm. In the absence of external cues, these cells demonstrate a period slightly longer than 24 hours. Environmental time cues, predominantly light, synchronize the sleep–wake cycle with the night–day cycle. The suprachiasmatic nuclei receive photic input from the retina via the retinohypothalamic tract. Efferent pathways from the suprachiasmatic nuclei project to the hypothalamus and other areas of the brain (14). Information is also transmitted indirectly to the pineal gland to regulate the hormone melatonin. Melatonin secretion is suppressed by light and maximal during the night, communicating day–night information to the rest of the body. The key role of light as the synchronizing signal for the circadian rhythm and night–day cycle is highlighted by the high prevalence of circadian rhythm disorders in persons with retinal blindness and the utility of timed bright light to shift circadian rhythms in patients whose rhythms are out of synchrony with the light–dark cycle.

Homeostasis and the Two-Process Model

The homeostatic regulation of sleep is necessary to ensure that the human body obtains an adequate amount of this essential bodily function. Thus, sleep deprivation results in an increased tendency to fall asleep and SWS and REM sleep increase during recovery sleep. The homeostatic process is independent of the circadian process, increasing during wakefulness and

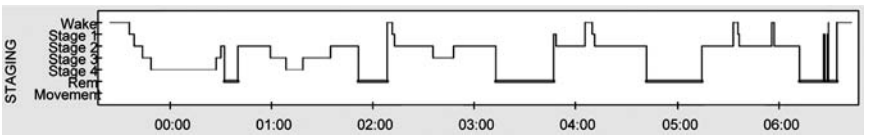


Figure 1 Hypnogram graphically demonstrating the progression of sleep stages or the "ultradian rhythm" of sleep.

declining during sleep. In essence, a sleep debt incurred during wakefulness is paid back during sleep.

The timing of sleep and level of daytime alertness can be explained by the interaction of the circadian process (C) with the homeostatic process (S) in the two-process model (15). The circadian or alerting signal compensates for increasing sleep debt to maintain wakefulness as the day progresses. Sleep occurs and is maintained by the decline of the alerting signal in the setting of a high sleep debt and is terminated by a rise in the alerting signal in the setting of diminished sleep debt. This model suggests practices that might worsen or improve insomnia. Taking naps during the day will tend to decrease sleep debt in the evening and diminish the tendency to fall asleep. In contrast, restricting sleep time will increase sleep debt and the tendency to fall asleep. Maintaining a regular wake up time will help maintain the synchrony of the circadian process with the light–dark cycle.

Sleep need and quality are genetically determined to a large degree with surveys, indicating adults report on average 7.5–8 hours of sleep per night (16,17). In addition to genetics, volitional factors play a role in determining our sleep length (18). Insufficient quantity of sleep (increased homeostatic drive) is an important cause of daytime sleepiness in the general population, with a cumulative effect experienced over time. Indeed, physiologic studies show that obtaining 6 hours or less of sleep per night over 14 days leads to similar levels of objective sleepiness as 2 nights of total sleep deprivation (19).

NOSOLOGY OF SLEEP DISORDERS

Disturbances in sleep physiology lead to sleep disorders. The International Classification of Sleep Disorders-2 (ICSD-2) defines and organizes sleep disorders in a classification scheme (20). Sleep disorders are classified under the following headings: insomnia, sleep-related breathing disorders, hypersomnias, circadian rhythm disorders, parasomnias, sleep-related movement disorders, isolated symptoms, apparently normal variants and unresolved issues, and other sleep disorders. Table 3 provides the ICSD-2 classification outline with more important clinical disorders included. A survey of 19 regional sleep centers in 1998 indicated that obstructive sleep apnea (67.8%), narcolepsy (4.9%), and restless legs syndrome (3.2%) were the three most frequent primary diagnoses made (21).

CLINICAL EVALUATION OF THE SLEEP PATIENT

Introduction

Sleep disorders encompass many different aspects of medicine including neurology, pulmonary medicine, otolaryngology, and psychiatry. Although the pathophysiology of sleep disorders is diverse, in most cases the patients

Table 3 International Classification of Sleep Disorders-2

I. Insomnia
- Adjustment insomnia (acute insomnia)
- Psychophysiological insomnia
- Paradoxical insomnia
- Idiopathic insomnia
- Insomnia due to mental disorder
- Inadequate sleep hygiene
- Behavioral insomnia of childhood

II. Sleep-related breathing disorders
- Central sleep apnea syndromes
  - Primary central sleep apnea
  - Central sleep apnea due to Cheyne–Stokes breathing pattern
  - Central sleep apnea due to high-altitude periodic breathing
  - Primary sleep apnea of infancy
- Obstructive sleep apnea syndromes
  - Obstructive sleep apnea, adult
  - Obstructive sleep apnea, pediatric
- Sleep-related hypoventilation/hypoxemic syndromes
  - Sleep-related nonobstructive alveolar hypoventilation, idiopathic
  - Congenital central alveolar hypoventilation syndrome
  - Sleep-related hypoventilation/hypoxemia due to pulmonary parenchymal or vascular pathology
  - Sleep-related hypoventilation/hypoxemia due to lower airways obstruction
  - Sleep-related hypoventilation/hypoxemia due to neuromuscular and chest wall disorders
- Other sleep-related breathing disorder

III. Hypersomnias of central origin not due to a circadian rhythm sleep disorder, sleep-related breathing disorder, or other cause of disturbed nocturnal sleep
- Narcolepsy with cataplexy
- Narcolepsy without cataplexy
- Narcolepsy due to medical condition
- Recurrent hypersomnia
  - Kleine–Levin syndrome
  - Menstrual-related hypersomnia
- Idiopathic hypersomnia with long sleep time
- Idiopathic hypersomnia without long sleep time
- Behaviorally induced insufficient sleep syndrome

IV. Circadian rhythm sleep disorders
- Delayed sleep phase type (delayed sleep phase disorder)
- Advanced sleep phase type (advanced sleep phase disorder)
- Irregular sleep–wake type (irregular sleep–wake rhythm)
- Free-running type (nonentrained type)
- Jet lag type (jet lag disorder)
- Shift work type (shift work disorder)

(*Continued*)

Table 3 International Classification of Sleep Disorders-2 (*Continued*)

V. Parasomnias
- Disorders of arousal (from non-REM sleep)
  - Confusional arousals
  - Sleepwalking
  - Sleep terrors
- Parasomnias usually associated with REM sleep
  - REM sleep behavior disorder
  - Recurrent isolated sleep paralysis
  - Nightmare disorder
- Other parasomnias
  - Sleep-related dissociative disorders
  - Sleep enuresis
  - Sleep-related groaning (catathrenia)
  - Exploding head syndrome
  - Sleep-related hallucinations
  - Sleep-related eating disorder

VI. Sleep-related movement disorders
- Restless legs syndrome
- Periodic limb movement disorder
- Sleep-related leg cramps
- Sleep-related bruxism
- Sleep-related rhythmic movement disorder

VII. Isolated symptoms, apparently normal variants and unresolved issues
- Long sleeper
- Short sleeper
- Snoring
- Sleep talking
- Sleep starts (hypnic jerks)
- Benign sleep myoclonus of infancy
- Hypnagogic foot tremor and alternating leg muscle activation during sleep
- Propriospinal myoclonus at sleep onset
- Excessive fragmentary myoclonus

VIII. Other sleep disorders
- Environmental sleep disorder

Appendix A: sleep disorders associated with conditions classifiable elsewhere
- Fatal familial insomnia
- Fibromyalgia
- Sleep-related epilepsy
- Sleep-related headaches
- Sleep-related gastroesophageal reflux disease
- Sleep-related coronary artery ischemia
- Sleep-related abnormal swallowing, choking, and laryngospasm

(*Continued*)

Table 3 International Classification of Sleep Disorders-2 (*Continued*)

Appendix B: other psychiatric and behavioral disorders frequently encountered in the differential diagnosis of sleep disorders
- Mood disorders
- Anxiety disorders
- Somatoform disorders
- Schizophrenia and other psychotic disorders
- Disorders usually first diagnosed in infancy, childhood, or adolescence
- Personality disorders

Source: From Ref. 20.

present with one of four symptoms: insomnia, sleepiness, unusual sleep behaviors, and disturbances in the timing of sleep (Table 4). An understanding of the disorders in each of these symptom categories can help the physician focus the history and physical exam and provide a head start in making the correct diagnosis. For example, in the evaluation of a patient with hypersomnia it is important to assess sleep duration (on weekdays and weekends), symptoms consistent with obstructive sleep apnea, restless legs syndrome/periodic limb movement disorder, depression, narcolepsy, and sedating medication use. Assessing the upper airway along with body measurements on physical exam will provide additional information on risk factors for obstructive sleep apnea. Thus, the history and physical exam should reduce the number of diagnoses being considered and guide further testing.

Sleep History

As with medicine in general, the sleep history serves to guide the development and refinement of the differential diagnosis. The clinician should address the following areas: the primary sleep complaint, sleep timing, sleep continuity (including duration and restorative nature), the impact of poor sleep on daytime function, identification of specific sleep disorders, identification of chronic conditions and medications that impact sleep and alertness, and a review of habits that impact sleep quality. The patient is often unaware of sleep-related events; therefore, the report of a bed partner is often useful, especially when evaluating sleep-disordered breathing, parasomnias, and periodic limb movements. Table 5 provides more details on what information should be included in a complete sleep history.

Age of onset is important in assessing the likelihood of specific disorders. For example, symptoms of narcolepsy most often begin in the second and third decades. Thus, the likelihood of narcolepsy is very low in a 50-year old with new onset sleepiness. An assessment of timing and duration of sleep provides information on the homeostatic and circadian forces at play. Individuals with sleep restriction often sleep longer by an hour or more on weekends

Table 4 Differential Diagnosis for Specific Sleep Complaints

Insomnia	Psychiatric disorders Psychophysiological insomnia Obstructive sleep apnea Inadequate sleep hygiene Idiopathic insomnia Restless legs syndrome Environmental sleep disorder Adjustment insomnia Delayed sleep phase disorder Medications Medical disorders
Hypersomnia	Insufficient sleep syndrome Obstructive sleep apnea Periodic limb movement disorder Medications Narcolepsy Idiopathic hypersomnia Mood disorders
Unusual sleep behaviors	Confusional arousals Sleepwalking Sleep terrors Rhythmic movement disorder REM sleep behavior disorder Sleep-related epilepsy Periodic limb movement disorder
Disturbances in the timing of sleep	Jet lag disorder Shift work sleep disorder Irregular sleep–wake rhythm disorder Delayed sleep phase disorder Advance sleep phase disorder Non-24 hr sleep–wake disorder

when they may not have to awaken early for work or other responsibilities. People who report difficulty falling asleep until early morning and difficulty awakening till the late morning may have delayed sleep phase syndrome as a cause for complaints of sleep onset insomnia or daytime sleepiness. A sleep diary kept over several weeks is valuable in the assessment of insomnia as it provides a day-to-day subjective assessment of time in bed, sleep latency, awakenings, naps, and sleep quality.

The daytime consequences of sleep disorders include fatigue, sleepiness, cognitive dysfunction, and depressed mood. In patients with excessive sleepiness, it is important to identify severity and timing of sleepiness and how it impacts

Table 5 The Sleep History in the Sleep Patient

I. Sleep complaints
- Onset
- Frequency
- Severity
- Progression

II. Sleep timing, continuity, duration, and restorative nature
- What time do you go to bed on weekdays/weekends?
- How long does it take for you to fall asleep?
- What time do you awaken on weekdays/weekends?
- Do you feel refreshed upon awakening?
- How many times do you awaken on a typical night? Do you have trouble falling back to sleep?
- What causes awakenings?
- Do you nap? When, how often, and how long?

III. The impact of poor sleep on daytime function
- Do you feel sleepy or fatigued during the day?
- Do you fall asleep unintentionally? In what situations and what time of the day?
- Do you have trouble concentrating or thinking?

IV. Identification of specific sleep disorders
- Obstructive sleep apnea—snoring, witnessed apneas, choking, dry mouth, nocturia
- Narcolepsy—cataplexy, sleep attacks, hallucinations, sleep paralysis
- Restless legs syndrome—motor restlessness, discomfort in the legs worse in the evening and relieved with movement

V. Identification of chronic conditions and medications that may impact sleep and alertness
- Chronic painful conditions
- Chronic conditions that produce fatigue (hypothyroidism, iron deficiency)
- Cardiopulmonary disorders that cause awakening with dyspnea
- Nocturnal gastroesophageal reflux
- Renal failure (restless legs syndrome)
- Rhinitis
- Depression/anxiety
- Neurological conditions (Parkinson's disease, spinal cord injury, closed head injury)
- Medications that cause sleepiness or disrupt sleep (glucocorticoids, antidepressants, narcotics, hypnotics)

VI. Habits that impact sleep quality
- Substance use (caffeine, alcohol)
- Poor sleep hygiene

VII. Family history
- Obstructive sleep apnea, restless legs syndrome, narcolepsy

daily functioning. Sleepiness has many presentations. Some patients may complain primarily of feelings of sleepiness or fatigue. Others may complain of frequent unintentional sleep episodes in specific situations. It is important to explore all these presentations in the interview. The Epworth Sleepiness Scale is a well-validated questionnaire used to assess the recent tendency to doze in specific situations. Details on this instrument are provided in Figure 2 (22).

Chronic medical conditions and habits can result in sleep disruption, sleepiness, or predispose to specific sleep disorders. It is important to identify these conditions by history, since sleep diagnostic testing may be effected by these factors and will often fail to provide information regarding these factors. Sleep disorders including obstructive sleep apnea, restless legs syndrome, and narcolepsy can have a genetic predisposition, making a family history useful in assessing the risk for these disorders.

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently try to work out how they would have affected you. Use the following scale to choose the most appropriate number for each situation:

0=would never doze; 1=slight chance of dozing; 2=moderate change of dozing; 3=high chance of dozing

1. Sitting and reading	0	1	2	3
2. Watching TV	0	1	2	3
3. Sitting, inactive in a public place (e.g., a theater or a meeting)	0	1	2	3
4. As a passenger in a car for an hour without a break	0	1	2	3
5. Lying down to rest in the afternoon when circumstances permit	0	1	2	3
6. Sitting and talking to someone	0	1	2	3
7. Sitting quietly after lunch without alcohol	0	1	2	3
8. In a car, while stopped for a few minutes in traffic	0	1	2	3

General population score: 4-8

Sleepiness: >10

Figure 2 The Epworth Sleepiness Scale. *Source*: Adapted from Ref. 22.

The Physical Examination

The physical examination of the sleep patient is useful in identifying risk factors for specific sleep disorders, factors that may impact therapy, and conditions that may be the result of sleep disorders (Table 6). Basic measurements include: blood pressure, height and weight, neck circumference, and room air pulse oximetry. Hypertension, obesity [based on the body mass index (weight/height^2)], and increased neck circumference (>17 inches in men and >16 inches in women) are important predictors of sleep-disordered breathing. A low blood oxygen saturation level suggests the presence of hypoventilation, as seen in obesity-hypoventilation syndrome and cardiopulmonary disease, predisposing to more severe nocturnal hypoxemia in the setting of obstructive sleep apnea.

Careful examination of the head, neck, and naso–oro–hypopharynx is essential. Craniofacial features that predispose to sleep-disordered breathing include retrognathia, micrognathia, and a narrow maxilla as reflected in a high-arched hard palate. The oro- and hypopharynx should be examined with and without a tongue blade to identify soft tissue features, including tongue size and position, soft palate, tonsils, and lateral narrowing of posterior oropharynx. The nasopharynx should be examined internally to identify obstruction due to nasoseptal deviation, turbinate hypertrophy, polyps, and secretions. Cardiopulmonary examination, including auscultation of the lungs and heart, evaluation of jugular venous pressure, and examination of the lower extremities for edema, is important in patients with suspected sleep-disordered breathing. Neurological exam is important in individuals suspected of having sleep disorders of neurological origin such as narcolepsy, restless legs syndrome/periodic limb movement disorder, and REM sleep behavior disorder.

Table 6 The Physical Examination in the Sleep Patient

I. Basic measurements
• Blood pressure
• Height and weight
• Neck circumference
• Pulse oximetry
II. Upper airway exam
• Craniofacial features (retrognathia, micrognathia, high-arched hard palate)
• Oropharynx (tongue, soft palate, tonsils, posterior lateral diameter)
• Nasal (nasoseptal deviation, turbinate hypertrophy, secretions)
III. Cardiopulmonary exam
• Auscultation of the heart and lungs
• Evaluation of jugular venous pressure and lower extremity edema
IV. Neurological examination
• Complete exam necessary in evaluation of parasomnias

When to Refer to a Sleep Center

Information from the history and physical examination will guide the development of a differential diagnosis and drive treatment. Some sleep disorders, such as insomnia and restless legs syndrome, can be successfully managed in the primary care environment. On the other hand, management of disorders requiring diagnostic testing or complicated treatment regimens, such as obstructive sleep apnea and narcolepsy, are beyond the scope of the general practitioner. For the patient with hypersomnia, when causes such as insufficient sleep, depression, and medications causing sleepiness have been excluded, a referral to a sleep center is indicated to exclude intrinsic sleep disorders. For the complaint of insomnia, acuity and severity of the problem should be considered before referral. Acute insomnia (symptoms <1 month in duration) can be managed by the primary physician through behavioral instructions, short-term hypnotics, and treatment of the inciting factor. The need for more intensive cognitive–behavioral therapy would indicate that referral to the specialist is in order. Psychiatric disorders, including depression, are frequently associated with insomnia. Patients with active psychiatric issues should receive appropriate psychiatric intervention before referral to a sleep specialist. Chronic severe insomnia may benefit from referral to a sleep center.

In general, patients suspected of having an intrinsic sleep disorder, especially one that has been refractory to treatment, should be referred to a sleep specialist. Parasomnias that are negatively affecting quality of life or posing a safety hazard should be referred. Patients with chronic treatment refractory circadian rhythm disorders should also be referred. See Table 7 for further information regarding when to refer to the sleep specialist.

The sleep center should provide facilities and technical personnel for the full array of diagnostic sleep testing, including polysomnography, multiple sleep latency testing, maintenance of wakefulness testing, and wrist actigraphy. Referring to centers accredited by the American Academy of Sleep Medicine and physicians certified by the American Board of Sleep Medicine ensures your patients will receive high-quality care.

Table 7 When to Refer to a Sleep Center

- Significant excessive daytime somnolence suspected to be secondary to an intrinsic sleep disorder
- Chronic, severe insomnia that has been resistant to interventions
- Parasomnias, especially those that raise safety concerns
- Circadian rhythm disorders
- Treated sleep disorders with persistent symptoms

SLEEP TESTING

Sleep testing is often required in the evaluation of excessive daytime somnolence (Table 8). Polysomnography measures sleep stages, respiration, electrocardiography, and leg movements. This test is ubiquitous in sleep medicine and is used to diagnose sleep related breathing disorders and parasomnias, among other disorders. Polysomnography is needed for the evaluation of insomnia in certain situations, specifically when the history suggests that sleep apnea or periodic limb movement disorder is present. The multiple sleep latency test is a daytime nap test used to objectively assess sleepiness in a sleep-conducive setting. This test is instrumental to the diagnosis of narcolepsy. The maintenance of wakefulness test assesses a patient's ability to remain awake and is used to document adequate alertness in patients with careers for which sleepiness would pose a hazard to the public (commercial driver, airline pilot). Actigraphy is a technique used outside the sleep laboratory that detects movements with a wristwatch-like device. Periods of inactivity correspond roughly to periods of sleep, providing an

Table 8 Types of Sleep Studies and Indications

Study	Description	Indications
Polysomnography	Overnight study that measures sleep, breathing, EKG, and limb movements	Evaluation of sleep disruption, parasomnia, sleep-disordered breathing, and periodic limb movements. Initiation of CPAP (continuous positive airway pressure) therapy
Multiple sleep latency test	Daytime study that measures time to fall asleep and enter REM sleep during 4–5 nap opportunities that occur at 2 hours intervals	Objective assessment of daytime somnolence, evaluation for narcolepsy
Maintenance of wakefulness test	Daytime study that measures sleep tendency during four sessions while the patient is trying to stay awake	Objective assessment of ability to remain awake with intention
Actigraphy	Measurement of diurnal activity with a portable device	Objective assessment of sleep duration and patterns in insomnia and circadian rhythm disorders

assessment of sleep and wake periods over several days. Actigraphy is a useful tool in many patients with insomnia or circadian rhythm disorders. Chapter 2 provides a detailed discussion of all these sleep-testing modalities.

THERAPEUTIC OPTIONS

Sleep centers, in addition to providing comprehensive assessment of sleep-related complaints, should be skilled in providing the full spectrum of effective therapies. This requires a multidisciplinary team including specialists in pulmonary medicine, neurology, psychiatry, or other medical specialty with expertise in sleep disorders medicine, as well as surgeons (otolaryngology) and dentists. Table 9 lists a range of therapies that are commonly used in the practice of sleep medicine.

Therapies for obstructive sleep apnea, the most common of the sleep-related breathing disorders, are aimed at maintaining a patent upper airway during sleep. These include positive airway pressure applied via a nasal or oronasal mask to the patient's face to splint open the upper airway, dental appliances, or mandibular splints worn in the mouth to protrude the mandible, and a number of surgical procedures aimed at addressing soft tissue or craniofacial factors that may predispose to upper airway obstruction. Medications that are used include hypnotics for insomnia, alerting medications for disorders of excessive somnolence, iron supplements and dopaminergic agents for restless leg syndrome/periodic limb movement disorder, melatonin for circadian rhythm disorders, clonazepam for parasomnias, and REM-suppressing antidepressants and sodium oxybate for cataplexy. Cognitive behavioral techniques, including stimulus control therapy, sleep restriction, and relaxation therapies, are used for therapy of chronic insomnia. Finally, light therapy via a bright light box at specific times of the day influences the circadian rhythm and can be used to treat circadian rhythm disorders.

Table 9 Therapies Used in Sleep Medicine

Therapy	Indications
Positive airway pressure	Sleep-related breathing disorders
Surgery	Sleep-related breathing disorders
Dental appliance	Sleep-related breathing disorders
Medications	Insomnia, excessive somnolence, restless legs syndrome, periodic limb movement disorder, circadian rhythm disorders, parasomnias, cataplexy
Cognitive–behavioral	Insomnia
Light	Circadian rhythm disorders

CONCLUSION

Sleep is an essential physiologic state for good health. Sleep disorders and complaints are very common and frequently encountered in primary care settings. A basic understanding of sleep physiology and sleep disorders is important to deal effectively with these complaints. A comprehensive sleep history and targeted physical exam will help formulate a differential diagnosis and guide further testing and treatment. Though some sleep issues can be addressed adequately in the primary care setting, a referral to a sleep specialist may be needed.

REFERENCES

1. Chokroverty S. An overview of sleep. In: Chokroverty S, ed. Sleep Disorders Medicine: Basic Science, Technical Considerations, and Clinical Aspects. 2nd ed. Boston: Butterworth-Heinemann, 1999:7–20.
2. Wheatland T. Sleep and dreams in literature. In: Carskadon MA, ed. Encyclopedia of Sleep and Dreaming. New York: Simon and Schuster Macmillan, 1995:333–335.
3. Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. Sleep Med Rev 2002; 6(2):97–111.
4. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993; 328(17):1230–1235.
5. Hublin C, Kaprio J, Partinen M, Koskenvuo M, Heikkila K, Koskimies S, Guilleminault C. The prevalence of narcolepsy: an epidemiological study of the Finnish Twin Cohort. Ann Neurol 1994; 35(6):709–716.
6. Phillips B, Young T, Finn L, Asher K, Hening WA, Purvis C. Epidemiology of restless legs symptoms in adults. Arch Intern Med 2000; 160(14):2137–2141.
7. Ohayon MM, Guilleminault C, Priest RG. Night terrors, sleepwalking, and confusional arousals in the general population: their frequency and relationship to other sleep and mental disorders. J Clin Psychiatry 1999; 60(4):268–276.
8. Ohayon MM, Caulet M, Priest RG. Violent behavior during sleep. J Clin Psychiatry 1997; 58(8):369–376.
9. Ohayon MM, Caulet M, Philip P, Guilleminault C, Priest RG. How sleep and mental disorders are related to complaints of daytime sleepiness. Arch Intern Med 1997; 157(22):2645–2652.
10. Dement WC. History of sleep physiology and medicine. In: Kryger MH, Roth T, Dement WC. Principles and Practice of Sleep Medicine. 3rd ed. Philadelphia: W. B. Saunders, 2000:1–14.
11. Walsleben JA, Kapur VK, Newman AB, Shahar E, Bootzin RR, Rosenberg CE, O'Connor G, Nieto FJ. Sleep and reported daytime sleepiness in normal subjects: the Sleep Heart Health Study. Sleep 2004; 27(2):293–298.
12. Burgess HJ, Trinder J, Kim Y, Luke D. Sleep and circadian influences on cardiac autonomic nervous system activity. Am J Physiol 1997; 273(4 Pt 2): H1761–H1768.

13. Chokroverty S. Physiological changes in sleep. In: Chokroverty S, ed. Sleep Disorders Medicine: Basic Science, Technical Considerations, and Clinical Aspects. 2nd ed. Boston: Butterworth-Heinemann, 1999:95–126.
14. Harrington ME, Mistlberger RE. Anatomy and physiology of the mammalian circadian system. In: Kryger MH, Roth T, Dement WC, eds. Principles and Practice of Sleep Medicine, 3rd ed. Philadelphia: W. B. Saunders, 2000:334–345.
15. Borbely AA. A two process model of sleep regulation. Hum Neurobiol 1982; 1:195–204.
16. Heath AC, Kendler KS, Eaves LJ, Martin NG. Evidence for genetic influences on sleep disturbance and sleep pattern in twins. Sleep 1990; 13(4):318–335.
17. National Sleep Foundation. NSF 2002 Sleep in America Poll. Washington, DC: National Sleep Foundation, 2002.
18. Carskadon MA, Dement WC. Normal human sleep: an overview. In: Kryger MH, Roth T, Dement WC, eds. Principles and Practice of Sleep Medicine, 3rd ed. Philadelphia: W. B. Saunders, 2000:15–25.
19. Van Dongen HP, Maislin G, Mullington JM, Dinges DF. The cumulative cost of additional wakefulness: dose–response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. Sleep 2003; 26(2):117–126.
20. American Academy of Sleep Medicine. International Classification of Sleep Disorders. 2nd ed. Westchester, IL: American Academy of Sleep Medicine, 2005.
21. Punjabi NM, Welch D, Strohl K. Sleep disorders in regional sleep centers: a national cooperative study. Coleman II Study Investigators. Sleep 2000; 23(4):471–480.
22. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991; 14(6):540–545.

2

Diagnostic Procedures in Sleep Medicine

Madeleine M. Grigg-Damberger

Department of Neurology, University of New Mexico School of Medicine and Pediatric Sleep Medicine Services, University Hospital Sleep Disorders Center, Albuquerque, New Mexico, U.S.A.

Sleep Test	***Quality Measured***
Nocturnal polysomnography (PSG)	*Simultaneous recording of multiple different biophysiological signals to study and characterize sleep and sleep disorders*
Video-polysomnography with extended electroencephalographic montages (VEEG-PSG)	*Distinguishes sleep-related epilepsy from atypical or injurious parasomnias*
Multiple sleep latency test (MSLT)	*Ability to fall asleep during day when permitted and whether REM sleep appears earlier than usual*
Maintenance of wakefulness test (MWT)	*Ability to stay awake during low levels of stimulation without resorting to extraordinary measures*
Portable (home) sleep studies (polysomnography)	*Screens for moderate to severe sleep-disordered breathing at home*
Overnight oximetry	*Monitors arterial oxygen saturation and heart rate in bed overnight*
Actigraphy	*Tracks sleep/wake patterns over long periods of time by monitoring body movements. Assumes periods of inactivity represent sleep while periods of activity represent wakefulness*
Sleep logs (sleep diaries)	*A graphic subjective perspective of a patient's sleep/wake patterns over a period of days to weeks*
Epworth sleepiness scale (ESS)	*Self-rating of a patient's likelihood of falling asleep in different situations*
Stanford sleepiness scale (SSS)	*Self-rating of a patient's degree of sleepiness at a single moment in time*

INTRODUCTION

Sleep is essential for our health and well-being and occupies approximately one-third of our existence. Before diagnostic tools were available, we characterized sleep based on behavioral criteria as a reversible state of consciousness with perceptual disengagement and relative insensitivity to the external environment accompanied by a posture with closed eyes and absent or only slight mobility (1). Because of its inactive nature, sleep was considered a passive state for many years. However, the development of polysomnography (PSG) provided physiological data revealing sleep as an active process crucial for maintaining normal body and hormonal functions including growth and tissue healing, learning and memory processing, and central nervous system repair (2).

This chapter provides a guide for clinicians to order appropriate tests for evaluating and treating patients with different sleep and sleep/wake problems. Each testing modality is described with special emphasis on its applications. Interpretation of specific test results and a discussion of test strengths and weaknesses will also be presented.

BACKGROUND OF POLYSOMNOGRAPHY

Richard Caton (3), a Liverpool 19th century physician, was the first to demonstrate how "feeble currents of varying direction" could be recorded from the exposed brain surface of every dog and rabbit that were studied. More than half a century passed before the Austrian psychiatrist, Hans Berger (4), published the seminal 1929 paper reporting how he recorded electrical activity from the scalp of human subjects through an intact skull. Berger was the first to identify and name the "alpha rhythm"—an electrical rhythm that oscillates at a frequency of 8 to 13 cycles per second (Hz) generated over the occipital scalp regions in humans during a state of relaxed wakefulness with eyes closed (Fig. 1). He was also the first to report that electroencephalographic (EEG) activity changes with sleep in humans. Berger's work was disregarded and ridiculed until Adrian and Matthews (5) confirmed the validity of "Berger's rhythms."

In 1937, Loomis et al. (6) were the first to describe and classify four stages of nonrapid eye movement (NREM) sleep. Their observations regarding the EEG patterns of NREM sleep hold true today. They noted that the posterior alpha rhythm disappeared with drowsiness and was replaced by a mixture of theta (4–7 Hz) and beta (>13 Hz) EEG activity during stage 1 NREM sleep (Fig. 2A). Stage 2 NREM was recognized by the presence of sleep spindles (bursts of rhythmical sinusoidal 12–14 Hz activity) and K-complexes (well-delineated biphasic waves consisting of a high-amplitude negative sharp wave immediately followed by a positive component). Both phenomena must last at least one-half second to qualify and are best recorded from electrodes placed over midline central scalp regions (Fig. 2B). Increasing amounts of

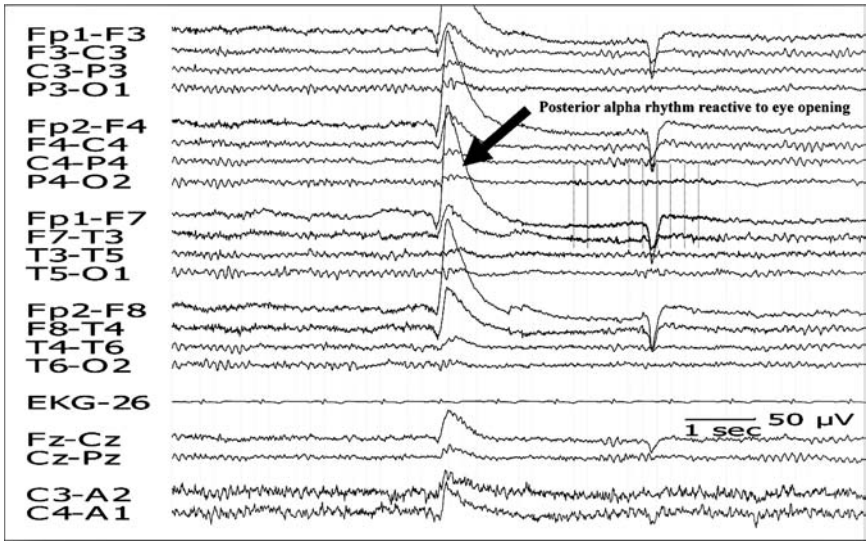


Figure 1 The posterior alpha rhythm (8–13 Hz) is best seen in the human electroencephalogram in a state of relaxed wakefulness with eyes closed. It disappears with eye opening (*arrow*).

high-amplitude (greater than 75 μV, less than 2 Hz) delta activity characterizes stages 3 and 4 NREM sleep or slow-wave sleep (Fig. 2C and D). Scalp-recorded EEG activity in humans during sleep normally lies within the range of 0.5 to 30 Hz. Electroencephalographic activity is arbitrarily classified into the following band frequencies: delta (<4 Hz), theta (4 to <8 Hz), alpha (8–13 Hz), and beta (>13 Hz). Examples of these frequencies appear in Figure 3.

Another 16 years passed before Aserinsky and Kleitman (7) at the University of Chicago in 1953 first described how cycles of rapid eye movements occurred regularly across the night in sleeping subjects. They placed skin electrodes along the lateral margins of each eye to observe the relationship between eye movements (electro-oculography, EOG) and EEG producing a "two-signal polysomnogram."

They identified that slow roving eye movements are characteristic of drowsiness, especially at sleep onset (Fig. 2A). They also discovered that rapid eye movements are characteristic of REM sleep (Fig. 4) and that eye movements rarely occur during slow-wave sleep (Fig. 2C and D) (8). Their work culminated in the landmark 1957 paper of Dement and Kleitman (9) in which they coined the term "REM sleep," identifying it by the presence of rapid eye movements and low-voltage fast EEG activity. They further observed that NREM and REM sleep alternated cyclically across a night of sleep.

At the beginning of the 20th century, Freud (10) suggested that paralysis during sleep was necessary to prevent us from acting out our

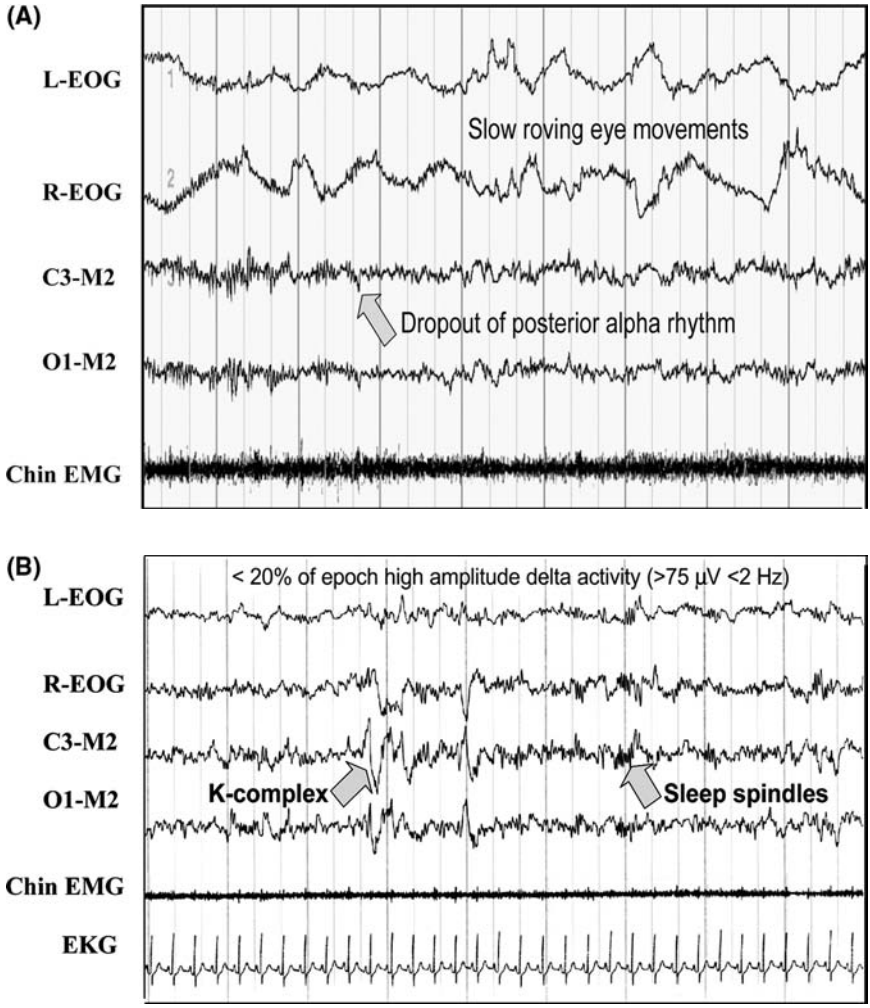


Figure 2 (**A**) Stage 1 NREM sleep typically signifies sleep onset with dropout of the posterior alpha rhythm (*arrow*) and the appearance of slowing roving eye movements. (**B**) Stage 2 NREM sleep requires the presence of sleep spindles or K-complexes. More than 20% of the epoch cannot contain delta ($>75\,\mu V$ ≤ 2 Hz) activity. Sleep spindles and K-complexes must last at least 0.5 sec to be scored. (**C**) Stage 3 NREM sleep is scored when 20–50% of the 30-sec epoch contains high-amplitude delta activity ($>75\,\mu V$ <2 Hz). (**D**) Stage 4 NREM sleep is scored when more than 50% of the 30-second epoch contains high-amplitude delta activity ($>75\,\mu V$ <2 Hz). (*Continued next page.*)

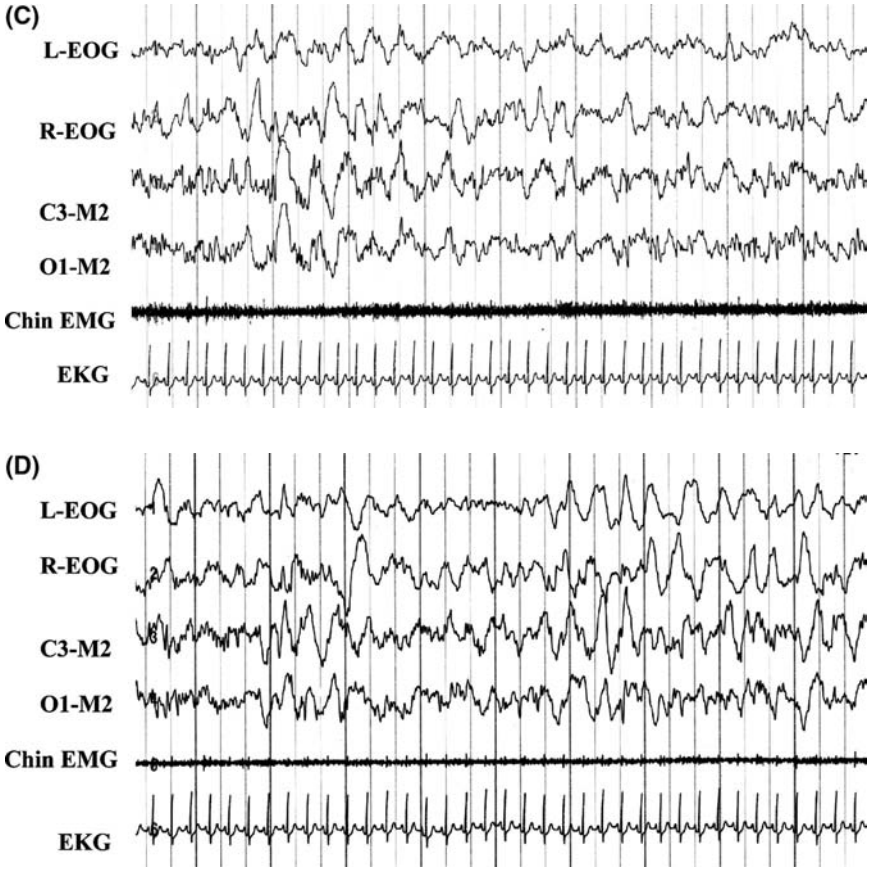


Figure 2 (*Continued.*)

dreams. This early speculation was later proven true when it was learned that skeletal muscles (save those innervating eye muscles and the diaphragm) are paralyzed during REM sleep and no other sleep stages. In France, Jouvet et al. (11) first described how muscle atonia occurred only during REM sleep in sleeping cats. Sleep researchers by the 1960s began routinely placing electromyography (EMG) electrodes on and below the chin to monitor changes in muscle activity and tone during sleep. They observed that chin muscle activity provides a measure of axial muscle tone. This tone gradually drops in amplitude and activity as NREM sleep deepens from stages 1 and 2 to slow-wave sleep (Fig. 2A–D), ultimately disappearing as it falls to its lowest amplitude in REM sleep (Fig. 3).

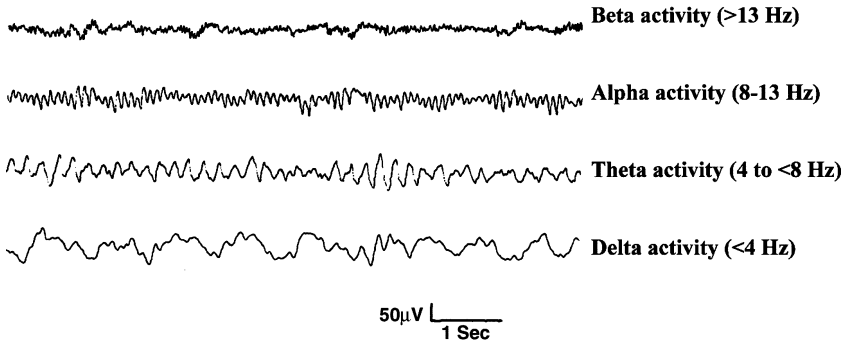


Figure 3 Different electroencephalographic band frequencies.

Different stages of sleep and wake are classified by simultaneously recording three biological signals (EEG, EOG, and chin EMG), resulting in a "three-channel polysomnogram." Typical electrode placement is demonstrated in Figure 5. In 1968, a group of sleep researchers met and developed consensus guidelines for staging and scoring sleep in normal human subjects. Two of these researchers wrote a manual of sleep scoring rules, which are still in use today. These rules are termed the "R & K" criteria after its editors, Rechtschaffen and Kales (12). Most sleep laboratories currently score sleep using R & K criteria (although these criteria are currently being revised). The R & K scoring criteria are summarized in Table 1.

In the mid-1960s, sleep researchers emerged from their sleep laboratories and began to evaluate and treat people with sleep problems,

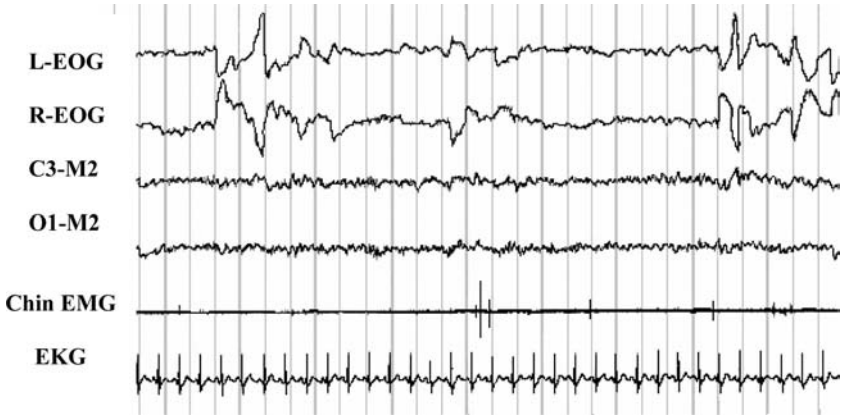


Figure 4 REM sleep is characterized by rapid eye movements, an electroencephalographic background of mixed frequencies, myoclonic twitches, and chin muscle atonia.

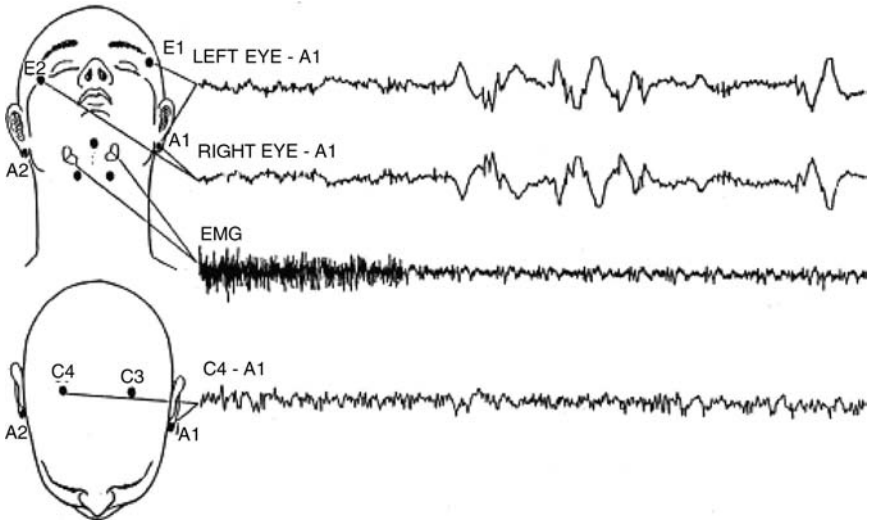
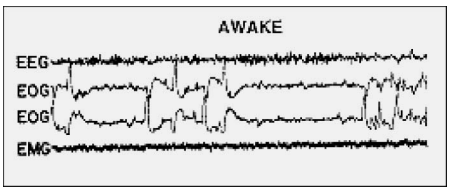
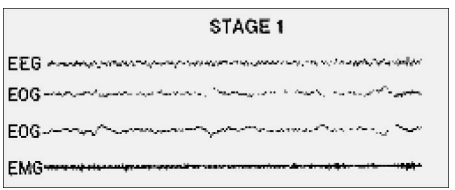
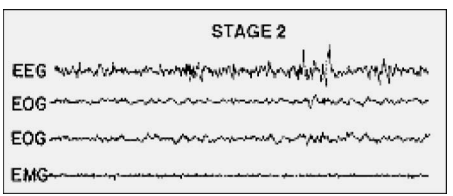


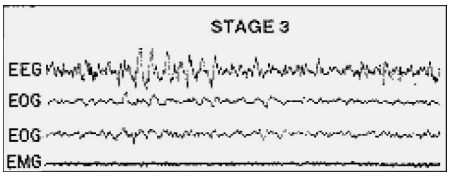
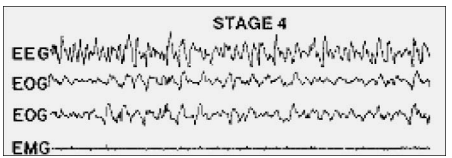
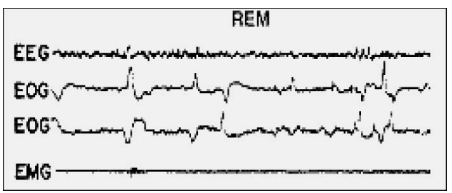
Figure 5 Sleep is recognized by recording electroencephalographic signals from central scalp regions (referenced to contralateral ear) along with chin electromyography (chin muscle tone) and electro-oculography (eye movements). Electrode placement is indicated.

especially those suffering from excessive daytime sleepiness. They also noted how often sleepy patients snored and discovered many had obstructive sleep apnea (13,14). By 1970, sleep researchers at Stanford University in California began routinely adding electrocardiography (EKG) and respiratory sensors to all-night in-laboratory polygraphic recordings, in order to confirm the presence of sleep apnea. Holland et al. (15) in 1974 first coined the term ''polysomnography'' for the technique of continuous all-night simultaneous recording of multiple electrical biophysiological signals. Sullivan and colleagues (16) in 1981 explained how obstructive sleep apnea could be treated by use of continuous positive airway pressure (CPAP). This therapy creates a pneumatic splint that overcomes obstruction and collapse in the upper airway. By the mid-1980s, sleep specialists began initiating and titrating CPAP while recording polysomnography.

Earlier, sleep researchers recognized the clinical features of the narcolepsy–cataplexy syndrome. They confirmed the diagnosis by discovering early REM sleep less than 15 minutes after sleep onset. This cardinal feature of narcolepsy was first identified by Yoss and Daly (17), and Vogel (18). Carskadon et al. (19) later developed and published guidelines for performing the multiple sleep latency test (MSLT), which provides an objective measure of daytime sleepiness. Two other polysomnography milestones were the recognition by Schenck et al. that REM sleep behavior disorder was associated with inappropriate

Table 1 Basic Rules for Scoring Sleep Using Rechtschaffen and Kales (R & K) Criteria

Sleep stage	Scoring criteria	Example
Waking (W)	>50% of the page (epoch) consists of alpha (8–13 Hz) activity or low-voltage mixed (2–7 Hz) frequency activity	
Stage 1 (1)	50% of the epoch includes relatively low-voltage mixed (2–7 Hz) frequency activity and <50% of the epoch contains alpha activity. Slow roving eye movements lasting several seconds are often seen in early stage 1	
Stage 2 (2)	Appearance of a sleep spindle and/or K-complex and <20% of the epoch contains scoreable high-voltage activity, which is >75 μV ≤2 Hz delta activity. Sleep spindles and K-complexes each must last >0.5 sec	

Stage 3 (3)	20–50% of the epoch consists of high voltage (>75 μV) ≤2 Hz delta activity	
Stage 4 (4)	>50% of the epoch consists of high voltage (>75 μV) ≤2 Hz delta activity	
REM sleep (R)	Defined by a relatively low-voltage mixed (2–7 Hz) frequency EEG with episodic rapid eye movements and absent or reduced chin EMG activity	

Abbreviations: EEG, electroencephalography; EMG, electromyography.

preservation of EMG activity during REM sleep (explaining the pathophysiology of dream enactment) (20), and the discovery that periodic limb movements during sleep were present in the majority of patients with restless legs syndrome (21). The latter was identified by recording EMG signals from electrodes attached over the skin of the anterior tibialis calf muscles (22).

By virtue of these diagnostic tests, sleep medicine came to be an independent medical specialty across the United States and the world. Sleep specialists had acquired the capability to diagnose and treat a variety of sleep disorders affecting people of all ages. Those interested in further information regarding the history of sleep medicine should read the personal account recently written by William Dement (23).

TERMS AND CLASSIFICATION OF SLEEP STUDIES

The American Academy of Sleep Medicine (AASM) has classified sleep studies into four different levels (I–IV) based upon the number of physiological signals simultaneously recorded and whether the study was attended by a technologist (Table 2) (24). A level I polysomnogram is the ''gold standard'' diagnostic procedure of sleep medicine. A level I study is performed by a sleep technologist in a sleep laboratory while simultaneously recording at least seven different physiological signals. The technologist must be present for the duration of the study. A level I study is the most accepted test for the diagnosis, quantification, and treatment of obstructive sleep apnea. An unattended portable home recording is an acceptable alternative

Table 2 American Academy of Sleep Medicine Standards of Practice Classification of Sleep Studies

Class I: *Attended polysomnography*
In-laboratory full-PSG attended by a technologist present during the recording
Class II: *Unattended polysomnography*
A PSG done at home without a technologist present during the recording (''unattended''), but recording all the same physiological parameters typically recorded during an in-laboratory PSG
Class III: *Modified portable sleep apnea testing*
A limited PSG measuring at least four different cardiorespiratory parameters without a technologist present during the recording
Class IV: *Continuous single or dual bioparameter recording*
Very limited PSG recording only 1–2 cardiorespiratory parameters unattended at home

Abbreviation: PSG, polysomnography.
Source: From Ref. 24.

only when patients are suspected to have severe disease and for whom "standard polysomnography is not readily available" (25). A level I study is typically recorded for 6 to 8 hours of sleep (longer in children who have inherently greater sleep needs) and preferably during the patient's typical bedtimes (usually overnight).

Indications for a Level I Polysomnogram

A level I study is time and labor intensive and best reserved for evaluating specific sleep disorders. An overnight in-laboratory level I polysomnogram (CPT code 95810) is indicated when evaluating patients for suspected (i) sleep-disordered breathing; (ii) narcolepsy or idiopathic hypersomnia; (iii) atypical, violent, or potentially injurious parasomnias; and (iv) nocturnal seizures when the clinical evaluation and daytime EEG remain inconclusive. Polysomnography (CPT code 95811) is often used to titrate continuous or bi-level positive airway pressure (CPAP or BiPAP) as a treatment for sleep-disordered breathing. Polysomnograms are sometimes repeated months or years later to retitrate CPAP (or BiPAP) following upper-airway surgery. Weight fluctuations and decreased positive airway pressure efficacy are also reasons to perform a retitration study.

A level I polysomnogram is usually not the first (or best) test to evaluate insomnia. A 2003 practice parameters update from the AASM (26) advised that insomnia is primarily diagnosed by a detailed medical, psychiatric, and sleep history, including an assessment of the patient's sleep/wake patterns and habits. Polysomnography is only indicated when a sleep-disordered breathing or periodic limb movement disorder is suspected. Other indications would include circumstances when the initial diagnosis is uncertain or precipitous arousals occur with violent or injurious behavior (27–29). Polysomnography is not indicated for the routine evaluation of transient or chronic insomnia or insomnia associated with psychiatric disorders. Similarly, an in-laboratory polysomnogram should not be the initial diagnostic test when evaluating restless legs syndrome. Rather, this is a clinical diagnosis based on the patient's symptoms during wakefulness. Consider polysomnography for restless legs syndrome only when the patient is refractory to initial therapies in order to search for other sleep disorders contributing to their sleep/wake complaints.

How to Perform Overnight Polysomnography

Patients arrive at the sleep laboratory a few hours before their usual bedtime. Electrodes and recording devices are attached by adhesive paste and collodion (a foul-smelling nontoxic electrode adhesive). Respiratory belts are positioned around the chest and abdomen. Once the "hook-up"

is complete, the technologist escorts the patient to a comfortable bedroom with an infrared video camera and machines capable of delivering pressurized air and/or oxygen to treat sleep-disordered breathing. The technologist then retreats to the recording control room. Before starting the study, the technologist performs a "biocalibration" to ensure that each of the 12–16 biophysiological channels (described below) are recording properly. Following this, the lights are turned off and the patient is permitted to sleep. The technologist notes the "lights out" time on the polysomnogram. The study is then recorded continuously until the final awakening (called "lights on").

Most sleep laboratories record two to six patients per night. Most often, one sleep technologist tests two patients a night. After patients are in bed, the sleep technologists monitor sleep from the control room via digital video and polysomnographic data displayed on a computer screen. Technologists are present throughout the recording ("attended polysomnography") to intervene if necessary and to identify (and correct if possible) artifacts, which often develop during the night. Throughout the study, they report their assessment of the patient's sleep on the computer file and in a technical log. After the final awakening in the morning, the electrodes are removed and the patient is offered a shower or bath prior to being discharged to home from the laboratory.

Physiological Signals Recorded During an Overnight Polysomnogram

Most recordings utilize computerized digital polysomnographic systems that monitor various biophysiological signals. A "comprehensive" attended in-laboratory polysomnogram typically includes the simultaneous recording of 12–16 of the following signals:

- *Electroencephalography* (*EEG*)—recorded from the central and occipital scalp regions and referenced to electrodes placed over the contralateral (opposite) mastoid
- *Electro-oculography* (*EOG*)—two electrodes, one on the left and the other on the right, 1 cm above the left outer canthus and 1 cm below the right outer canthus, referenced to the contralateral mastoid
- *Chin electromyography* (*EMG*)—two to three electrodes placed over and under the chin sampling mentalis and submentalis muscle activity
- *Leg electromyography* (*EMG*)—electrodes placed on the skin overlying the left and right anterior tibialis calf muscles to monitor for periodic limb movements and confirm arousals
- *Airflow*—measured via a thermal sensor and nasal cannula pressure transducer

- *Respiratory effort*—using strain gauges, piezo sensors, or elastic bands encircling the chest and abdomen, these devices provide qualitative data by assessing changes in the cross-sectional area (and circumference) of the thorax and abdomen with inspiration (expansion) and expiration (contraction)
- *Pulse oximetry*—measures arterial oxygen saturation (SaO_2) from a probe placed on a finger, earlobe, toe, or the nose. The pulse waveform helps differentiate true oxygen desaturations from motion artifact
- *Snoring*—monitored by placing a microphone over the larynx or hanging it over the bed
- *Electrocardiogram* (*EKG*)—a single channel is monitored by placing an electrode on the skin just below the right clavicle referenced to an electrode on the left lateral chest wall at the level of the seventh rib
- *Body position*—recorded by the sleep technologist and/or position sensors. Position sensors detect when the patient is sleeping supine, prone, sitting, or in the right or left lateral decubitus position.

Depending upon the clinical scenario, sleep laboratories also monitor:

- *Carbon dioxide*—measured via nasal cannula (end-tidal CO_2, $etCO_2$) or skin surface electrodes placed over the chest (transcutaneous CO_2, $tcCO_2$) to identify sleep-related hypercapnea in children, neuromuscular weakness, and obesity-hypoventilation syndromes
- *Expanded electroencephalography* (*EEG*) *montages*—extra EEG channels added when sleep-related epileptic seizures are suspected
- *Video-polysomnography*—a time-locked audiovisual recording used to correlate sleep/wake behaviors with polygraphic findings and monitor body position. Indicated when studying patients with violent or injurious sleep-related behavior, atypical or unusual parasomnias, or suspected sleep-related seizures
- *Esophageal pressure manometry* (*Pes*)—placement of a balloon catheter in the esophagus to detect respiratory event-related arousals and increased upper-airway resistance
- *Intraesophageal pH probe*—placed in the lower esophagus to correlate episodes of gastroesophageal reflux with polysomnography
- *Arm*—electromyographic electrodes placed over the left and right wrist extensor muscles to assess for inappropriate preservation of skeletal muscle activity during REM sleep in patients with REM sleep behavior disorder
- *Nocturnal penile tumescence* (*NPT*)—placement of strain gauges over the base and tip of the penis to measure penile rigidity during REM sleep in patients with suspected erectile dysfunction.

Technologists and clinicians may select different combinations of biological signals depending on the pathology of interest. Although completeness is desirable, simultaneous monitoring of every signal may increase sleep impairment in the "foreign" sleep laboratory environment producing suboptimal results. Therefore, signal selectivity is the key to a successful sleep study.

Understanding How Overnight Polysomnography Is Scored and Analyzed

Before interpretation by a sleep specialist, a sleep technologist categorizes the sleep events for each 30-second polysomnography epoch. Categorizing or "scoring" an entire overnight polysomnogram is time and labor intensive. Even with computerization, it takes a technologist 2 to 4 hours to score 600 to 800 epochs of polysomnography. Computer programs have "automatic" scoring modes, but most technologists find manual scoring more reliable.

Typically, the technologist first scores each epoch from "lights out" to "lights on" as a particular stage of sleep or wake using the R & K sleep stage scoring criteria (Table 1) (30). The technologist then identifies, classifies, and electronically denotes any and all events in the study including respiratory disturbances, limb movements, arterial oxygen desaturations, unusual behaviors, and changes in respiratory or cardiac rate or rhythms. Arousal and awakenings are marked, noting their relationship to respiratory events, periodic limb movements, oxygen desaturations, arrhythmias, hypercapnea events, seizures, or parasomnias. Arousals without apparent cause are termed "spontaneous." Once scored, the computer program tallies and tabulates all data and generates tables for interpretation. Table 3 provides commonly accepted definitions of sleep architecture data.

One of the major advantages of digital media is the ability to select an optimal time scale to view and score the particular biological signal. For example, the "classic" 30-second epoch offers the best view of sleep stages and arousals, whereas seizure activity is best displayed using a 10-second epoch (similar to standard EEGs). Respiratory events are best viewed using 90 to 120-second epochs or longer if observing periodic breathing patterns. Cardiac rhythms are best observed with a 25-second epoch. Figure 6A–D demonstrates examples of events in their optimal time scales.

Understanding the Results of a Level I Polysomnogram

Once scored and analyzed, the polysomnography information is collated into an easily readable pictorial "hypnogram" (Fig. 7) summarizing the patient's sleep across the entire recording. Understanding a polysomnography report and "reading" a hypnogram are easy once sleep architecture and the specifics of common sleep disorders are known.

Table 3 Sleep Study Data Definitions

- *Time in bed*: Time in minutes from lights out until the final awakening
- *Sleep period time*: Time in minutes from sleep onset to the final awakening
- *Total sleep time* (*TST*): Time in minutes from sleep onset until the final awakening less wake after sleep onset (WASO)
- *Sleep efficiency* (*SE*): Ratio of total sleep time/time in bed (TST/TIB), a measure of the percentage of TIB spent sleeping
- *Sleep onset*: Time in minutes after lights out when the first 30-sec epoch of any stage of sleep is observed
- *Sleep latency*: Time in minutes from lights out to sleep onset
- *REM sleep latency*: Elapsed time in minutes from sleep onset to, but not including, the first scoreable epoch of REM sleep
- *Sleep stage percentages*: Percentages of total sleep time spent in each particular stage of sleep (e.g., stages 1, 2, 3, 4, REM), determined by dividing recording time in each stage by the total sleep time
- *Number of awakenings and arousals*: Number of awakenings and arousals after sleep onset until, but not including, the final awakening
- *Number of stage shifts*: Number of times sleep changes from one stage to another during the study from sleep onset until the final awakening (excludes sleep onset and the final awakening)
- *Arousal and awakening indexes*: Mean number of arousals (or awakenings) per hour of sleep calculated by number of arousals (or awakenings) $\times$ 60 divided by the total sleep time. Arousal and awakening indices may further specify what caused these arousals (e.g., due to respiratory events, periodic limb movements, etc.)

Normal Sleep Architecture Varies Most with Age

Sleep is an active process in which different physiological stages alternate and evolve in a periodic manner across a given sleep period. Normal healthy subjects exhibit an alternating pattern of NREM–REM "sleep cycles" across a prototypical night's sleep otherwise known as the "ultradian rhythm" (Fig. 8). The first NREM–REM sleep cycle is a sequential descent from lighter to deeper stages of NREM sleep (stages 1–4), followed by an ascent (stages 3 and 2), then a brief period of REM sleep. The first NREM–REM sleep cycle in a young adult lasts about 90 minutes (80 minutes of NREM sleep followed by 10 minutes of REM sleep). Four to five sleep cycles are usually observed across a night's sleep in the laboratory (Fig. 8). NREM–REM sleep cycles last a mean of 90–110 minutes; the first are often shorter (70–110 minutes) while the later cycles are longer (90–120 minutes).

REM sleep is first seen (called the "REM latency") 70–110 minutes after sleep onset. The first REM sleep period is usually short (5–15 minutes) with a paucity of eye movements. REM periods progressively lengthen across the night. In contrast, slow-wave sleep is usually maximal during

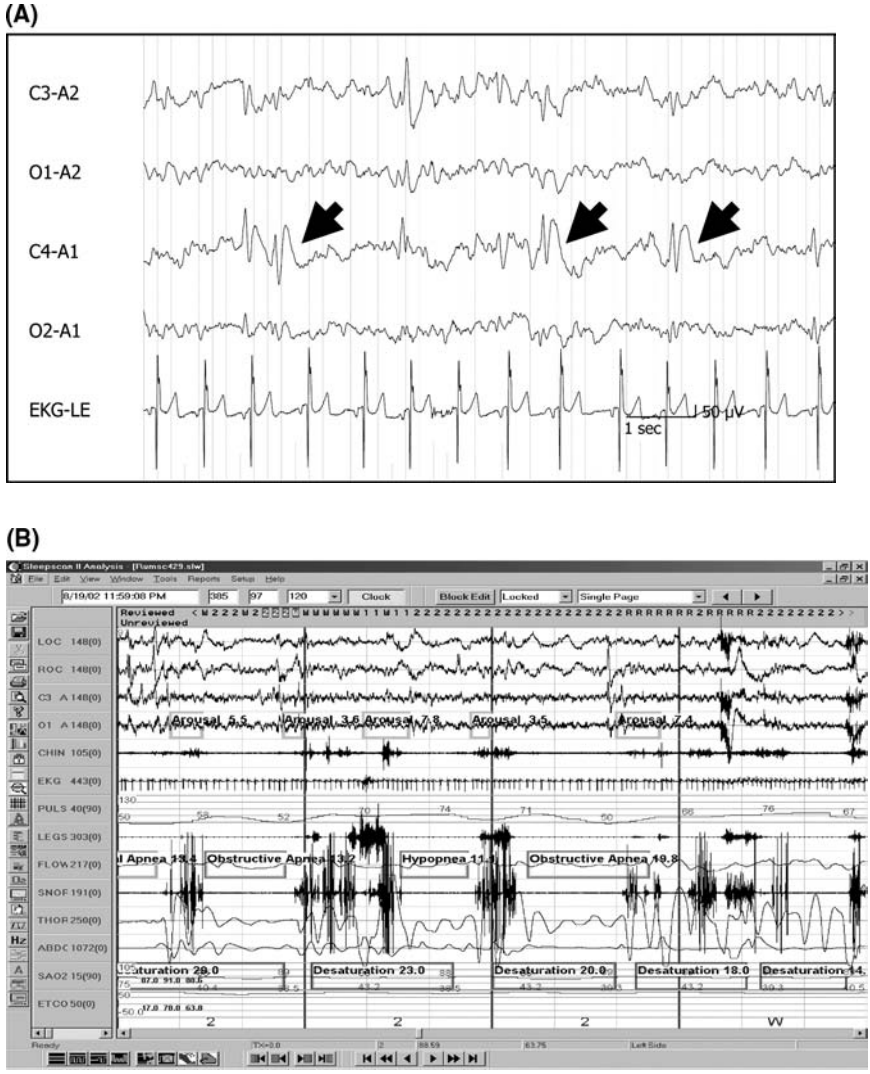
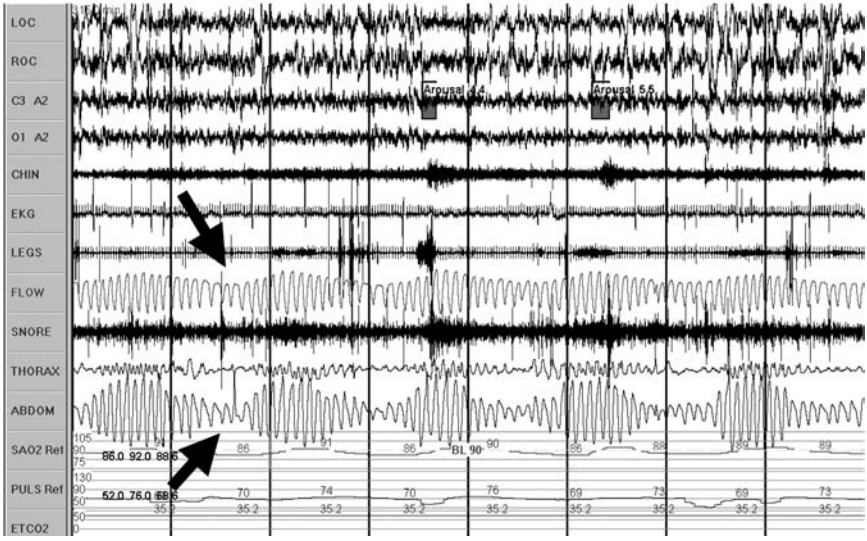


Figure 6 (**A**) Recognizing epileptiform discharges is difficult when recording only a few electroencephalography channels. Changing the screen size to a 10-sec epoch is helpful. Note the arrows pointing to central spikes, which may be mistaken for K-complexes. (**B**) Obstructive apneas and hypopneas are often best analyzed during longer epochs such the 120-sec epoch shown below. The patient's sleep-disordered breathing is best appreciated in the "flow" channel. (**C**) Periodicity of Cheyne–Stokes breathing (*arrows*) best recognized using 4-min epochs. (**D**) Periodicity of limb movements (*arrows*) is best identified using long epoch lengths lasting minutes at a time. (*Continued next page.*)

(C)



(D)

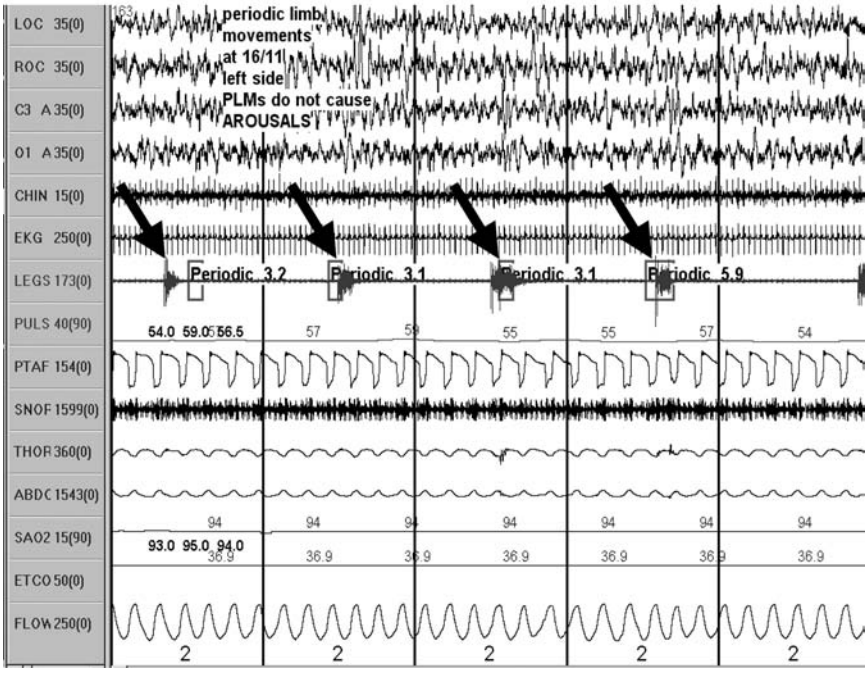


Figure 6 (*Continued.*)

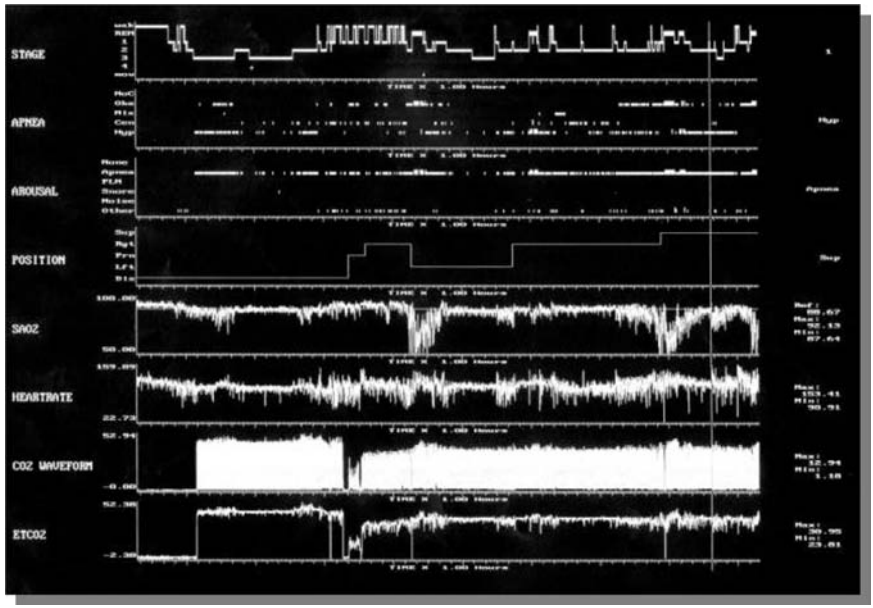


Figure 7 A representative hypnogram demonstrating sleep stages, apneas, arousals, body position, pulse oximetry, heart rate, and carbon dioxide levels across a full night of polysomnography.

the first two NREM–REM sleep cycles. By the early morning, sleep often alternates between stages 2 and REM. A healthy young adult spends about 3–8% of total sleep time in stage 1, 45–55% in stage 2, 15–20% in slow-wave sleep, and 20–25% in REM.

Age is the strongest and most consistent factor influencing sleep architecture across the night (Fig. 9). Young children spend 25–40% of total sleep time in slow-wave sleep (mostly stage 4), which dominates the first three hours of their sleep. Such generous amounts of slow-wave sleep explain in part the predilection of young children to sleepwalking and other partial arousals from deep NREM sleep, especially in the first 90–180 minutes after sleep onset. In sharp contrast, stage 4 sleep is significantly diminished in the healthy elderly.

Quantities (and percentages of total sleep time) of slow-wave sleep decrease while those of stage 1 increase gradually across adult life. Sleep need declines with age. The normal term infant sleeps 16–18 hours per 24-hour period, 14–15 hours by age 16 weeks, and 13–14 hours by age 6–8 months. Circadian rhythms of wakefulness and sleep are usually established by four months of age, continuing to consolidate by 6–7 months (i.e., tending to sleep more at night than during the day). Young children average 9–10 hours of sleep per day, adolescents most often need 8.5–9.25 hours,

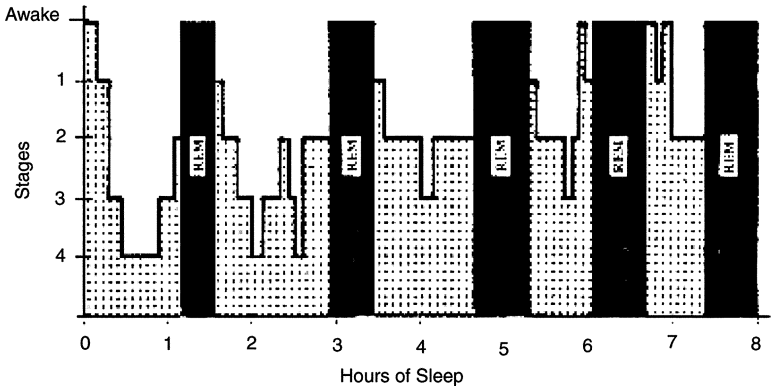


Figure 8 Hypnogram in a normal young adult.

adults 7–8 hours, and the elderly 5–6 hours. Children have few awakenings and young adults average only two awakenings per night (often unrecalled). The elderly typically experience five or more awakenings per night, recalling one or two. Sleep efficiency remains stable from childhood through age 30, followed by a decline for men beginning in the fourth decade and for women in the fifth decade. A gradual increase in the number of awakenings and arousals after sleep onset is observed across adulthood.

The percentage of total sleep time devoted to REM sleep is 55% in infancy, which falls to 30–35% in children aged 9–12 months and reaches adult levels of 20–25% between ages 2 and 5 (31). Infants are "little narcoleptics" entering sleep through REM or indeterminate sleep, although by age six months only 18% of sleep onsets are REM sleep. REM latency is 60 minutes by age 2–3 years, reaching adult values by age five with an average of 90 minutes (range 70–110 minutes). The percentage of total sleep time devoted to REM sleep (20–25%) is well maintained even among the healthy elderly, with only a minor fall in the percentage among men. Table 4 provides a summary of normal sleep in 218 men studied in decades ranging from 20 to over 60 years of age (32).

First Night Effects: Difficulty Sleeping in the Laboratory

Strange environments with unfamiliar sensations such as the sleep laboratory often disrupts sleep and alters sleep architecture. Sleep physicians should not assume that a single night in the sleep laboratory represents a typical night's sleep. Indeed, two to four consecutive nights of sleep are needed before a patient's home sleep patterns are observed. These alterations in sleep architecture are called "first night effects" and include an increase in sleep onset latency, increased amounts of stages 1 and wake time, delays in onset of stage 4 and REM sleep, increased numbers of stage shifts, and less percentage of REM sleep.

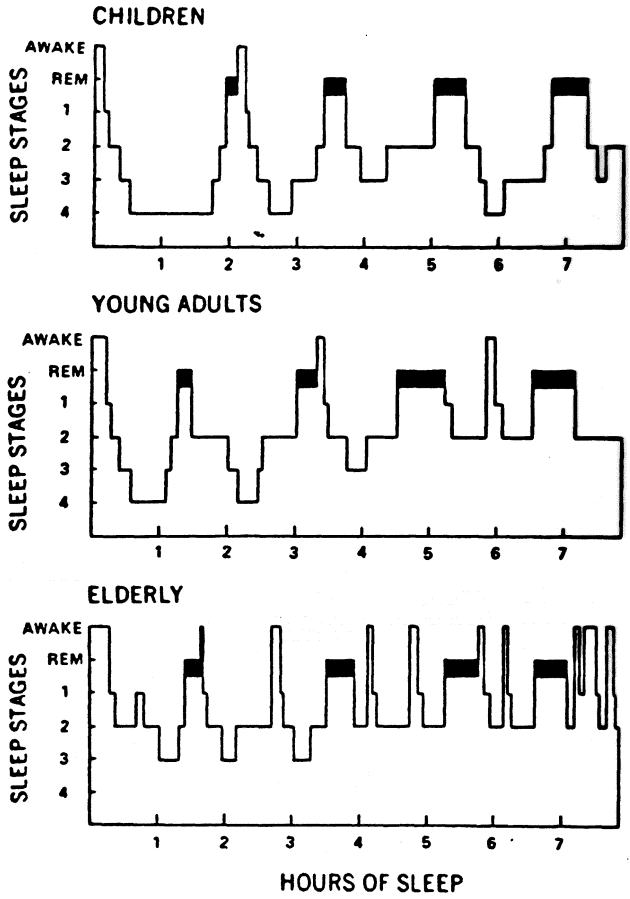


Figure 9 How sleep changes with age.

Ideally, the first night effect would be eliminated by spending multiple nights in the sleep laboratory. However, this is not practical as third-party payers will not cover multiple consecutive polysomnograms for the most common indication—obstructive sleep apnea. Fortunately, a single night of polysomnography provides a reasonable measure of the presence and severity of sleep-disordered breathing and sometimes allows the introduction of CPAP in the second half of the study. First night effects impair the clinician's ability to make sweeping statements regarding an individual's sleep architecture. Nevertheless, observations can still be made regarding improvement in sleep architecture following introduction of CPAP. This "rebound" phenomenon usually takes the form of increased slow-wave and/or REM sleep and marked decreases in arousals and awakenings.

Table 4 Normative Sleep Parameters in Men, Ages 20 to 60+ Years

	Age (yr)				
	20–29 ($n=44$)	30–39 ($n=23$)	40–49 ($n=49$)	50–59 ($n=41$)	>60 ($n=29$)
Total time in bed ± SD (min)	405 ± 44	393 ± 58	404 ± 49	393 ± 51	396 ± 43
Total sleep time ± SD (min)	347 ± 63	340 ± 71	329 ± 55	332 ± 64	298 ± 61
Total wake time ± SD (min)	58 ± 61	53 ± 48	75 ± 47	61 ± 45	97 ± 51
Sleep latency ± SD (min)	12 ± 13	13 ± 10	14 ± 14	9 ± 11	15 ± 15
Sleep efficiency ± SD (%)	86 ± 14	86 ± 12	82 ± 11	84 ± 11	75 ± 13
Stage 1% ± SD	4 ± 3	3 ± 2	5 ± 3	5 ± 3	6 ± 3–4
Stage 2% ± SD	49 ± 9	50 ± 10	52 ± 12	54 ± 10	51 ± 9
Slow-wave sleep % ± SD	16 ± 7	15 ± 8	9 ± 9	7 ± 8	5 ± 6
REM sleep % ± SD	18 ± 7	18 ± 8	16 ± 6	18 ± 6	13 ± 6
Awakenings per hour of sleep ± SD	1.5 ± 1.2	1.3 ± 0.8	1.8 ± 0.8	1.8 ± 0.7	2.2 ± 1.0

Abbreviations: REM, rapid eye movement; SD, standard deviation.
Source: From Ref. 32.

Polysomnography and Arousals

Arousals and awakenings are laboriously tallied and linked to respiratory events and periodic limb movements. Without identifiable cause they are considered "spontaneous." Most laboratories score arousals and awakenings using the AASM Atlas Task Force EEG Arousal Scoring Rules summarized in Table 5 (33). Based on these consensus criteria, an arousal is defined as an abrupt shift in EEG frequency, which may include alpha, theta, and/or frequencies greater than 16 Hz but not sleep spindles. Arousals must last at least three seconds and those occurring during REM sleep must be accompanied by a transient return of chin EMG activity. The arousal index reports the average number of arousals per hour of sleep, while the awakening index indicates the average number of awakenings per hour of sleep. The arousal and awakening indices, along with wake-after-sleep-onset are quantifiable measures of sleep fragmentation.

Because normative data are limited, it is unknown how many arousals per hour of sleep are too many. Significant variation exists in the general population, with age playing a major role. Boselli et al. (34) found that normal subjects aged 10–19 years had arousal indices of 14 ± 2 per hour of sleep, whereas those aged 20–39 years had indices of 15 ± 3. Subjects aged 40–59 years had indices of 18 ± 2, while those ≥60 had indices of 27 ± 3. Mathur and Douglas (35) reported 31 normal subjects with a mean age of 37 years, with arousal indices averaging 21 per hour (range 6–63). Arousal indices averaged 8 per hour (range 3–16) among a group of normal children

Table 5 American Academy of Sleep Medicine Atlas Task Force Electroencephalography (EEG) Arousal Scoring Rules

1. An electroencephalographic (EEG) arousal is an abrupt shift in EEG frequency (which can be theta, alpha, and/or beta frequencies but not spindles)
2. At least 10 sec of continuous sleep of any sleep stage must have been present before an EEG arousal can be scored
3. A minimum of 10 sec must follow an arousal before a second arousal can be scored
4. The EEG frequency shift must be $\geqslant$3-sec to be scored as arousal
5. Arousals during nonrapid eye movement (NREM) sleep do not require a concurrent increase in chin electromyography (EMG) activity to be counted
6. Arousals in rapid eye movement (REM) sleep are scored only if they are accompanied by increases in chin EMG activity
7. Arousals cannot be scored solely on increases in chin EMG without seeing EEG frequency shifts in EEG channels
8. K-complexes, delta waves, or artifacts are not scored as arousals unless accompanied by an abrupt EEG frequency shift in at least one derivation:
   - If a K-complex, delta waves, or artifact precede the EEG frequency shift, they cannot be used to reach the 3-sec duration criteria;
   - If a K-complex, delta waves, or artifact occur within the EEG frequency shift, they can be included in fulfilling the 3-sec duration criteria
9. Pen-blocking artifact can be used to reach the 3-sec criteria only if it occurs contiguous with an EEG arousal pattern
10. Arousals during alpha–delta sleep (if no other pathophysiological events are present) need to last at least 3-sec to be counted. Do not score an arousal unless a 10-sec free period of alpha-free sleep precedes the change

Source: From Ref. 33.

aged 0–11 years (36). Taken together, an arousal index of 20 or less per hour may be within normal limits during an in-laboratory polysomnogram, especially if most arousals are without particular identifiable cause.

Sleep specialists and technologists must carefully consider arousal-causing phenomena during polysomnography. Normal subjects have far fewer respiratory-related arousals than patients with sleep-disordered breathing (35). Excessive daytime sleepiness among obstructive sleep apnea patients relates more to the number of arousals than desaturation events. Respiratory arousals have more pathophysiological effects than nonrespiratory arousals (37). Clinically significant and symptomatic respiratory-related arousals may last only 1.5–2 seconds, shorter than the AASM ''3-second'' rule, prompting some laboratories to score shorter arousals when clearly triggered by apneas or hypopneas.

Sleep Apnea Severity on Polysomnography

Sleep apnea is the periodic limitation of airflow during sleep, resulting in oxygen desaturations and arousals (Chaps. 5 and 6). Respiratory disturbances

observed (and scored) on polysomnography include apneas, hypopneas, respiratory event-related arousals (RERAs), and "inspiratory flow limitation events." Definitions for each of these events continue to evolve taxing sleep medicine beginners and experts alike.

Sleep clinicians do agree on the definitions of the various apneas. In adults, an apnea in sleep is the absence of airflow through the nose and mouth evident by an 80–100% fall in the amplitude of the airflow signal for 10 or more seconds compared to a baseline established over the preceding 2 minutes. Apneas are further classified as central, obstructive, or mixed in type based upon respiratory effort. Thoracic and abdominal respiratory effort ceases during absent airflow in central apneas, while continued or increased respiratory effort occurs during obstructive apneas. In mixed apneas, respiratory effort is absent in the initial portion of the event followed by resumption of respiratory effort. Many sleep laboratories score mixed apneas as obstructive events because they are most often due to upper-airway obstruction (38). Figure 10 shows representative examples of each apnea type as well as a hypopnea.

Sleep clinicians and laboratories have great difficulty agreeing on definitions of hypopneas and RERAs. The severity of obstructive sleep apnea reported on polysomnography can vary as much as 13-fold depending upon laboratory-specific definitions of hypopneas and other more subtle limitations in airflow (39). Struggling for uniformity, the AASM Clinical Practice Review Committee in 2001 defined a hypopnea in adults as a respiratory event causing a 30% or greater fall in airflow from baseline for 10 or more

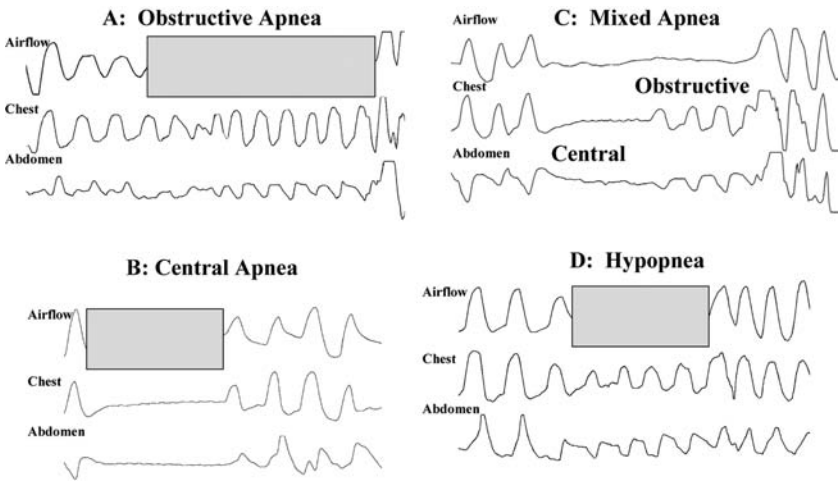


Figure 10 Representative examples of apneas and hypopneas recorded during polysomnography.

seconds associated with a 4% or greater fall in oxygen saturation (40). An earlier AASM Task Force on sleep-disordered breathing in adults (1999) (38) advised that no attempt was needed to distinguish apneas from hypopneas because they have the same pathophysiology and both cause symptoms and signs of obstructive sleep apnea.

The definitions of RERAs remain inconsistent depending on how they are measured. Guilleminault et al. (41) first recognized that sleep is fragmented by RERAs in some symptomatic obstructive sleep apnea patients without any or few (<5/hr of sleep) apneas or hypopneas. Using esophageal manometers, they identified that RERAs in these patients correlated with increasingly negative esophageal pressure. They called these "Pes events" and the sleep-disordered breathing syndrome associated with them was named "upper-airway resistance syndrome." Although esophageal manometry remains the gold standard for detecting this syndrome, nasal cannula pressure transducers are currently used in most sleep centers due to patient comfort and ease of use. Ayappa et al. (42) found that nasal pressure transducers recognized 88% of Pes events. These are called "flow limitation" or "inspiratory flow limitation" events and cause a slight flattening during inspiration in the flow signal of insufficient amplitude to score as a hypopnea.

How many obstructed breathing events per hour of sleep are abnormal? The Centers for Medicare and Medicaid Services in the United States will cover the prescription of CPAP for obstructive sleep apnea in an adult whose in-laboratory polysomnogram documents five or more apneas and hypopneas per hour of sleep, provided the subject has symptoms of excessive daytime sleepiness, impaired cognition, mood disorders or insomnia, or has documented hypertension, ischemic heart disease, or a history of stroke (43). The Centers for Medicare and Medicaid Services is also willing to provide CPAP to "asymptomatic" patients with an apnea–hypopnea index of 15 or greater. Obstructive sleep apnea severity can be determined by as little as 2 hours of polysomnography, allowing for the introduction of CPAP in the second half of the study (a so-called "split-night" PSG).

The Centers for Medicare and Medicaid services define obstructive sleep apnea as recurrent episodes of complete or partial upper-airway obstruction during sleep accompanied by unexplained excessive daytime sleepiness and two or more other symptoms including choking or gasping during sleep, recurrent awakenings from sleep, unrefreshing sleep, daytime fatigue, or impaired concentration. They define apnea in an adult as a cessation of airflow for 10 or more seconds and a hypopnea as an abnormal respiratory event lasting 10 or more seconds with 30% or greater reduction in thoracoabdominal movement or airflow, as compared to baseline including a 4% or greater oxygen desaturation.

Many sleep specialists object to the requirement of a 4% or greater desaturation to score a hypopnea because apneas and hypopneas can cause

Table 6 Obstructive Sleep Apnea Severity Criteria

Sleep apnea severity	RDI	Apnea duration (sec)	Oxygen desaturation	Effects of respiratory events on EKG
Mild	<20	<20	>85	Mild sinus brady-tachyarrhythmia
Moderate	20–40	20–40	75–85	Brief asystole (<3 sec) or prominent sinus brady-tachyarrhythmia
Severe	>40	>40	<75	Asystole >2 sec or ventricular tachycardia

Abbreviations: RDI, respiratory disturbance index; EKG, electrocardiogram.
Source: From Ref. 45.

arousals or awakenings with minimal (1–3%) or no oxygen desaturations. This is especially true in children or patients with normal baseline oxygen saturations, lung volumes, weight, and lung function. Failure to score these events may underestimate the severity of a patient's obstructive sleep apnea. This may result in a disparity between the patient's complaints and the severity of their sleep-disordered breathing as documented on polysomnography.

The average number of apneas and hypopneas per hour of sleep is called the apnea–hypopnea index. Liberal definitions of obstructive sleep apnea now prevail with an index of 5 or more per hour as abnormal. Patients with more than 20 obstructive apneas per hour of sleep have a significant increase in mortality during long-term follow-up (44). The respiratory disturbance index is the average number of respiratory disturbances per hour of sleep. How this index is counted and reported varies among sleep laboratories, with some reporting all respiratory disturbances including RERAs, others reporting hypopneas only because they caused arousals, and still others only reporting hypopneas that caused 4% (or 3%) or greater desaturations.

Sleep specialists gauge the severity of obstructive sleep apnea based upon the apnea–hypopnea index and respiratory disturbance index. Other factors impacting on disease severity include apnea and hypopnea length, the degree of sleep fragmentation and oxygen desaturation, EKG abnormalities, the respiratory rate, and baseline oxygen saturation and carbon dioxide levels. Ratke's (45) sleep apnea severity criteria shown in Table 6 provide a helpful measure for the clinician.

Periodic Limb Movements Scored on Polysomnography

Restless legs syndrome is a movement disorder characterized by an irresistible urge to move the legs, often accompanied by uncomfortable leg sensations

(see Chap. 4 for more details). This syndrome is worse at rest, especially in the evening or at night, and temporarily relieved by moving or walking. The nocturnal exacerbation in symptoms often contributes to difficulties falling asleep or maintaining sleep, especially in the first half of the night.

Periodic limb movements are involuntary unilateral or bilateral stereotypic movements occurring intermittently during sleep. Although the majority (80–90%) of restless legs syndrome patients demonstrate periodic limb movements during polysomnography, not all patients have periodic limb movements on a single polysomnogram. Therefore, the presence of periodic limb movements is not necessary to make the diagnosis of restless legs syndrome. Periodic limb movements involve a sequence of four or more limb movements recurring at 5 to 90-second intervals, with each movement lasting 0.5–5 seconds. Most periodic limb movements last 1.5–2.5 seconds and recur at 20 to 40-second intervals (Fig. 6D). Periodic limb movement-related arousals are scored when they occur following limb movement termination by no more than 1–2 seconds. Periodic limb movements are measured from limb movement onset to limb movement onset.

Periodic limb movements typically involve both legs and occasionally the arms (rarely the trunk). Movements are often bilateral but may shift or predominate in one limb and are typically recorded from EMG electrodes placed over the anterior tibialis muscles bilaterally. Additional electrodes may be added over the wrist extensors in patients with suspected REM sleep behavior disorder. Periodic limb movement EMG activity can include everything from a sustained tonic contraction to a polyclonic burst with a frequency of approximately 5 Hz. A periodic limb movement in a patient with restless legs syndrome captured on video-polysomnography begins with a leg jerk followed milliseconds later by a tonic contraction resembling a Babinski (plantar extensor) toe response with tonic extension of the great toe. This is sometimes accompanied by clonic activity, ankle dorsiflexion, and knee flexion.

Periodic limb movements can be observed immediately after sleep onset, although they are most frequent in stage 2 sleep. These movements decrease during slow-wave sleep and are uncommon in REM sleep except in patients with narcolepsy–cataplexy. While awake, restless legs syndrome patients may have periodic limb movements lasting as long as 10 seconds.

Sleep technologists score periodic limb movements, noting whether they cause arousals or awakenings. They discard those related to respiratory events and generate a periodic limb movement index (average number of periodic limb movements per hour of sleep) and a periodic limb movement arousal index (average number of periodic limb movements causing arousals per hour of sleep). The International Classification of Sleep Disorders (46) attempted to quantify periodic limb movement severity in adults, rating indices of 50 or more as severe, 25 or more as moderate, and 5 or more as mild. An index of 25 or greater often fragments sleep architecture.

An AASM Standards of Practice review paper recommends treatment of periodic limb movement disorder (periodic limb movements associated with sleep dysfunction) only when the periodic limb movement arousal index is greater than 10–15 (47). In children, five or more periodic limb movements per hour are abnormal, although frequently they do not cause arousals.

Deciding whether or not periodic limb movements are significant or abnormal is challenging. Indeed, an index of five or more occurs in as many as 11% of asymptomatic normal young adult subjects and 45–55% of healthy elders. Clinicians should consider periodic limb movements that do not cause arousals "asymptomatic" parasomnias. Similarly, periodic limb movements are often seen in obstructive sleep apnea patients while titrating CPAP and usually do not cause arousals and only occasionally require treatment. Patients with narcolepsy–cataplexy often have periodic limb movements, but treating them causes little overall improvement in their sleep/wake complaints. Periodic limb movements and restless legs syndrome can be secondary phenomena, triggered by a variety of medical and neurological disorders as well as medications or other pharmacological agents. Identifying the cause or significance of periodic limb movements during polysomnography is challenging and clinicians at times must resist the urge to treat them.

Strengths and Weaknesses of Overnight In-Laboratory Polysomnography

Suspected obstructive sleep apnea is the most common indication for a class I polysomnogram. Neil Douglas (48) recently argued that although in-laboratory polysomnography is a good method for diagnosing sleep apnea, evidence is lacking that it identifies patients with the disorder more accurately than home sleep studies. Despite this notion, class I polysomnography does have advantages. First, a skilled sleep technologist is present to identify and repair sensor failure issues. Second, CPAP can be introduced in the second half of recording. And third, long-term CPAP compliance is better when the patient is first introduced to the therapy in the sleep laboratory. In addition, in-laboratory polysomnography can generate a true apnea–hypopnea index based on time slept (not time in bed). This is important because an apnea–hypopnea index based on time in bed may be falsely low, thus underestimating sleep apnea severity, particularly when a patient has extensive wake after sleep onset time.

A class I polysomnogram provides greater detail regarding the impact of the obstructive sleep apnea on the patient's sleep, especially in regard to arousals, awakenings, and alterations in sleep stage architecture. This matters because sleep fragmentation, rather than desaturations, are considered the cause of sleep apnea symptoms. Few can contest that class I polysomnography with video and expanded EEG montages remains the

best method for studying atypical or injurious parasomnias and sleep-related epilepsy.

Class I polysomnograms have several disadvantages. Most studies involve a single night's sleep in an artificial environment, providing at best a narrow view of a patient's natural sleep. Level I studies are expensive and time-consuming to record, score, and interpret. First night effects are more common with in-laboratory studies than home studies (49,50). Obstructive sleep apnea patients in the laboratory "with all those wires attached" often spend more time supine and have less REM and slow-wave sleep than at home producing an inaccurate snapshot of their sleep-disordered breathing. Obstructive sleep apnea can fluctuate from night to night (50,51), with one study finding apnea–hypopnea indices lower than another (50). Causes for this variance include body position during sleep, sleep stage percentages, alcohol use, sleep deprivation, nasal congestion, intercurrent illness, and medication side effects. Because a false-negative polysomnogram is possible, the clinician should consider repeating the study if the clinical suspicion is high.

Polysomnography demand is greater than availability and patients can wait weeks or months for a class I study. Almost every technique used to monitor respiration during polysomnography provides qualitative (not quantitative) information and can malfunction or provide false-positive data. Wary of this, most sleep laboratories record breathing during sleep with multiple different devices, providing redundant information to confirm the presence of sleep-disordered breathing. Finally, standards for scoring events in polysomnography continue to evolve. Definitions of a clinically significant apnea–hypopnea index or respiratory disturbance index vary, thus reducing or increasing the number of patients diagnosed with obstructive sleep apnea.

Customizing Level I Polysomnography to Specific Clinical Scenarios

Split-Night Polysomnography

Long waiting lists for in-laboratory polysomnography and cost containment by third-party payers have led many sleep laboratories to perform "split-night" studies when evaluating obstructive sleep apnea. In this scenario, if significant sleep apnea occurs in the first two or more hours of the study, the sleep technologist arouses the patient and initiates CPAP therapy. Pressures are gradually increased until the majority of untoward events are eliminated (snoring, apneas, hypopneas, arousals, cardiac arrhythmias, and oxyhemoglobin desaturations) in all body positions and sleep stages, especially during supine REM sleep when obstructive sleep apnea is often most severe. A split-night study has limitations. Sleep apnea severity may not be evident until the later portions of the study, leaving insufficient time

to establish effective CPAP pressures. Moreover, introducing CPAP to a sleepy patient in the middle of the night may make the patient's initial experience unpleasant. Although CPAP is useful for upper-airway resistance syndrome and mild sleep apnea patients, it is most often used in patients with symptomatic obstructive sleep apnea with an apnea–hypopnea index $\geq$20.

Diagnosing Hypoventilation During Sleep

Sleep-disordered breathing in some patients manifests only as a sleep-related hypercapnea, which goes unrecognized unless carbon dioxide (CO_2) levels are measured. These levels are routinely monitored in children during polysomnography, since sleep apnea may be subtle in this population, presenting with noisy breathing instead of snoring, flow limitation in the nasal pressure transducer, paradoxical breathing, or hypercapnea (called "obstructive hypoventilation").

Hypercapnea can be the sole respiratory abnormality during sleep in patients with neuromuscular disease, alveolar hypoventilation, or obesity-hypoventilation syndromes. Many patients with sleep-related hypercapnea have only slight drops in their baseline oxygen saturations when sleeping. In fact, oxygen desaturation has never been a reliable indicator of hypercapnea. Breathing during sleep can be reported as falsely normal in such patients unless hypercapnea is documented. Be advised that patients with obesity, chronic obstructive pulmonary disease, neuromuscular disease, and kyphoscoliosis may hypoventilate during sleep and have normal arterial blood gases when awake.

Carbon dioxide levels should be monitored in all children, patients with neuromuscular disease, bariatric surgery candidates, and those suspected of sleep-related hypoventilation. This is done by either sampling expired air at the nose using a nasal cannula ($etCO_2$) or by attaching a heated skin sensor on the chest ($tcCO_2$). End-tidal carbon dioxide accurately measures moment-to-moment changes and is the preferred method for recording carbon dioxide levels in sleeping children (52).

Unfortunately, end-tidal carbon dioxide often malfunctions or provides falsely low values in patients with nasal obstruction or nasal secretions, obligate mouth breathers, and those receiving supplemental oxygen or CPAP during the polysomnogram.

Transcutaneous carbon dioxide monitoring provides a semiquantitative index of trends in alveolar ventilation (53) that varies from the $paCO_2$, which typically lags 10–25 seconds behind an event (52). The accuracy of transcutaneous carbon dioxide measurements during sleep has been demonstrated (54). Skin sensors may leak, resulting in falsely high oxygen and falsely low carbon dioxide levels. These sensors must be heated, and rotated every 4 hours to avoid burning the underlying chest skin.

Guilleminault et al. (55) compared the utility of transcutaneous and end-tidal carbon dioxide measurements to esophageal pressure measurements for recognizing apneas, hypopneas, and upper-airway resistance during NREM sleep in children with obstructive sleep apnea. They found that all three devices recognized 82% of apneas and hypopneas but only 33% of upper-airway resistance events, as indicated by esophageal pressure recordings ($tcCO_2$ 33%, $etCO_2$ 80%). They defined a $\geq$4 mmHg rise in the respiratory-related transcutaneous carbon dioxide level as abnormal and significant. Generally speaking, a $\geq$6–8 mmHg rise in the end-tidal carbon dioxide level in direct relation to a respiratory event is considered abnormal.

Sleep-related hypoventilation can be defined and measured in the sleep laboratory. The $paCO_2$ usually increases 2–7 Torr (mmHg) during sleep in normal adults (56). Therefore, sleep-related hypoventilation in adults is indicated by a $\geq$10 Torr rise in the $paCO_2$ level during sleep compared to the baseline level awake supine. Chronic hypercapnia is defined as a $paCO_2$ consistently higher than 45 Torr (57). There is paucity of available data regarding end-tidal capnography cut points in children (58–60). One study (59) reported end-tidal carbon dioxide levels were abnormal if $>$45 mmHg for $>$60% of the total sleep time, $>$50 mmHg for $>$10% of the total sleep time, and/or any single value $>$53. Another study (60) reported abnormal levels if $>$45 mmHg for $>$10% of the total sleep time and any single value 50 mmHg or higher.

Sleep-Disordered Breathing and Polysomnography in Children

Children are not little adults when it comes to sleep apnea. Indeed, obstructive apneas and hypopneas in young children often last only 6–9 seconds, far shorter than the 10-second minimum duration in adults. Obstructive sleep apnea in children presents with noisy breathing rather than frank snoring and respiratory events and may cause little or no oxygen desaturation, fewer arousals, and little or no disruption of overall sleep architecture.

Sleep apnea in children can be confined only to REM sleep (but then may be quite severe). Finally, obstructive sleep apnea in children can manifest as upper-airway resistance syndrome characterized by a sustained increased respiratory effort, prolonged inspiratory flow limitation events, or excessive negative pressure swings within the esophagus with or without sleep-related hypercapnia.

How many obstructed breathing events are too many in a child? Marcus et al. (59) defined pathologic respiration in children as five or more apneas and hypopneas per hour of sleep or more than one obstructive apnea per hour of sleep. Acebo et al. (61) suggested an obstructive apnea–hypopnea index of 1.5 or more per hour of sleep (mean $\pm$ 2 SD) was abnormal in older children and young adults. Because little normative data are available for hypopneas in children, the International Classification of Sleep Disorders-2 Task Force proposed using an apnea–hypopnea index criterion of one or

more obstructive apneas or hypopneas per hour of sleep. They also advised not to tally central apneas when diagnosing pediatric obstructive sleep apnea. Table 7 provides normative data for respiratory events in children suggested by Witmans et al. (62), and data culled from three studies (58–60).

Afternoon Nap Polysomnography in Children

A few sleep specialists and laboratories perform "afternoon nap" studies to screen for obstructive sleep apnea in children. Nap studies are similar to an overnight level I polysomnogram except that they are only recorded for four hours. Recording slow-wave and REM sleep during a nap study is optimal, but these stages may not occur unless the patient is sleep deprived or given sedation. Marcus et al. (63) initially reported that sedated nap studies had a sensitivity of 74% and a positive predictive value of 100% for diagnosing obstructive sleep apnea, but a second larger study of theirs revealed that sleep apnea severity could not be predicted by nap studies (64). The difference in predictive value between nap and overnight studies is probably related to decreased total sleep times and reduced amounts of REM sleep during nap studies. Overnight polysomnography is often done in children to evaluate obstructive sleep apnea severity prior to adenotonsillectomy. If severe sleep apnea is present, overnight hospitalization and monitoring should occur following surgery. An afternoon nap study can identify a child with obstructive sleep apnea, but does not measure its severity, and the absence of obstructive sleep apnea on an afternoon nap does not eliminate the diagnosis. Since third-party payers reimburse patients for only so many sleep studies, it may be preferable to stick with overnight polysomnography when diagnosing and rating the severity of obstructive sleep apnea in children.

Evaluating Sleepwalking, Sleep Terrors, and Confusional Arousals with Polysomnography

Sleepwalking, sleep terrors, and confusional arousals are parasomnias typically emerging from slow-wave sleep (rarely stage 2) within 60–90 minutes of falling asleep (see Chap. 8 for more information). Severity and duration of episodes relates to the depth and duration of slow-wave sleep just prior to the NREM partial arousal. Video-polysomnography with extended EEG montages helps identify features suggestive of these parasomnias such as precipitous arousals from slow-wave sleep accompanied by simple or complex behaviors. The post-arousal EEG during a confusional arousal or sleepwalking is often obscured by muscle or movement artifact. The tracing that persists usually reveals partial or almost complete persistence of sleep with any of a number of associated patterns, including diffuse rhythmic delta slowing, a mixture of theta and delta activity, stage 1 theta patterns, repeated microsleeps, or a diffuse and poorly reactive alpha rhythm. Schenck et al. (65) found that 2% of episodes were heralded by

Table 7 Normative Data for Respiratory Events in Children

				$EtCO_2$[a]		Pulse oximetry[b]	
Age range	Obstructive apnea	Central apnea	AHI	Abnormal if	Maximum value (mmHg)	Normal (%)	Nadir (%)
1–16 yr ($n = 50$)	<1 event per hour of sleep	—	<1.5 events per hour ($n = 41$)	>45 Torr >60% of TST or >50 Torr >10% of TST	53	96 ± 2	92
11 mo to 18 yr ($n = 70$)	<1.2 events per hour of sleep	<1 per hour of sleep	—	>45 Torr for >10% of TST	50	97 ± 0.2	92

[a]Only useful in children without underlying lung disease.
[b]Maximum changes in SaO_2 do not apply to children with cyanotic heart disease.
Abbreviations: AHI, apnea–hypopnea index; $EtCO_2$, end-tidal carbon dioxide; Torr, mmHg; TST, total sleep time; >, greater; <, less; ±, greater or equal to; Nadir, lowest normal value.
Source: From Ref. 62.

hypersynchronous delta activity and heart rate acceleration for 10–30 seconds before the motor behaviors began.

Therefore, although previously considered useful in identifying confusional arousals, hypersynchronous delta slowing preceding an abrupt arousal from sleep is now thought to have a low specificity for sleepwalking. In fact, this phenomenon is much more common in obstructive sleep apnea patients whose apneas trigger confused arousals. Heart rate acceleration in NREM partial arousal disorders typically begins with onset of the motor behavior. The degree of tachycardia is often the best indicator of attack severity: more severe for sleep terrors, less so for confusional arousals and agitated sleepwalking, and least for quiet sleepwalking.

The clinician must understand that a normal polysomnogram does not rule out sleepwalking. Moreover, a sleep study done to confirm a parasomnia as the cause for a sleep-related violent crime does not confirm that the parasomnia occurred at the time of the violent behavior because as many as 1–4% of adults (if not more) are sleepwalkers. Polysomnography is warranted in atypical or injurious parasomnias and also to identify other sleep disorders, which may precipitate NREM partial arousals such as obstructive sleep apnea or its treatment, other forms of sleep-disordered breathing, periodic limb movements, and forced awakenings due to environmental noise. Polysomnography is useful in distinguishing NREM partial arousals from REM sleep behavior disorder, obstructive sleep apnea-induced arousals from REM sleep mimicking REM sleep behavior disorder (''pseudo-REM sleep behavior disorder''), sleep-related epilepsy, nocturnal dissociative disorders, panic attacks, and parasomnia overlap disorders.

Diagnosing REM Sleep Behavior Disorder with Polysomnography

REM sleep behavior disorder is a syndrome of abnormal dream enactment behaviors emerging from REM sleep that can injure the patient or bed partner. The disorder is associated with sleep disrupting excessive EMG muscle tone and/or excessive limb EMG muscle twitching during REM sleep on polysomnography (see Chap. 8 for more details). Patients with this disease (or their bed partners) often present with sleep-related injuries. These patients exhibit complex violent behaviors, which represent the enactment of unpleasant, violent dreams. Patients with REM sleep behavior disorder lose the peripheral skeletal muscle atonia normally present during REM sleep. This inappropriate presence (and even augmentation) of EMG activity and tone during REM sleep allows them to act out their violent dreams. The majority of patients with this disorder are men who present in the fifth to sixth decades of life. More than two-thirds will have (or will develop) neurodegenerative diseases dominated by Parkinsonism and dementia (most often α-synucleinopathies such as dementia with Lewy bodies or multiple

system atrophy) (66). REM sleep behavior disorder occurs in about one-eighth of patients with narcolepsy–cataplexy. This disorder may be triggered by medications or medication withdrawal and must be distinguished from the "pseudo-REM sleep behavior disorder" seen in patients with obstructive sleep apnea.

The diagnosis of REM sleep behavior disorder is suggested if bizarre violent dream-enacting behavior occurs 90 minutes or more after sleep onset. A class I in-laboratory polysomnogram is required for diagnostic purposes. Additional EMG electrodes on the arms (wrist extensors) and legs (quadriceps femoris and anterior tibialis muscles) and time-locked video-polysomnography with expanded EEG recording techniques help make the diagnosis by capturing events and demonstrating REM sleep without atonia. A sudden increase in chin EMG activity or prominent muscle twitches with rapid eye movements are often observed with the onset of REM sleep in this disorder. Excessive amounts of sustained or intermittent loss of REM atonia and/or excessive phasic muscle twitch activity in the submental and/or limb EMG channels are seen during REM sleep. Some patients display only arm and hand behaviors, making it crucial to place additional EMG electrodes on the wrist extensors. Behaviors captured on video-polysomnography emerging from REM sleep consist of excessive limb and/or body jerking, complex vigorous and/or violent body movements, and vocalizations. If REM sleep behavior disorder patients are awakened from an episode, they promptly become alert and usually recall dream imagery correlating directly with the observed motor behaviors and vocalizations.

Chin- and limb-EMG movements during REM sleep in this disorder exhibit great variability. At times, chin EMG is increased while the limbs are atonic, or vice versa. Increases in muscle tone and movements can be lateralized to only one limb, or shift back and forth. Some have reported violent behaviors not accompanied by tachycardia, prompting speculation that this represents paresis of the sympathetic nervous system (inactivation of locus coeruleus) during REM sleep (67).

Polysomnographic abnormalities are not confined to REM sleep in this disorder. Indeed, periodic limb movements during NREM sleep occur in 75% of REM sleep behavior disorder patients. Some studies suggest that these patients have increased percentages of slow-wave sleep and increased amounts of delta slow-wave activity ("delta power"). Sleep architecture, the appropriate cycling between periods of NREM and REM sleep across the night, is preserved in these patients although some have more stage 1 sleep.

Diagnosing Sleep-Related Epilepsy with Video-Polysomnography

Approximately 20% of epilepsy patients have seizures exclusively during sleep. Sleep-related epilepsy should be considered when nocturnal paroxysmal

motor behaviors are frequent, brief, stereotyped, and associated with dystonic posturing, hypermotor movements, or automatisms. In addition, sleep-related epilepsy can emerge anytime across the sleep period or upon awakening and may or may not respond to a trial of benzodiazepines. The AASM Standards of Practice Indications for Polysomnography guidelines recommends the use of video-polysomnography with extended EEG montages to diagnose nocturnal behaviors or movements thought to represent sleep-related epileptic seizures when the clinical history and prior routine sleep-deprived EEGs have been inconclusive (68,69). This recording technique is also employed when evaluating patients with atypical or injurious parasomnias.

The American Clinical Neurophysiology Society guidelines (70) recommended at least six channels of EEG when recording polysomnography in patients with suspected seizures. They specify montages to be designed using FP1, FP2 (or other frontal placements), C3, C4, O1, O2, T3 (now T7), and T4 (now T8) electrodes. Foldvary et al. (71) found that the likelihood of correctly recognizing a temporal lobe seizure progressively increased as more EEG channels were used, but not necessarily for seizures arising from the frontal lobes. Sleep-related epileptic seizures are most likely to be identified if all 21 EEG electrodes are placed using the International 10/20 system (72,73). Figure 11 demonstrates the advantage of using 21 electrodes to identify an electrographic seizure emanating from the frontal lobe during NREM sleep.

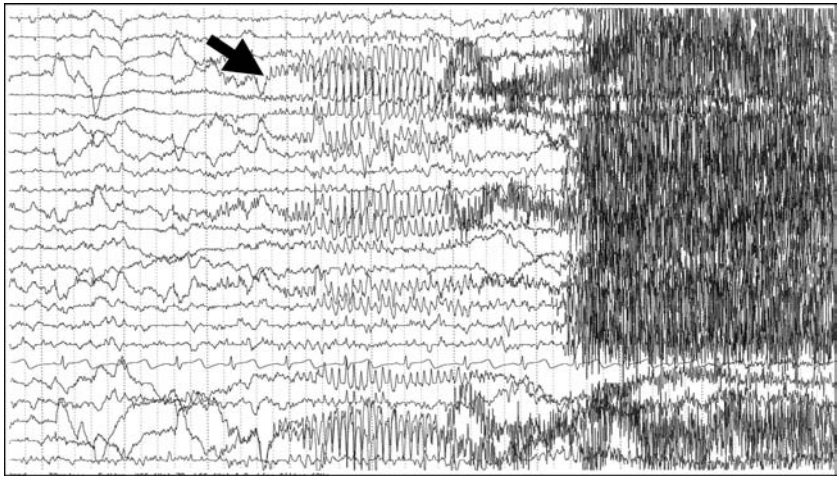


Figure 11 An electrographic seizure is best identified when recorded at a paper speed of 30 mm/sec with expanded electroencephalographic montages (seizure onset indicated by the arrow).

Unfortunately, limited numbers of polysomnography channels are available for EEG, forcing clinicians to design "expanded EEG" (really "limited") montages that place additional electrodes over scalp areas suspected as the source of a patient's seizures. For example, frontal and midline electrodes such as FP1, FP2, F3, F4, FZ, and CZ with an occipital electrode as reference are added when evaluating patients with suspected nocturnal frontal lobe seizures. Good-quality video recordings using infrared cameras with zoom capabilities are essential. Multiple spells must be recorded, especially when seizures are frontal lobe in origin. Frontal lobe seizures are often brief, lasting less than a minute, and the EEG during the seizure is commonly obscured by artifact. Approximately 20% of nocturnal frontal lobe seizures have no scalp ictal EEG correlate. In these cases, the diagnosis is made by noting the stereotypic nature of repeated attacks.

The diagnosis is confirmed by capturing five or more typical "spells" with stereotypical semiology. A typical approach is to obtain a single night of video-polysomnography with extended EEG montages to rule out non-epileptic sleep disorders, followed by 1–3 days of continuous video-EEG epilepsy monitoring with the patient hospitalized (off all medications) on the inpatient neurology service to capture a sufficient number of spells. One study found that video-polysomnography with extended EEG montages established the correct diagnosis in 35% of subjects, supported the suspected diagnosis in another 30%, and was inconclusive in 34% of 122 patients with atypical parasomnias (74). Most of these patients had sleep-related epilepsy or night terrors.

Video-polysomnography with extended EEG montages can identify epileptic parasomnias, which are often misdiagnosed and mistreated. Disadvantages of this method include the time required to attach additional electrodes as well as the expense and size of the computer files. Ultimately, most patients with sleep-related epileptic seizures require prolonged inpatient video-EEG epilepsy monitoring, especially if they have only 1–2 "spells" during a single night of video-polysomnography with extended EEG montages, even when 21 electrodes are employed.

Portable (Home) Sleep Studies

Portable sleep studies are attractive, as they have the potential to increase screening for obstructive sleep apnea. However, screening home sleep studies (Table 2) are of minimal use in the United States, as they provide limited amounts of data regarding breathing during sleep. Therefore, these studies should only be used to confirm a diagnosis of moderate to severe obstructive sleep apnea. Furthermore, Medicare, Medicaid, and many health insurance providers only reimburse for in-laboratory or in-hospital sleep studies.

When evaluating portable monitoring, the clinician must understand the signals being recorded and the data provided. If the home sleep study is negative, yet clinical suspicion of a sleep disorder remains, in-laboratory polysomnography should be done.

Level II Full Unattended Polysomnography

A level II sleep study, as opposed to level I, is not attended by a technologist. These studies require a minimum of seven channels, compared to four channels for a level III study, and 1–2 channels for level IV studies. Level I and II studies correlate well when performed in the sleep laboratory simultaneously (75–77). Portier et al. (78) compared level II polysomnography done at home to level I attended in-laboratory polysomnography. They found that the apnea–hypopnea index differed by more than 10 events per hour of sleep among 35% of the study subjects. If the apnea–hypopnea index from the level II home study was used to diagnose the presence or absence of obstructive sleep apnea (e.g., apnea–hypopnea index >15/hr), 10% of patients would have been misclassified as either normal or abnormal. Gagnadoux et al. (79) compared a level II study recorded at home to a level II study performed in the sleep laboratory with a ward nurse viewing telemonitored data. Twenty-three percent of the home studies needed repeating due to technical uninterpretability, compared with only 11% of the laboratory-based studies. Apnea–hypopnea index differences of >10/hr were observed in 43% of studies. Using an apnea–hypopnea index cutoff of >10/hr resulted in misclassification of obstructive sleep apnea as normal or abnormal 11% of the time. Discordant studies were most likely in patients with mild obstructive sleep apnea (apnea–hypopnea index 10–20 per hour of sleep). The Sleep Heart Health Study used level II devices recorded at home. They found the respiratory event data technically acceptable in 91% of their initial home studies, as opposed to only 75% of the sleep staging or arousal data (80). Potential advantages of level II studies include reduced expense by avoiding technologist, in-laboratory, or in-hospital costs; less "first night effects"; and greater availability. However, level II studies are not always feasible. Indeed, two studies found that 26–34% of patients were excluded from home testing because of transportation issues, inconvenience, or inability to handle the equipment (77,78).

Currently, there is little to gain from doing level II studies. Most third-party medical insurance providers will not pay for a level II study unless it is done in a sleep laboratory or hospital. In addition, the study still requires labor-intensive scoring. The AASM Standards of Practice Committee recently published practice parameters for using portable sleep studies. They could not recommend type II studies for use in either attended or unattended settings. When such a level of diagnostic polysomnography is needed, it should be done in-laboratory as a level I polysomnogram.

Level III Cardiorespiratory Home Sleep Studies

Level III sleep studies are used to screen for obstructive sleep apnea. These studies require a minimum of four channels, including respiratory movement, airflow, oxygen saturation, and heart rate or EKG. Level III studies do not provide information regarding sleep because they do not record EEG, EOG, or chin EMG. The apnea–hypopnea index is reported as events per hour in bed, not events per hour of sleep. If a patient lies awake much of the night, the apnea–hypopnea index may be falsely low, diluted by the wake time. Few studies have been published regarding the reliability of level III cardiorespiratory sleep studies recorded at home. One study used a level III device measuring airflow, chest wall impedance, oximetry, heart rate, snore, and body position recorded at home. They found 89% agreement between this and a level I in-laboratory study (81). They estimated that using level III devices to identify obstructive sleep apnea would reduce costs by 66%. Another study (82) found that 18% of home level III studies were technically inadequate when using a device, which records nasal pressure, chest/abdominal wall motion, body position, and oximetry. Thirty percent of patients had indeterminate tests; 83% of these were found to have an apnea–hypopnea index >15 on a level I study. They suggested that screening level III studies would reduce costs by 42%. Another study reported that 89% of level III home studies demonstrated good agreement with level I studies when recording airflow, heart rate, body position, and oximetry with actigraphy added as a surrogate measure of sleep (83). The authors suggested that the addition of actigraphy modestly improved their study device's correlation with the in-laboratory polysomnography apnea–hypopnea index.

Boyer and Kapur (84) assessed level III devices and studies. They found that although level III studies improve cost and time to diagnosis compared with a level I study, unusable data loss is a significant problem (7–33% of home studies). In general, level III studies cost half as much as a level I study. Reuven et al. (85) compared cost and value of level I and III studies using decision analysis models, which include costs related to missed diagnoses and the need for repeated studies. They found that in-laboratory level I polysomnography was more cost effective. Chervin et al. (86) found that in-laboratory polysomnography provided a more favorable cost-utility measured by quality-adjusted life-years gained when compared with home testing or empirical therapy of obstructive sleep apnea. The AASM Standards of Practice guidelines recently recommended that attended type III studies were acceptable to rule in apnea–hypopnea indices >15/hr and rule out obstructive sleep apnea (apnea–hypopnea index <15). Unattended type III studies were not recommended to either rule in (apnea–hypopnea index >15) or rule out obstructive sleep apnea (apnea–hypopnea index <15).

Level IV Polysomnography and Pulse Oximetry

Level IV studies record 1–2 channels of cardiorespiratory data. A myriad of level IV devices are commercially available to screen for obstructive sleep apnea. Most record oxygen saturation either alone or in combination with a thermistor, nasal pressure transducer, or snoring microphone. The most commonly used level IV device is a pulse oximeter that records overnight oxygen saturation and heart rate data at home. Oximetry has poor sensitivity and specificity for diagnosing or confirming obstructive sleep apnea.

The classic obstructive sleep apnea oximetry pattern reveals repetitive drops of 2–4% or greater in oxygen saturation, usually lasting less than 60 seconds, followed by recovery to 90% or greater of baseline. Some patients flatten their baseline saturation to $<90\%$ during supine REM sleep. Sensor problems may also cause this phenomenon. Oximetry identifies most patients with moderate to severe sleep apnea, but often records false-negatives in patients with milder disease or upper-airway resistance syndrome whose respiratory events cause little or no oxygen desaturation. Brouillette et al. (87) found that abnormal overnight oximetry in 349 children with suspected obstructive sleep apnea had a positive predictive value of 97%, although the negative predictive value was only 47%. Therefore, oximetry can identify sleep apnea if results are positive but cannot exclude the disease if results are negative. Kirk and colleagues (88) found that home oximetry performed in children had both a low sensitivity (67%) and specificity (60%) for identifying an apnea–hypopnea index >5. Abnormal oximetry results are not specific for sleep apnea, and are often seen in patients with lung disease. Clinicians should understand that modern pulse oximeters have $\pm 2\%$ accuracy between oxygen saturation values of 70–99% and $\pm 3\%$ between 50% and 69%, but many suggest that 80% is the lowest reliable value (89).

Pulse oximeters can provide inaccurate readings for a number of reasons. Oximetry signal is susceptible to body movements, contact with skin, and regional circulation. Movement artifact and poor perfusion in hypovolemic, hypotensive, or cold patients can impair readings.

Inappropriately long sampling rates and inadequate light transmission detection because of tissue edema, dark skin color, thick skin, or improper probe placement and excessive ambient room light can interfere with oximeter accuracy. Venous pulsations can be misinterpreted as arterial in origin and artificially increased oxygen saturation values can be seen in heavy tobacco smokers whose carboxyhemoglobin levels are $>10\%$ hemoglobin. One in-laboratory study found that the pulse oximetry probe signal was inaccurate or malfunctioned in 10% of patients even when a technologist intervened to avoid poor signals (90). The AASM Standards of Practice guidelines advise that level IV studies are not recommended to rule in, rule out, or confirm the diagnosis of sleep apnea.

Autotitrating CPAP

Continuous positive airway pressure is the primary therapy for most sleep-disordered breathing. The optimal CPAP pressure needed to prevent apneas, hypopneas, RERAs, and snoring in all sleep stages and body positions is almost always identified by titrating CPAP during an attended in-laboratory polysomnogram. Higher CPAP pressures are often needed when sleeping supine and during REM sleep (91). Most CPAP devices provide a fixed level of pressure. The sleep specialist reviews the CPAP titration and recommends the minimal pressure, which eliminated all or nearly all respiratory events. CPAP users who awaken tired or feel this pressure is "too high" or "too low" are good candidates for an autotitrating-CPAP (auto-CPAP) study.

Autotitrating-CPAP machines adjust the moment-to-moment CPAP pressure by sensing the degree of pressure needed to prevent upper-airway collapse. These devices "sense" the optimal CPAP pressure by identifying "flow limitation" or by analyzing snoring acoustics. An "auto-CPAP study" involves a patient wearing one of these devices for a few days. The machine contains a computer program, which can summarize length of use and pressures required. This information is used to confirm the patient's habitual sleep duration and further hone the pressure requirement previously established during a laboratory-based CPAP titration. Some patients who cannot tolerate traditional CPAP prefer to use auto-CPAP long term.

Auto-CPAP has a number of advantages. These machines provide lower mean CPAP pressures over the course of a night, delivering higher pressures when the patient needs it most, such as during REM sleep or when sleeping supine. For example, a fixed CPAP pressure of 12 cm H_2O may be needed only during REM sleep supine, whereas 8 cm is sufficient the rest of night. Auto-CPAP can presumably make these adjustments on the fly. As a result, these devices deliver mean CPAP pressures 37% lower than fixed CPAP machines (92). An auto-CPAP home titration study may provide sufficient information to avoid a second in-laboratory polysomnogram to retitrate CPAP when pressures are considered inadequate. These devices can be used for days or weeks to confirm patient compliance with recommended bedtimes and CPAP use.

As of now, there is insufficient medical evidence whether auto-CPAP is as effective (or more effective) as CPAP for treating obstructive sleep apnea. The AASM Standards of Practice Committee stated in its 2002 review that auto-CPAP reduced the apnea–hypopnea index to acceptable levels (< 10/hr) in greater than 80–95% of patients studied. The Committee could not provide stronger recommendations for auto-CPAP because systematic studies comparing it with traditional CPAP and placebo have not been done.

Certain caveats should be mentioned when interpreting "auto-CPAP study." Devices that adjust their pressure based solely on acoustic vibrations (snores) may not "sense" in patients who do not snore or who have undergone

upper-airway surgery for sleep apnea (93). Many different devices and technologies are available and systematic comparisons have not been published. Therefore, different devices may not provide the same results in a given patient.

Advantages and Disadvantages of Portable Sleep Studies

Advantages of portable sleep studies include their low cost and increased availability. In addition, these studies are performed in the natural home environment, avoiding first night effects. Because they only record cardiorespiratory data, it takes fewer resources to score and interpret the data. Disadvantages include inconclusive studies due to inaccurate data or data loss, the inability to initiate a trial of CPAP in the second half of study if indicated, and the inability to identify other sleep disorders, which may cause symptoms (e.g., restless legs syndrome, periodic limb movement disorder, and narcolepsy–cataplexy). Furthermore, portable studies cannot assess the impact of sleep-disordered breathing on sleep efficiency and sleep architecture.

Level II and III home studies inaccurately diagnose 10% of patients as compared to level I studies, a major disadvantage of these studies (94). Research is needed to determine the cause of this discrepancy. Possible explanations include normal night-to-night variability, first night effects, and/or technical differences in the devices. Although proponents of portable monitoring argue that home sleep studies are cheaper, more research is needed to compare outcomes including costs, quality of life, morbidity, mortality, and response to treatment when obstructive sleep apnea is diagnosed using portable devices versus level I polysomnography (with or without split-night protocols).

DIAGNOSTIC SLEEP MEDICINE TESTS THAT MEASURE SLEEPINESS

Excessive daytime sleepiness poses risks not only to the patient but also to society due to safety concerns. Many patients are unaware of their sleepiness, complaining only of tiredness, fatigue, apathy, or low energy (95). Some patients with severe sleepiness deny their symptoms, making witness accounts necessary for an accurate history (94). Sleep specialists routinely use subjective tools in assessing patients' sleepiness. The two most commonly used subjective methods for assessing sleepiness in adults are the Stanford Sleepiness Scale and the Epworth Sleepiness Scale, shown in Table 8.

The Stanford Sleepiness Scale (97) asks patients to rate their degree of sleepiness at a single moment in time using a range of scores from 1 to 7. A score of 1 represents "feeling active and vital, alert, wide awake." Increasing values indicate decreased alertness with 7 equating to "nearly asleep." Patients are often asked to complete this scale just before each nap opportunity during

Table 8 Subjective Measures of Excessive Daytime Sleepiness

I. Epworth Sleepiness Scale

How likely are you to doze off or fall asleep in the following situations, in contrast to just feeling tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently, try to work out how they would have affected you. Use the following scale to choose *the most appropriate number* for each situation:

0 = would never doze
1 = slight chance of dozing
2 = moderate chance of dozing
3 = high chance of dozing

Situation	Chance of dozing
Sitting and reading	_____
Watching television	_____
Sitting, inactive in a public place (e.g., theater or meeting)	_____
As a passenger in a car for an hour without a break	_____
Lying down to rest in the afternoon when circumstances permit	_____
Sitting and talking to someone	_____
Sitting quietly after lunch without alcohol	_____
In a car, while stopped for a few minutes in traffic	_____

Source: From Ref. 96.

II. Stanford Sleepiness Scale

Circle one number which best describes your level of alertness or sleepiness right now.

Scale	Characteristics
1	Feeling active and vital; wide awake
2	Functioning at a high level, but not at peak; able to concentrate
3	Relaxed; awake; not a full alertness; responsive
4	A little foggy, not at peak; let down
5	Fogginess; beginning to lose interest in remaining awake; slowed down
6	Sleepiness; prefer to be lying down; fighting sleep; woozy
7	Almost in reverie; sleep onset soon; lost struggle to remain awake
8	Asleep

Source: From Ref. 97.

a multiple sleep latency test or maintenance of wakefulness test (MWT). This scale is fast and easy to use, although reference values do not exist and it has not been validated with other physiological measures.

The Epworth Sleepiness Scale provides a subjective measure of how sleepiness interferes with an individual's common daily activities (96). It consists of a simple self-administered questionnaire, which asks a patient to rate the likelihood of dozing or falling asleep in eight sedentary situations. For each situation, patients estimate their propensity to sleep on a four-point scale (0 = never doze to 3 = high probability). Situations range from lying quietly in the afternoon when circumstances permit to sitting, talking with someone. Scores from each of the eight situations yield a total score ranging from 0 to 24. Johns (98), who designed the scale, used healthy medical students (hopefully not sleep deprived) to establish a normal value of 7.6. He considered a score from 0 to 10 within normal limits, while a score of 10 represented the upper limit of normal alertness and scores greater than 12 represented pathological sleepiness (96). The higher the score, the greater the sleepiness. An Epworth Sleepiness Scale score of >15 suggests marked sleepiness. Most patients with narcolepsy–cataplexy score in this range.

How reliable is this scale? Many people are unaware of the extent of their sleepiness because their sleep disorders are chronic and insidious. Others have difficulty distinguishing sleepiness from fatigue. Some claim a need to sleep, but have difficulty given the opportunity. An individual who is well-rested and well-slept should be able to remain awake throughout the day, saving a natural mid-afternoon dip in alertness. At best, a weak correlation is observed between the Epworth Sleepiness Scale and mean sleep latencies on the multiple sleep latency test (99). Johns (98) studied how well the Epworth correlated with both the multiple sleep latency test and treatment responses among patients with obstructive sleep apnea. He found that Epworth scores dropped with treatment and observed a weak correlation between sleep latency and these scores. In a later study, he found that a number of questions on the scale did not correlate with the sleep latency (98). Of note, the Epworth Sleepiness Scale has not been validated for other diagnoses or for use in children.

Objective tests to confirm excessive daytime sleepiness include polysomnography, the multiple sleep latency test, and the maintenance of wakefulness test. When a diagnosis of narcolepsy–cataplexy is considered, a class I polysomnogram is necessary to identify other sleep disorders causing or contributing to the sleepiness. Indeed, sleep disorders such as obstructive sleep apnea, periodic limb movement disorder, and REM sleep behavior disorder occur more frequently in patients with narcolepsy–cataplexy than in the general population (100). A multiple sleep latency test assesses the patient's ability to fall asleep during the day when permitted. A maintenance of wakefulness test evaluates a patient's ability to stay awake during the day without extraordinary measures. A polysomnogram in patients with

narcolepsy often shows rapid sleep onset, a short REM latency ($\leq$15 minutes after sleep onset), increased number of arousals in stage 1 and 2 sleep, and periodic limb movements in NREM and REM sleep.

Multiple Sleep Latency Test

The multiple sleep latency test is a widely accepted objective polygraphic test for confirming pathologic daytime sleepiness and the inappropriate early appearance of REM sleep after sleep onset (19). This test measures the underlying physiological tendency for an individual to fall asleep in the absence of alerting factors (101), based on the postulate that the time required to fall asleep in settings conducive to sleep is the best indicator of internal sleep drive (102). Guidelines for performing the test were first published in 1986 by Carskadon et al. (19).

General Description of the Multiple Sleep Latency Test

Patients are allowed four or five opportunities to nap at 2-hour intervals across their usual "day" beginning 1.5–3 hours after awakening. During each nap opportunity, patients have 20 minutes to "try and fall asleep." If sleep occurs in a given nap opportunity, patients are allowed 15 minutes of sleep to observe whether REM sleep appears inappropriately after sleep onset. The appearance of REM sleep within 15 minutes after sleep onset is called a "sleep-onset REM period" (SOREMP). Sleep onset is scored after observing one 30-second epoch of any stage of sleep and sleep latency is the time in minutes from lights out until this epoch. REM sleep in adults normally first appears 90 minutes after sleep onset (range 70–110 minutes). Normal individuals may have a single SOREMP in the morning, but two or more are abnormal except in infants. REM sleep latency is the time in minutes from the beginning of sleep onset during a given nap to the beginning of the first epoch of REM sleep. The mean sleep latency is calculated as the arithmetic mean of all four or five nap opportunities. A non-sleeping nap is counted as a 20-minute sleep latency. If the multiple sleep latency test is for diagnosing narcolepsy, a fifth nap is required if only one SOREMP occurs in the first four naps. A fifth nap is not necessary if the mean sleep latency is $<$5 minutes and $\geq$2 SOREMPs are observed among the first four naps.

Proper performance of the multiple sleep latency test requires meticulous attention to detail and close adherence to the standardized protocol. Deviations can invalidate test results. No patient should be scheduled until first undergoing a thorough sleep medicine consult and examination followed by careful planning of how to achieve valid results. The patient should be weaned off stimulants and other drugs that alter sleep architecture and REM latencies for at least 15 days (or at least five times the half-life of the drug and longer-acting metabolite). Occasionally, it is neither practical nor feasible to stop a patient's medication(s) prior to the test. In this

instance, the clinician must consider the impact of these medications on the results when interpreting the test.

The patient's sleep/wake schedule must be standardized and "adequate" for at least seven days prior to a sleep latency test. For confirmation, the patient should provide a sleep diary of his or her sleep/wake patterns for 1–2 weeks before the test. The test should be done the day following a nocturnal level I polysomnogram to confirm that the patient slept a sufficient sleep during the nocturnal polysomnnogram (<6 hours). A urine drug screen is requested on the day of the test to confirm the absence of stimulant(s). The multiple sleep latency test must be done during a patient's customary wake times, particularly challenging for shift workers who have irregular sleep/wake schedules.

A patient undergoing a multiple sleep latency test should: (i) eat all meals at least 1 hour before a scheduled nap opportunity; (ii) stay out of bed to avoid napping between naps; (iii) be observed between naps to ensure that no in-between napping occurs; (iv) be dressed in street clothes; and (v) avoid caffeine, alcohol, and alertness-altering medications the day of the study. The study bedroom should be dark, quiet, and temperature-controlled. Patients can loosen their clothes if desired. Before each nap opportunity, the same standard protocol should be followed. The patient should cease all tobacco use 30 minutes prior to test onset. Physical activity should be stopped 15 minutes prior to the test and preparation for bed should occur 10 minutes before test onset. Five minutes before each nap, the technologist should reconnect the patient's electrodes and perform calibrations to ensure that the electrodes are functioning properly. Five seconds before each nap the technologist should give the patient these instructions: "Relax and let yourself fall asleep. I will inform you when the nap is over."

The patient is discharged home following test completion. The technologist scores the test staging each epoch from lights out to lights on during each nap. Sleep onset is identified and the mean sleep latency is calculated. The number of SOREMPs is noted. The sleep specialist reviews the level I polysomnogram performed the night before the test as well as the 1–2-week sleep diary and the urine drug screen before interpreting the multiple sleep latency test.

Indications for the Multiple Sleep Latency Test

The multiple sleep latency test should be performed to address specific clinical questions and should not be considered a "screening tool." The test is most often ordered as part of the diagnostic evaluation of potential narcolepsy or idiopathic hypersomnia patients. Occasionally, the test is performed to confirm persistent sleepiness despite optimal treatment of obstructive sleep apnea. Some of these patients will have both sleep apnea and narcolepsy. Indeed, patients with narcolepsy have a higher incidence of obstructive sleep apnea (103).

Repeat testing is indicated in a few specific instances. The clinician may feel that the initial test did not represent the true ability of a patient to fall asleep. Causes include unplanned environmental noise and failure to follow the standardized testing protocol. Sometimes, clinicians repeat the test if the initial result was negative and the clinical suspicion of narcolepsy or idiopathic hypersomnia is high. On the other hand, repeat testing may be performed to rule out narcolepsy after eliminating confounders causing a false positive in the initial study such as insufficient sleep, irregular sleep/wake habits, and/or sedating drugs.

The multiple sleep latency test is not a good measure of treatment response in patients with confirmed narcolepsy with cataplexy or idiopathic hypersomnia. Short sleep latencies and SOREMPs can occur in patients who feel their narcolepsy is well controlled with medication. The maintenance of wakefulness test is a better measure of continuing sleepiness despite optimal treatment. The multiple sleep latency test is not routinely indicated for evaluation of sleepiness in patients with insomnia, depression, circadian rhythm disorders, or sleepiness in association with medical or neurological disorders.

Interpretation of the Multiple Sleep Latency Test

Latency to sleep onset is usually scored as the time from lights out until the first 30-second epoch of any sleep stage. If the majority of a 30-second epoch is wake, the epoch is scored as wake. Stage 1 sleep is scored if the majority (>50%) of the 30-second epoch meets criteria. A brief return of alpha activity lasting less than 50% of the epoch does not preclude scoring the epoch as stage 1 sleep. The first multiple sleep latency tests published by Richardson et al. (104) in 1978 used three consecutive epochs of stage 1 sleep or one epoch of stages 2–4 or REM sleep to define sleep onset. They found that patients with narcolepsy ($n = 49$) had mean sleep latencies of 2.9 ± 2.7 minutes in five naps. Sleepy patients without narcolepsy or apnea ($n = 63$) had mean sleep latencies of 8.7 ± 4.9 minutes and control subjects ($n = 13$) had latencies of 13.4 ± 4.3 minutes. Among the narcolepsy patients, 96% had two or more SOREMPs, 2% had only one, and 2% only two. Among the idiopathic hypersomnia subjects, 92% had no SOREMPS and 8% had one. None of their controls had SOREMPs.

Most sleep laboratories use the guidelines published by Carskadon et al. (19) to define sleep onset as a single epoch of any stage of sleep. Benbadis et al. (105) compared how definitions of sleep onset changed mean sleep latency values among a group of patients with narcolepsy. They found a mean sleep latency of 6.2 minutes when sleep onset was defined as one epoch of stage 1 and 7.5 minutes when sleep onset was defined as three epochs of stage 1. Thus, using the one-epoch criterion changed sleepiness severity from normal to moderate in 16% of patients.

Normal adult controls usually have mean sleep latencies between 10 and 20 minutes. A mean sleep latency score of less than 5 minutes confirms pathological daytime sleepiness (104). Mean sleep latency scores between 5 and 10 minutes are indeterminate or within a "diagnostic gray area." Roth et al. (106) suggest that if a single cutoff point is needed, 8 minutes is most rational with a mean sleep latency of <8 minutes abnormal and >8 minutes normal. A recent meta-analysis showed that the mean sleep latency in narcolepsy patients was 3.1 ± 2.9 minutes. Most patients with narcolepsy–cataplexy have mean sleep latencies below five minutes and two or more SOREMPs. Less normative data and studies are available regarding the multiple sleep latency test in children. In general, the mean sleep latency averages 15–20 minutes in prepubertal children, 10 minutes in young adults, 11–12 minutes in middle-aged adults, and 9 minutes after age 70 (107,108).

Mean sleep latencies are influenced by the prior night's sleep. Investigators have shown that one night of total sleep deprivation results in mean sleep latencies of less than five minutes and 2 nights of total sleep deprivation reduce the sleep latency to less than one minute (102). Significant effects on mean sleep latency do not usually occur unless the patient sleeps less than 4 to 5 hours the night before the test (109). The final multiple sleep latency test interpretation must account for deviations from the standard protocol, findings from nocturnal polysomnography, medications, and relevant medical or psychosocial factors. Mean sleep latencies are affected by age, sleep continuity, amount of sleep on preceding nights, time of day, and drug usage. Drugs such as sedative-hypnotics, antihistamines, and stimulants may alter the mean sleep latency. Other medications such as tricyclic antidepressants, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, and stimulants suppress REM sleep, delay REM sleep latency, and block the appearance of SOREMPs. Other factors affecting SOREMPs include sleep deprivation, time of day, and body position (110). Any SOREMP appearance requires clinical correlation. REM sleep on a multiple sleep latency test most often occurs during morning naps, probably related to the circadian propensity for the occurrence of REM (Chap. 9). Two SOREMPs usually indicate narcolepsy–cataplexy but can be observed in association with sleep apnea, drug withdrawal, severe depression, and myotonic dystrophy (Chap. 7) (110).

Strengths and Limitations of the Multiple Sleep Latency Test

Repeated clinical studies demonstrate that the multiple sleep latency test is a valid and accurate measure of sleepiness with a high test–retest reliability in both normal healthy subjects (111) and patients with narcolepsy–cataplexy (112). The test is most reliable when analysis is coupled with a thoughtful and thorough clinical evaluation (112–114). The test has excellent interreader reliability (115,116). Despite these advantages, the multiple sleep latency test has several limitations. Precise normative ranges for mean sleep

latencies are not well defined. Whether a single "pathological cutoff" should be used for all patient groups or the data should be reported as 1, 1.5, or 2 standard deviations below the mean has not been determined. Limited normative data are available for mean sleep latencies in children, college students, and the elderly. Moreover, since many adults and children suffer from chronic partial sleep deprivation, it is unclear whether or not normative data should include partially sleep-deprived subjects.

A multiple sleep latency test can provide invalid false-negative results. This is the case if the long sleep latency was due to performance anxiety, pain, fear, worry, environmental noise, hypervigilance to minor stimuli, covert use of stimulants, medication effects, poor sleep the preceding night during polysomnography, and/or a strong desire to stay awake. A patient's desire to finish the test and go home can cause a "last nap effect," lengthening the sleep latency for the final nap of the day (117). Motivation can compromise the results of the test. Indeed, changing the instructions to patients from "try to go to sleep" to "try to remain awake" increased mean sleep latencies by 300%. Patients with narcolepsy–cataplexy, especially children and those early in the course of the disease, can have false-negative tests. The mean sleep latency in children with narcolepsy may be 7–10 minutes (rather than five minutes for adults) and some children do not have the two or more SOREMPs often observed in adults with narcolepsy–cataplexy.

A false-positive test can also occur. Common causes of short sleep latencies include effects from sedative medications, sleep curtailment, and poor sleep prior to testing. Some individuals can fall asleep anytime, even when showing no other signs or complaints of sleepiness. Harrison and Horne (118) characterized these "star sleepers" as blessed with "high sleep ability without sleepiness." Lastly, although good inter-reader reliability is reported for the multiple sleep latency test, false-positive and false-negative results can occur especially when interpreting an epoch containing ambiguous REM sleep.

Maintenance of Wakefulness Test

The maintenance of wakefulness test examines a patient's ability to stay awake without resorting to extraordinary measures during low levels of stimulation. Mitler et al. (119) designed this test to quantitate the effectiveness of sleepiness therapies and confirm a patient's ability to stay awake when safety is an issue.

Maintenance of Wakefulness Testing Procedures

Maintenance of wakefulness testing protocols are far less standardized than those for the multiple sleep latency test. Normative data are limited and protocols vary widely among laboratories making test interpretation difficult. Testing conditions are similar to those of the multiple sleep latency test,

except that the patient sits in a recliner and is instructed to ''try and remain awake'' (not ''try to fall asleep''). Nap trials typically last 20–40 minutes. Many laboratories utilize the 40-minute protocol published in 1997 by Doghramji et al. (120) (called the MWT40 protocol). This protocol consists of four opportunities to resist falling asleep at 2-hour intervals across a patient's usual ''day.'' It should follow a nocturnal level I polysomnogram. During each test trial, the patient sits in street clothes in a dimly lit room and is given the same instruction: ''Please sit still and remain awake for as long as possible. Look directly ahead of you, and do not look directly at the light.'' The patient is not allowed to use extraordinary measures to stay awake such as slapping the face or singing.

Indications for the Maintenance of Wakefulness Test

The maintenance of wakefulness test is usually performed to assess the ability of a previously sleepy patient to stay awake following treatment of their sleep-inducing condition. Testing protocols are sometimes requested to confirm if a sleepy person is capable of remaining awake to operate a vehicle or work a certain job, particularly when their occupation involves public transportation or issues regarding public (and patient) safety. Occasionally, tests are performed on patients with narcolepsy–cataplexy, monosymptomatic narcolepsy, or idiopathic hypersomnia who are on stimulant or stimulant-like medications to assess response to treatment. This occurs most often within the context of a drug study protocol.

Interpreting the Maintenance of Wakefulness Test

Normative data for the maintenance of wakefulness test are limited and currently no clear ''normal'' standards exist. Doghramji et al. (120) reported a mean sleep latency of 35.2 ± 7.9 minutes using their MWT40 protocol in normal control subjects. Sleep onset was defined as three continuous epochs of stage 1 sleep or one epoch of any other stage of sleep. When sleep onset was defined by the first epoch of any stage of sleep, the mean sleep latency dropped to 32.6 ± 9.9 minutes. They suggested the lower limits of normal to be 12.9 minutes (± 2 standard deviations) with 9% of their control subjects falling below this lower cut-off limit.

Abnormal values for this test can be gleamed from studies of patients with known hypersomnias. One such study (121) using a 20-minute protocol revealed that only 1.5% of 530 narcolepsy patients were able to remain awake during all four trials, compared to 55% of controls (tested in another study). The mean sleep latency among patients with narcolepsy was 6.0 ± 4.8 minutes. Of note, 15% of narcolepsy subjects were under the 12-minute lower limit of normal (corresponding to the fifth percentile for normals). Patients with narcolepsy were only able to stay awake for an average of six minutes, compared to 19 minutes in normal controls (119).

Patients with narcolepsy and cataplexy were least able to remain awake. Poceta et al. (122) studied how mean sleep latencies lengthened following treatment of obstructive sleep apnea. They found that treating these patients with CPAP increased the MWT40 mean sleep latency from 18.0 ± 12.3 minutes to 31.9 ± 10.4 minutes.

Strengths and Weaknesses of the Maintenance of Wakefulness Test

The maintenance of wakefulness test is difficult to interpret with limited normative data and widely varying testing protocols. People undergoing the test to certify their fitness to work are often highly motivated to remain awake, compromising their test results. No data exist showing that laboratory-based maintenance of wakefulness or multiple sleep latency test results correlate with sleep/wake behavior in the "real world." Similarly, no data correlate maintenance of wakefulness test findings and risk for adverse consequences of sleepiness in daily life situations. Therefore, this test is most often used as a research tool to test efficacy of different therapies in patients with excessive daytime sleepiness. Among patients with narcolepsy, the test appears to be a more sensitive measure of clinical response to stimulant medications than the multiple sleep latency test.

SLEEP LOGS AND DIARIES

Sleep specialists often request patients to keep a 2–3-week or longer record of their sleep/wake habits, charting them on a graph (Fig. 12). These sleep logs help summarize the patient's perception of the amount and quality of their sleep. Patients (or their caretakers) are asked to record their sleep/wake habits, including bed and nap times, estimates of time to fall asleep, number and duration of awakenings and naps and whether they were intentional or not, methods for waking (spontaneous, via alarm, or by a family member), timing and doses of medications, and use of caffeine, alcohol, tobacco, and hypnotics.

Sleep logs are useful for identifying insufficient, irregular, or excessive sleep. They are also helpful for tracking sleep hygiene, insomnia, or circadian rhythm disorders, and documenting if a patient is well-slept for multiple sleep latency or maintenance of wakefulness testing. Sleep logs can provide patients (or parents) with easily readable graphic illustrations of their sleep and are useful when evaluating the effects of different treatments (123).

Sleep logs and diaries provide subjective information regarding a patient's sleep patterns. Although sleep logs have a low correlation with objective measures of sleep (123,124), they still provide a better assessment than retrospective global characterizations reported during the initial sleep consult (e.g., "I never sleep") (125). Sleep logs help patients develop a more

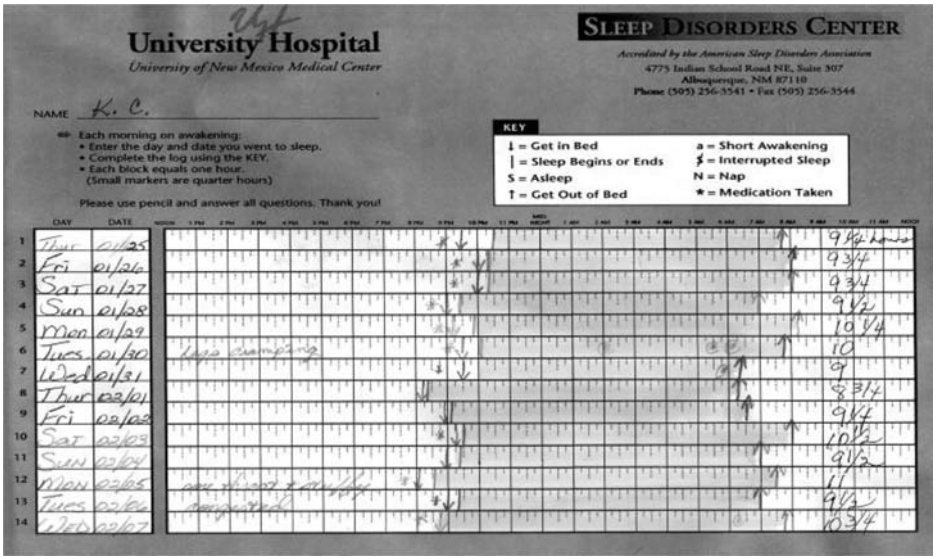


Figure 12 Example of a sleep log.

objective assessment of their sleep disturbance and give insight into factors contributing to their problems. As an educational and therapeutic tool, it helps patients understand the impact of recommended therapeutic strategies, which can improve treatment compliance. It also improves sleep/wake behavior and sleep hygiene. At least seven consecutive days of a sleep log is needed to obtain a representative profile of a patient's sleep/wake patterns (126,127). Some patterns become evident only after longer periods of time. A good sleep diary for use in children can be downloaded from the National Institutes of Health web site (128).

ACTIGRAPHY

Actigraphy is a simple and inexpensive method for studying circadian rhythms and patterns of sleep/wakefulness over extended periods of time. Actigraphy uses actigraphs, which are miniaturized computer devices resembling wristwatches capable of detecting, collecting, and storing movement data continuously for days to weeks. Periods of inactivity are assumed to represent sleep. Actigraphs are usually worn on the wrist of the nondominant hand, although the optimal device location is controversial. Two studies found no difference whether actigraphic data were collected from the dominant or nondominant wrist, ankle, or trunk. On the other hand, one study revealed greater movement detection when the actigraph was worn on a wrist compared to an ankle or trunk (129,130). Other studies revealed that wrist placement detected more movements with the dominant wrist best for detecting wakefulness (131,132).

Most actigraphs use analogue linear accelerometers to detect body movement. These data are digitized and tallied into 1-minute epochs and then stored in the internal memory. Actigraphs filter out electrical activity <0.25 Hz or >2–3 Hz since voluntary human movements are rarely >3–4 Hz and tremor or shivering is usually >5 Hz. Patients wearing actigraphs keep daily sleep logs detailing bedtimes and artifact-producing activities to reduce data misinterpretation. For example, without an accurate sleep log a patient watching television or removing the device to shower can be misidentified as sleeping. In addition, patients with insomnia lying quietly attempting to fall asleep may be misinterpreted as sleeping (133). This can result in a $\geq$2-hour discrepancy of total sleep times between polysomnography and actigraphy (124).

Actigraphs provide a reasonable representation of sleep/wake patterns when worn long enough. Acebo et al. (134) found collecting only 1–2 nights of actigraphic data in preschool children and adolescents provided unreliable sleep profiles. Five nights of data were needed to estimate sleep start time, minutes awake during the night, and sleep efficiency. Seven nights were needed to report total minutes of nighttime sleep and sleep period time from sleep onset to awakening. Total sleep time derived by actigraphy is reliable (correlation coefficient of 0.81), but since the mean number of motor movements varies widely from night to night, a minimum of at least seven continuous 24-hour periods of recording are recommended (135). For some patients, longer acquisition times are needed to appreciate trends affecting the sleep schedule, such as weekends or work schedule changes.

Actigraphy, unlike polysomnography, is not associated with first night effects. Actigraphy and polysomnography correlate well (correlation coefficient 0.97) when differentiating sleep from wake and determining the total sleep time (136), although actigraphy is less reliable at accurately identifying sleep offset or sleep efficiency (137). Indeed, sleep efficiency measured via actigraphy correlates only 65% with polysomnography derived values. The correlation between polysomnography and actigraphy to recognize sleep epoch by epoch is 85–90% among normal healthy young and middle-aged adults (138,139). This correlation falls to 80% or less among the elderly, shift workers, or patients with sleep disorders (136). Agreement between actigraphy and polysomnography to detect wake after sleep onset in healthy adults and children ranges from 70% to 79% (138,139). Actigraphy often underestimates sleep onset latency by misidentifying quiet wakefulness as sleep (140). Sleep onset latency on actigraphy is currently defined as the first minute of actigraphic-estimated sleep. Correct identification of sleep onset latency by actigraphy is improved if sleep onset is defined as the beginning of the first period containing 20 minutes of actigraphic-identified sleep with no more than one minute of intervening wakefulness (141). Actigraphy is complimentary rather than a substitute for polysomnography when studying sleep/wake patterns.

A study comparing the reliability of actigraphy and sleep logs during space flight demonstrated that actigraphy was superior at determining sleep onset and offset, as well as sleep efficiency, and sleep duration (142). Sadeh et al. found that sleep patterns in infants and kindergarten children were most reliably identified if sleep logs were combined with actigraphy (143,144). Actigraphy was more reliable because sleep logs kept by parents omitted significant details over time.

Indications for Actigraphy

Actigraphy is a convenient, cost-effective method to continuously assess sleep disorders over extended periods of time. It is a useful adjunct for diagnosing circadian rhythm disorders, insomnia, and periodic limb movement disorder. Actigraphy can also monitor the treatment response of previously confirmed sleep disorders and can supplement sleep logs to evaluate unusual complaints such as, "I have not slept for several nights."

The AASM Standards of Practice Committee recently updated the practice parameters for actigraphy in studying sleep and circadian rhythms (135). They found it a reliable and valid method for detecting sleep in healthy normal individuals who sleep quietly. They found it less reliable in patients with sleep disturbed by periodic limb movements, excessive motor movements, or respiratory events (136). For this reason, actigraphy is not indicated for the routine diagnosis of sleep disorders. In healthy normal subjects, actigraphy provides reliable data regarding sleep timing, duration, onset, and offset but not sleep latency, or the number and duration of nighttime awakenings or number of naps (145).

Actigraphy is most often used as a research tool to study sleep/wake patterns in selected study populations (e.g., infants, children, adolescents, elderly, the demented), confirming their sleep/wake habits. Specially configured actigraphs worn on each ankle have been used in patients with restless legs syndrome or periodic limb movement disorder. A validity study found that although actigraphy underestimated leg EMG activity in periodic limb movements, it still correlated well enough (correlation coefficient 0.78) with polysomnography to be useful when monitoring treatment responses in patients with restless legs syndrome and periodic limb movements (146).

Actigraphy is not indicated for routine diagnosis, assessment of severity, or management of sleep disorders. Actigraphy alone is not reliable at identifying obstructive sleep apnea (147). Despite this limitation, actigraphy is a useful tool for the clinician. It can confirm circadian rhythm disorders and reveal patient misconceptions regarding sleep timing and duration. Treatment efficacy can be objectively evaluated, particularly for restless legs syndrome and insomnia. Actigraphy is particularly helpful when evaluating the efficacy of behavioral interventions, bright light therapy, melatonin, and medications on a patient's sleep/wake patterns.

Diagnoses Facilitated by Actigraphy

As previously mentioned, actigraphy should be considered when evaluating and treating patients with insomnia or when characterizing and treating circadian rhythm disorders. Diagnosis of circadian rhythm disorders requires several steps. Sleep consultation and examination followed by a 1–2-week sleep log and actigraphy provides the best approach. Actigraphy should confirm the schedule outlined in the sleep log. Actigraphy often suggests one of the four main circadian sleep disorder patterns, which include delayed sleep phase disorder, advanced sleep phase disorder, non-24-hour sleep/wake rhythm disorder (free-running pattern), or an irregular sleep/wake rhythm disorder (Chap. 9).

Patients with a non-24-hour sleep/wake circadian rhythm disorder exhibit a chronic pattern of delayed sleep onset and wake time each 24-hour period by a fixed amount (one or a few hours), suggesting that their internal biological clock runs independently of day/night zeitgebers. The patient in Figure 13A exhibits this disorder with a daily delay of approximately one hour in sleep onset and wake times. The actigraph in Figure 13B shows sleep/wake patterns consistent with delayed sleep phase syndrome, common in adolescents and young adults. In this syndrome, the major sleep episode is delayed in relation to desired clock times, resulting in sleep-onset insomnia, difficulty awakening at a socially convenient (e.g., for work, school) time, and deprivation. Almost a mirror image of this syndrome, advanced sleep

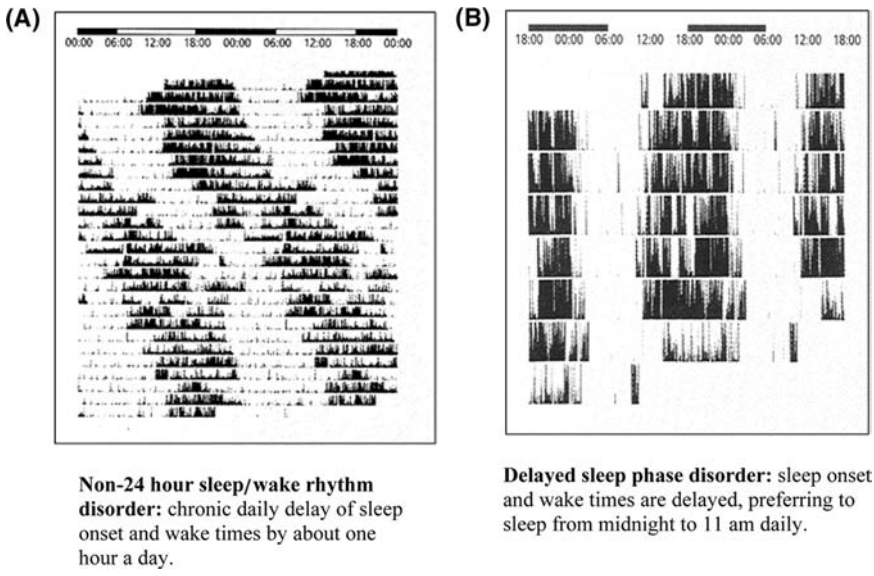


Figure 13 (**A**) and (**B**) Examples of how actigraphy is used to diagnose circadian rhythm disorders.

phase syndrome is a circadian rhythm disorder more common in older persons. In this syndrome, the major sleep episode is advanced in relation to desired clock times, causing irresistible sleepiness and sleep onset early in the evening with undesirable early morning awakenings. Lastly, some patients display irregular sleep/wake patterns without recognizable sleep onset or wake times. Patients with this circadian rhythm disorder exhibit sleep periods of varying duration that are completely disorganized.

Actigraphy is particularly useful when diagnosing sleep state misperception, a type of insomnia. This disorder is diagnosed by uncovering a discrepancy between the fragmented sleep reported on the sleep log and the consolidated sleep indicated by the actigrapher. Other insomnia patterns (e.g., sleep onset, sleep maintenance, early morning awakenings) can also be confirmed by actigraphy coupled with sleep logs. Actigraphy is quite effective at identifying irregular sleep/wake patterns, insufficient sleep, excessive sleep needs, excessive time spent in bed not sleeping, and sleep period length. It can also help patients realize they get more (or less) sleep than they thought they did.

Strengths and Weaknesses of Actigraphy

Actigraphy offers many advantages when investigating sleep disorders. Actigraphs are small, simple to use, inexpensive, and readily accepted by patients. They provide an easily readable graphic representation of an individual's natural sleep/wake patterns over days to weeks. Actigraphy is usually done at home, which is advantageous with the exception that the environment is uncontrolled with no sleep technologist available to intervene should technical difficulties arise. Some insomnia patients lie very still attempting to fall asleep, and actigaphy miscodes this as sleep rather than quiet wakefulness. Conversely, excessive motor activity in sleeping patients with restless legs syndrome may be miscoded as wakefulness. Some devices must be removed when bathing, and if the patient does not chart this or other device removals, then these periods appear as sleep. Actigraphy often needs repeating because the first recording is "technically inconclusive," especially if the accompanying sleep log is incomplete. Acebo et al. (134) found 28% of weekly actigraph recordings unreadable in their study of sleep in children and adolescents. Lastly, curiosity causes some patients to open the device "just to see what's inside," often damaging the device or the data.

CONCLUSION

Sleep specialists have an ever-expanding array of diagnostic tools to diagnose and treat sleep disorders. A solid understanding of these diagnostic methods and their indications will ensure these tests are employed appropriately. General practitioners should use this information while deciding when to refer a patient to a sleep specialist, as many of these testing procedures

require specialized equipment and training. In this manner, patients will be assured of getting the best care possible for their sleep disorders.

ACKNOWLEDGMENT

I would like to recognize my dear husband, Stan Damberger, for his editing of this chapter.

REFERENCES

1. Tobler I. Is sleep fundamentally different between mammalian species? Behav Brain Res 1995; 69:35
2. Zee PC, Turek FW. Introduction to sleep and circadian rhythms. In: Turek FW, Zee PC, eds. Regulation of Sleep and Circadian Rhythms. New York: Marcel Dekker, Inc., 1999:1–17.
3. Caton R. The electric currents of the brain. Br Med J 1875; 2:278.
4. Berger H. Über das Elektroenkelphalogramm des Menshcen. Arch Pyschiatr Nervenkr 1929; 87:527–570.
5. Adrian ED, Matthews BHC. Berger rhythms: potential changes from occipital lobes in man. Brain 1934; 57:355.
6. Loomis AL, Harvey EN, Hoban G. Cerebral states during sleep studied by human brain potentials. J Exp Psychiatry 1937; 21:127–144.
7. Aserinsky E, Kleitman N. Regularly occurring periods of eye motility, and concomitant phenomena during sleep. Science 1953; 118:273–274.
8. Aserinsky E, Kleitman N. Two types of ocular motility occurring during sleep. J Appl Physiol 1955; 8:1–10.
9. Dement W, Kleitman N. Cyclical variations in EEG during sleep and their relation to eye movements, body motility and dreaming. Electroenceph Clin Neurophysiol 1957; 9:673–690.
10. Freud S. The interpretation of dreams (1900–1901). In: Strachey J, ed. Standard Edition of the Complete Psychological Works of Sigmund Freud. Vol. 5. London: Hogarth Press, 1958:567–568.
11. Jouvet M, Michel M, Courjon J. Sur un stade d'activitė ėlectrique cėrėbrale rapide au cours du sommeil physiologique. CR Soc Biol (Paris) 1959; 153:1024–1028.
12. Rechtschaffen A, Kales A, eds. A Manual of Standardized Technology, Techniques, and Scoring System for Sleep Stages of Human Subjects. Los Angeles: UCLA Brain Information Service/Brain Research Institute, 1968.
13. Jung R, Kuhlo W. Neurophysiological studies of abnormal night sleep and the pickwickian syndrome. Prog Brain Res 1965; 18:140–159.
14. Gastaut H, Tassinari C, Duron B. Etude polygraphique des manifestations episodiques (hypniques et respiratoires) du syndrome de Pickwick. Rev Neurol 1965; 112:568–579.
15. Holland V, Dement W, Raynal D. Polysomnography corresponding to a need for improved communication. Presented at an Annual Meeting of the Sleep Research Society, Jackson Hole, Wyoming, 1974.

16. Sullivan CE, Issa FG, Berthon-Jones M, Eves I. Reversal of obstructive sleep apnea by continuous positive airway pressure applied through the nares. Lancet 1981; 1:862.
17. Yoss RE, Daly DD. Criteria for the diagnosis of the narcoleptic syndrome. Proc Staff Meet Mayo Clin 1957; 33:320.
18. Vogel G. Studies in the psychophysiology of dreams. III. The dream of narcolepsy. Arch Gen Psychiatry 1960; 3:421.
19. Carskadon MA, Dement WC, Mitler MM, Roth T, Westbrook PR, Keenan S. Guidelines for the multiple sleep latency test (MSLT): a standard measure of sleepiness. Sleep 1986; 9:519–524.
20. Schenck CH, Bundlie SR, Ettinger MG, Mahowald MW. Chronic behavioral disorders of human REM sleep: a new category of parasomnia. Sleep 1986; 9:293–308.
21. Coleman RM, Pollack CP, Weitzman ED. Periodic nocturnal myoclonus occurs in a wide variety of sleep–wake disorders. Trans Am Neurol Assoc 1978; 103:230–235.
22. Lugaresi E, Tassinari CA, Coccagna G, Ambrosetto C. Particularites cliniques et polygraphiques du syndrome d'impatience des membres inferieurs. Rev Neurol (Paris) 1965; 113:545–555.
23. Dement W. A personal history of sleep disorders medicine. Clin Neurophysiol 1990; 7:17.
24. Ferber R, Millan R, Coppoloy M, et al. Amercian Sleep Disorders Association: portable recording in assessment of obstructive sleep apnea. Sleep 1994; 17:378–392.
25. Standards of Practice Committee of the American Sleep Disorders Association (now American Academy of Sleep Medicine). Practice parameters for the use of portable recording in the assessment of obstructive sleep apnea. Sleep 1994; 17:372–377.
26. Littner M, Hirshkowitz M, Kramer M, Kapen S, Anderson WM, Bailey D, Berry RB, Davila D, Johnson S, Kushida C, Loube DI, Wise M, Woodson BT. Practice parameters for using polysomnography to evaluate insomnia: an update. Sleep 2003; 26:754–760.
27. Lichstein KL, Riedel BW, Lester KW, Aguillard RN. Occult sleep apnea in a recruited sample of older adults with insomnia. J Consult Clin Psychol 1999; 67:405–419.
28. Jacobs EA, Reynolds CF, Kupfer DJ, Lovine PA, Ehrenpreis AB. The role of polysomnography in the differential diagnosis of chronic insomnia. Am J Psychiatry 1988; 145:346–349.
29. Vgontzas AN, Kales A, Bixler EO, Manfredi RL, Vela-Bueno A. Usefulness of polysomnographic studies in the differential diagnosis of insomnia. Int J Neurosci 1995; 82:47–60.
30. Rechtschaffen A, Kales A, eds. A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects. Washington, D.C.: U.S. Government Printing Office, 1968.
31. Anders TF, Sadeh A, Appareddy V. Normal sleep in neonates and children. In: Ferber R, Kryger M, eds. Principles and Practice of Sleep Medicine in the Child. Philadelphia: WB Saunders, 1995:7–18.

32. Hirshkowitz M, Moore CA, Hamilton CA, Hamilton CR, Rando KC, Karacan I. Polysomnography of adults and elderly: sleep architecture, respiration, and leg movements. J Clin Neurophysiol 1992; 9:56–62.
33. Sleep Disorders Atlas Task Force. EEG arousal: scoring rules and examples. Sleep 1992; 15:173–184.
34. Boselli M, Parrino L, Smerieri A, Terzano MG. Effect of age on EEG arousals in normal sleep. Sleep 1998; 21:351–357.
35. Marthur R, Douglas NJ. Frequency of EEG arousals from nocturnal sleep in normal subjects. Sleep 1995; 18:330–333.
36. Tasali, Mendelson, et al. Sleep 2001; (suppl 24):A217.
37. Brooks DRL, Horner LF, Kozar CL, Render-Teixerira, Phillipson EA. Obstructive sleep apnea as a cause of systemic hypertension: evidence from a canine model. J Clin Invest 1997; 99:106–109.
38. American Academy of Sleep Medicine Task Force (W. Flemons, Chair). Sleep-related breathing disorders in adults: recommendations for syndrome definition and measure techniques in clinical research. Sleep 1999; 22:667–689.
39. Redline S, Bonekat W, Gottlieb D, Iber C, Kiley J, Quan S, Rapport D, Sanders M, Smith P, Whitney C. Variation in the apnea hypopnea index (AHI) according to hypopnea definition [abstr]. Am J Respir Crit Care Med 1997; 155:A128.
40. Meoli AL, Casey KR, Clark RW, the Clinical Practice Review Committee of the American Academy of Sleep Medicine. Hypopnea in sleep disordered breathing in adults. Sleep 2001; 24:469–470.
41. Guilleminault C, Stoohs R, Clerk A, et al. A cause of excessive daytime sleepiness. The upper airway resistance syndrome. Chest 1993, 104:781–787.
42. Ayappa I, Norman RG, Krieger AC, et al. Noninvasive detection of respiratory effort related arousals (RERAs) by a nasal cannula/pressure transducer system. Sleep 2000; 23:763–771.
43. CMS website: www.hcfa.gov/pubforms/06_cim/ci60.htm.
44. He J, Dryger MH, Zorick FJ, et al. Mortality and apnea index in obstructive sleep apnea. Chest 1988; 94:9–14.
45. Ratke RA. Sleep disorders: laboratory evaluation. In: Ebersole JS, Pedley TA, eds. Current Practice of Clinical Electroencephalography. 3rd ed. Philadelphia: Lippincott Williams and Wilkins, 2003:803–832.
46. Diagnostic Classification Steering Committee (Thorpy MJ, Chair). International Classification of Sleep Disorders: Diagnostic and Coding Manual. Rochester, Minnesota: American Sleep Disorders Association (now the American Academy of Sleep Medicine), 1990.
47. American Sleep Disorders Association Standards of Practice Committee. Practice parameters for the use of polysomnography in the evaluation of insomnia. Sleep 1995; 18:55–77.
48. Douglas NJ. Home diagnosis of the obstructive sleep apnoea/hypopnoea syndrome. Sleep Med Rev 2003; 7:53–59.
49. Kingshott RN, Douglas NJ. The effect of in-laboratory polysomnography on sleep and objective daytime sleepiness. Sleep 2000; 23:1109–1113.
50. LeBon O, Hoffman G, Tecco J, et al. Mild to moderate sleep respiratory events. One negative night might not be enough. Chest 2000; 118:353–359.

51. Meyer TJ, Eveloff SE, Kline LR, et al. One negative polysomnogram does not exclude obstructive sleep apnea. Chest 1993; 103:756–760.
52. American Thoracic Society. Cardiorespiratory sleep studies in children. Establishment of normative data and polysomnographic predictors of morbidity. Am J Respir Care Med 1999; 160:1381–1387.
53. Parisi RA. Respiration and respiratory function: technique of recording and evaluation. In: Chokroverty S, ed. Sleep Disorders Medicine: Basic Science, Technical Considerations and Clinical Aspects. 2nd ed. Boston: Butterworth-Heineman, 1999:215–221.
54. Sanders MH, Kern NB, Costantino JP, Stiller RA, Strollo PJ Jr, Studnicki KA, Coates JA, Richards TJ. Accuracy of end-tidal and transcutaneous PCO2 monitoring during sleep. Chest 1994; 106:472–483.
55. Guilleminault C, Pelayo R, Leger D, Clerk A, Bocian RCZ. Recognition of sleep-disordered breathing in children. Pediatrics 1996; 98:873–882.
56. Birchfield RI, Sieker HO, Heyman A. Alterations in respiratory function during natural sleep. J Lab Clin Med 1959; 54:216–222.
57. Carroll N, Branthwaite MA. Control of nocturnal hypoventilation by nasal intermittent positive pressure ventilation. Thorax 1988; 43:349–353.
58. Witmans MB, Marcus CL, Keens TG, Ward SL. Normal polysomnographic values for obstructive hypopneas in infants and children. Sleep 2003; 26:A142.
59. Marcus CL, Omlin KJ, Basinki DJ, et al. Normal polysomnographic values for children and adolescents. Am Rev Respir Dis 1992; 146:1235–1239.
60. Uliel S, Tauman R, Greenfield M, Sivan Y. Normal polysomnographic respiratory values in children and adolescents. Chest 2004; 125:872–878.
61. Acebo, Millman, et al. Sleep, breathing, and cephalometrics in older children and young adults. Part I: normative values. Chest 1996; 109:664–672.
62. Witmans MB, Marcus CL, Ward SL, Keens T. Improving pediatric polysomnography. Sleep Rev 2004; 62–66.
63. Marcus CL, Keens TG, Ward SLD. Comparison of nap and overnight polysomnography in children. Pediatr Pulmonol 1992; 13:16–21.
64. Saaeed MM, Keens TG, Stabile MW, Bolokowicz J, Davidson Ward SL. Should children with suspected obstructive sleep apnea and normal nap studies have overnight sleep studies? Chest 2000; 118:360–365.
65. Schenck CH, Pareja JA, Patterson AL, Mahowald MW. Analysis of polysomnographic events surrounding 252 slow-wave sleep arousals in thirty-eight adults with injurious sleepwalking and sleep terrors. J Clin Neurophysiol 1998; 15(2):159–166.
66. Tachibana N, Kimura K, Kitajima K, Shinde A, Kimura J, Shibasaki H. J Neurol Neurosurg Psychiatry 1997; 63(5):678–681.
67. Ferini-Strambi L, Oldani A, Zucconi M, Smirne S. Cardiac autonomic activity during wakefulness and sleep in REM sleep behavior disorder. Sleep 1996; 19(5):367–369.
68. American Sleep Disorders Association. Practice parameters for the indications for polysomnography and related procedures. Sleep 1987; 20(6):406–422.
69. American Academy of Sleep Medicine. Practice parameters for the indications for polysomnography and related procedures: an update for 2005. Sleep 2005; 28:499–519.

70. American Electroencephalographic Society Guideline Fifteen: guidelines for polygraphic assessment of sleep-related disorders (polysomnography). J Clin Neurophysiol 1994; 11(1):116–124.
71. Foldvary N, Caruso AC, Mascha E, Perry M, Klem G, McCarthy V, Qureshi F, Dinner DS. Identifying montages that best detect electrographic seizure activity during polysomnography. Sleep 2000; 23:221–229.
72. American Electroencephalographic Society Guideline Thirteen: guidelines for standard electrode position nomenclature. J Clin Neurophysiol 1994; 11(1): 111–113.
73. Jasper HH. The 10–20 electrode system of the International Federation. Electroencephalogr Clin Neurophysiol 1958; 10:370–375.
74. Aldrich MS, Jahnke B. Diagnostic value of video-EEG polysomnography. Neurology 1991; 41:1060–1066.
75. Orr WC, Eiken T, Pegram V, et al. A laboratory validation study of a portable system for remote recording of sleep-related breathing disorders. Chest 1994; 105:160–162.
76. Mykytyn U, Sajkov D, Neill AM, et al. Portable computerized polysomnography in attended and unattended settings. Chest 1999; 115:114–122.
77. Fry JM, DiPhillipo MA, Curran K, et al. Full polysomnography in the home. Sleep 1998; 21:635–642.
78. Portier F, Portmann A, Czernichow P, et al. Evaluation of home versus laboratory polysomnography in the diagnosis of sleep apnea syndrome. Am J Respir Care Med 2000; 162:814–818.
79. Gagnadoux F, Pelletier-Fleury N, Phillipe C, et al. Home unattended versus hospital telemonitored polysomnography in suspected obstructive sleep apnea syndrome: randomized crossover trial. Chest 2002; 121:753–759.
80. Redline S, Sanders M, Lind B, et al. Methods for obtaining and analyzing unattended polysomnography data for a multicenter study. Sleep 1998; 21:759–767.
81. Parra O, Garcia-Esclasans N, Montserrat JM, et al. Should patients with sleep apnea/hypopnea syndrome be diagnosed and managed on the basis of home sleep studies? Eur Respir J 1997; 10:1720–1724.
82. Dingli K, Coleman EL, Vennella M, et al. Evaluation of a portable device for diagnosing obstructive sleep apnea/hypopnea syndrome. Eur Respir J 2003; 21:253–259.
83. Elbez M, Roue GM, Lofaso F, et al. Utility of actigraphy in the diagnosis of obstructive sleep apnea. Sleep 2002; 25:527–531.
84. Boyer S, Kapur S. Role of portable sleep studies for the diagnosis of obstructive sleep apnea. Curr Opin Pul Med 2003; 9:465–470.
85. Reuven H, Schweitzer E, Tarasiuk A. A cost-effective analysis of alternative at-home or in-laboratory technologies in the diagnosis of obstructive sleep apnea syndrome. Med Decis Making 2001; 21:451–458.
86. Chervin RD, Murman DL, Malow BW, et al. Cost-utility of three approaches to the diagnosis of sleep apnea: polysomnography, home testing and empirical therapy. Ann Intern Med 1999; 130:496–505.
87. Brouillette RT, Morielli A, Leimanis A, Waters KA, Luciano R, Ducharme FM. Nocturnal pulse oximetry as an abbreviated testing modality for pediatric obstructive sleep apnea. Pediatrics 2000; 105:405–412.

88. Kirk VG, Bohn SG, Flemons WW, Remmers JE. Comparison of home oximetry monitoring with laboratory polysomnography in children. Chest 2003; 124: 1702–1708.
89. Pressman MR. Primer of Polysomnographic Interpretation. Boston: Butterworth-Heineman, 2002.
90. Yamashiro Y, Kryger MH. Nocturnal oximetry: is it a screening tool for sleep disorders? Sleep 1995; 18(3):167–171.
91. Oksenberg A, Silverberg DS, Arons E, Radwan H. The sleep supine position has a major effect on optimal nasal continuous positive airway pressure: relationship with REM and NREM sleep, body mass index, and age. Chest 1999; 116:1000–1006.
92. Teschler H, Berthon-Jones M. Intelligent CPAP system: clinical experience. Thorax 1998; 53(suppl 3):S49–S54.
93. Berry R, Parish J, Hartse K. The use of auto-titrating continuous positive airway pressure for treatment of adult obstructive sleep apnea: an American Academy of Sleep Medicine review. Sleep 2002; 25:148–173.
94. Guilleminault C, Brooks SN. Excessive daytime sleepiness: a challenge for the practicing neurologist. Brain 2001; 124:1482–1491.
95. Chervin RD. Sleepiness, fatigue, tiredness, and lack of energy in obstructive sleep apnea. Chest 2000; 118:373–379.
96. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991; 14:540–545.
97. Hoddes E, et al. Quantification of sleepiness: a new approach. Psychophysiology 1973; 10:431.
98. Johns MW. Reliability and factor analysis of the Epworth sleepiness scale. Sleep 1992; 15:376–381.
99. Chervin RD, Aldrich MA, Pickett R, et al. Comparison of the results of the Epworth sleepiness scale and the multiple sleep latency test. J Psychosom Res 1997; 42:145–155.
100. Nishino S, Mignot E. Pharmacological aspects of human and canine narcolepsy. Prog Neurobiol 1997; 52:27–78.
101. Carskadon MA, Dement WC. The multiple sleep latency test: what does it measure? Sleep 1982; 5:S67–S72.
102. Aldrich MS. Sleep Medicine. New York: Oxford University Press, 1999:117.
103. Guilleminault C, Dement WC. 235 cases of excessive daytime sleepiness. J Neurol Sci 1977; 31:13–27.
104. Richardson G, Carskadon MA, Flagg W, et al. Excessive daytime sleepiness in man: multiple sleep latency measurements in narcoleptic and control subjects. Electroencephalgr Clin Neurophysiol 1978; 45:621–627.
105. Benbadis SR, Perry MC, Walgamuth BR, et al. The MSLT: comparison of sleep onset criteria. Sleep 1996; 19:632–636.
106. Roth T, Roehrs TA, Rosenthal IL. Measurement of sleepiness and alertness: MSLT. In: Chokroverty S, ed. Sleep Disorders Medicine. 2nd ed. Boston: Butterworth-Heinemann, 1999:133–139.
107. Levine B, et al. Daytime sleepiness in young adults. Sleep 1988; 11:39.
108. Roehrs T, Roth T. Multiple sleep latency test: technical aspects and normal values. J Clin Neurophysiol 1992; 9:63.

109. Carskadon MA, Dement WC. Cumulative effects of sleep restriction on daytime sleepiness. Psychophysiology 1981; 18:107–113.
110. Mitler MM. The multiple sleep latency test as an evaluation for excessive somnolence. In: Guilleminault C, ed. Sleeping and Waking Disorders: Indications and Techniques. California: Addision Wesley Menlo Park, 1982:145–155.
111. Zwyghuizen-Doorenbos A, et al. Test–retest reliability of the MSLT. Sleep 1988; 11:562.
112. Folkerts M, Rosenthal L, Roehrs T, Krstevska S, Murlidhar A, Zorick F, Wittig R, Roth T. The reliability of the diagnostic features in patients with narcolepsy. Biol Psychiatry 1996; 40:208–214.
113. Mitler MM, van den Hoed J, Carskadon MA, et al. REM sleep episodes during the multiple sleep latency test in narcoleptic patients. Electroencephalogr Clin Neurophysiol 1979; 46:479–481.
114. Aldrich MS, Chervin RD, Malow B. Value of the Multiple Sleep Latency Test (MSLT) for the diagnosis of narcolepsy. Sleep 1997; 20:620–629.
115. Benbadis SR, Qu Y, Perry MC, Dinner DS, Warnes H. Interrater reliability of the multiple sleep latency test. Electroencephalogr Clin Neurophysiol 1995; 95:302–304.
116. Drake CL, Rice MF, Roehrs T, Rosenthal L, Guido P, Roth T. Scoring reliability of the multiple sleep latency test in a clinical population. Sleep 2000; 23:911–913.
117. Bishop J, Wise M. Technical problems associated with performing the multiple sleep latency test (MSLT) in children [abstr]. Sleep Res 1996; 25:481.
118. Harrison Y, Horne JA. "High sleepability without sleepiness." The ability to fall asleep rapidly without other signs of sleepiness. Neurophysiol Clin 1996; 26:15.
119. Mitler MM, Gujavarty KS, Browman CP. Maintenance of wakefulness test: a polysomnographic technique for evaluating treatment efficacy in patients with excessive somnolence. Electroencephalogr Clin Neurophysiol 1982; 53:658–661.
120. Doghramji K, Mitler M, Sangal B, Shapiro, Taylor S, et al. A normative study of the maintenance of wakefulness test (MWT). Electroencephalogr Clin Neurophysiol 1997; 103:554–562.
121. Mitler MM, Walsleben J, Sangal RB, Hirshkowitz M. Sleep latency on the maintenance of wakefulness test (MWT) for 530 patients with narcolepsy while free of psychoactive drugs. Electroencephalogr Clin Neurophysiol 1998; 107:33–38.
122. Poceta JS, Timms RM, Jeong DU, Ho S, Erman M, Mitler MM. Maintenance of wakefulness test in obstructive sleep apnea syndrome. Chest 1992; 101: 893–897.
123. Carskadon M, Dement W, Mitler M, et al. Self report versus sleep laboratory findings in 122 drug-free subjects with the complaint of chronic insomnia. Am J Psychiatry 1976; 133:1382–1388.
124. Hauri PJ, Wisbey J. Wrist actigraphy in insomnia. Sleep 1992; 15(4):293–301.
125. Babkoff H, Weller A, Lavidor M. A comparison of prospective and retrospective assessments of sleep. J Clin Epidemiol 1996; 49:455–460.
126. Lacks P, Morin CM. Recent advances in the assessment and treatment of insomnia. J Cons Clin Psychol 1992; 60:586–594.

127. Mullington J, Spielman A, Well R, Hoffman R. Subjective estimation of nocturnal sleep length and stability of sleep patterns. Sleep Res 1988; 17:342.
128. National Institutes of Health. Star sleeper website, star sleeper sleep diary for children can be downloaded from web www.nhlbi.nih.gov/health/public/sleep/starslp/teachers/sleep_diary.htm.
129. Jean-Louis G, von Gizycki H, Zizi F, Spielman A, Hauri P, Taub H. The actigraphic data analysis software: I. A novel approach to scoring and interpreting sleep–wake activity. Percept Mot Skills 1997; 85(1):207–216.
130. Sadeh A, Sharkey KM, Carskadon MA. Activity-based sleep–wake identification: an empirical test of methodological issues. Sleep 1994; 17:201–207.
131. Middlekoop HA, Van Dam E, Smilde-van den Doel DA, Van Dijk G. 45-hour multiple-site actimetry in 20 healthy subjects: relations between body and limb movements and the effects of circadian sleep-wakefulness. Sleep–Wake Research in the Netherlands, 1995:681–684.
132. Middlekoop HA, Van Dam E, Smilde-van de Doel DA, Van Dijk G. 45-hour continuous quadruple-site actimetry: relations between trunk and limb movements and effects of circadian sleep–wake rhythmicity. Psychophysiol 2002; 34(2):199–203.
133. Levine B, Lumley M, Roehrs T, et al. The effects of acute sleep restriction and extension on sleep efficiency. Int J Neurosci 1988; 43:139–143.
134. Acebo C, Sadeh A, Seifer R, et al. Estimating sleep patterns with activity monitoring in children and adolescents: how many nights are necessary for reliable measures? Sleep 1999; 22(1):95–103.
135. Littner M, Kushida CA, McDowell Anderson W, Bailey D, Berry RB, Davila DG, Hirshkowitz M, Kapen S, Kramer M, Loube D, Wise M, Johnson SF. American Academy of Sleep Medicine Standards of Practice Committee report. Practice parameters for the role of actigraphy in the study of sleep and circadian rhythms: an update for 2002. Sleep 2003; 26(3):337–341.
136. Jean-Louis G, von Gizycki H, Zizi F, et al. Determination of sleep and wakefulness with the actigraphic data analysis software (ADAS). Sleep 1996; 19:739–743.
137. Reid K, Dawson D. Correlation between wrist activity monitor and electrophysiological measures of sleep in a simulated shiftwork environment for younger and older subjects. Sleep 1999; 52:157–159.
138. Sadeh A, Hauri PJ, Kripke DF, Lavie P. The role of actigraphy in the evaluation of sleep disorders. Sleep 1995; 18:288–302.
139. Sadeh A, Acebo C. The role of actigraphy in sleep medicine. Sleep Med Rev 2002; 6:113–124.
140. Blood ML, Sack RL, Percy DC, Pen JC. A comparison of sleep detection by wrist actigraphy, behavioral response, and polysomnography. Sleep 1997; 20:388–395.
141. Cole RJ, Kripke DF, Gruen W, Mullaney DJ, Gillin JC. Automatic sleep/wake identification from wrist activity. Sleep 1992; 15:461–469.
142. Monk T, Buysse D, Rose LR. Wrist actigraphic measures of sleep in space. Sleep 1999; 22:948–954.
143. Sadeh A. Evaluating night wakings in sleep-disturbed infants: a methodological study of parenteral reports and actigraphy. Sleep 1996; 19:757–762.

144. Tikotzky L, Sadeh A. Sleep patterns and sleep disruptions in kindergarten children. J Clin Child Psychol 2001; 30:581–591.
145. Lockley SW, Skene DJ, Arendt J. Comparison between subjective and actigraphic measures of sleep and sleep rhythms. J Sleep Res 1999; 8(3):175–184.
146. Sforza E, Zamagni M, Petiau C, et al. Actigraphy and leg movements during sleep: a validation study. J Clin Neurophysiol 1999; 16(2):154–160.
147. Middlekoop HA, Knuistingg Neven A, van Hilten JJ, et al. Wrist actigraphic assessment of sleep in 116 community based subjects suspected of obstructive sleep apnea syndrome. Thorax 1995; 50(3):284–289.

3

Insomnia: Difficulty Falling and Staying Asleep

Oneil S. Bains

Section of Sleep Medicine, Virginia Mason Medical Center, Seattle, Washington, U.S.A.

Symptoms of Insomnia	***Diagnoses***
Difficulty initiating sleep	*Adjustment insomnia*
Difficulty maintaining sleep	*Psychophysiological insomnia*
Daytime fatigue	*Paradoxical insomnia* *Inadequate sleep hygiene* *Idiopathic insomnia* *Insomnia due to: Mental disorder* *Insomnia due to: Drug or substance* *Insomnia due to: Medical condition*

INTRODUCTION

Many people complain of occasional nights fraught with difficulty falling or staying asleep. These complaints often go beyond mere annoyance or inconvenience, representing an issue with significant medical, social, and economic impacts (Tables 1 and 2) (1–5). The complaint of insomnia is universal across cultures and genders. Despite the frequency of this complaint, our poor understanding of insomnia and its root causes still plagues our ability to successfully manage this condition. Indeed, for many people the word "insomnia" has different meanings and nuances. Despite this, physicians caring for patients with this sleep complaint must use a single definition.

Insomnia is the complaint of difficulty initiating or maintaining sleep combined with daytime impairment. The type of impairment can be varied and may include a change in alertness, energy, cognitive function, behavior, or emotional state. Individual sleep need varies significantly. Some people have no impairment of performance with five hours of sleep per night, whereas others need greater than nine hours to preserve daytime functioning. Thus, the requirement of daytime sequelae differentiates individual sleep need from the complaint of insomnia. In this chapter, we will explore the epidemiology, etiologies, and clinical approach to insomnia and offer clinical situations to highlight important clues in managing this common problem.

EPIDEMIOLOGY

Insomnia is the most common sleep complaint in the industrialized world. The National Sleep Foundation, in conjunction with the Gallup Organization, conducted telephone interviews with 1000 Americans to examine the prevalence and severity of insomnia (Table 3) (6). Approximately one-third of Americans are reported to suffer with insomnia. Of these, 75% reported occasional problems sleeping, which averaged 5.2 nights per month. The remaining 25% of patients had chronic problems, with an average of 16.4 nights of insomnia per month. Many other studies have examined the prevalence of

Table 1 Impact of Insomnia

- Increased medical illnesses
- Increased psychiatric disorders
- Increased physician office visits
- Reduced quality of life
- Hospitalized twice as often
- More medications taken
- Higher rate of absenteeism
- Decreased work performance, including decreased concentration, difficulty performing duties, and more work-related accidents

Table 2 Economic Impact of Insomnia

Direct costs	• Medications: US $1.97 billion (both prescription and over the counter) • Services: US $11.96 billion
Indirect costs	• Decreased productivity • Higher accident rate • Increased absenteeism • Increased comorbidity
Total annual cost estimates	• Range from US $30.5 to US $107.5 billion

insomnia. In one study performed in a primary care setting, nearly half of patients experienced insomnia. One-third of that population mentioned the insomnia to their physician and only 5% sought treatment (7–9). Using stringent criteria, the prevalence of insomnia in the general adult population ranges from 9% to 18.6%. In these studies, insomnia was defined by the presence of disrupted sleep every night for two weeks or by similar or more stringent criteria (10–13). Overall the complaint of insomnia is widespread, possibly representing the common expression of several underlying pathologies.

PATHOPHYSIOLOGY

Determining the etiology of insomnia is challenging, since the cause is often multifactorial and the complaint can be present for years. Identified risk factors include advancing age, female gender, the presence of medical or psychiatric illness, and engaging in shift work. A theoretical insomnia model created by Spielman et al. (14) points to predisposing, precipitating, and perpetuating factors for the disorder (Table 4). Each factor contributes to the development of insomnia and the relative importance of each factor changes over time.

Everyone is hypothesized to have some degree of predisposition to insomnia. Those with a high predisposition are more likely to develop insomnia from a precipitating event. For example, a person suffering from chronic pain with a high predisposition is more likely to develop subsequent

Table 3 Self-Reported Prevalence of Insomnia: National Sleep Foundation Survey ($N = 1000$)

No insomnia	64%
Occasional insomnia (average 5.2 nights per month)	27%
Chronic insomnia (average 16.4 nights per month)	9%

Table 4 Predisposing, Precipitating, and Perpetuating Factors in Insomnia

Predisposing	Precipitating	Perpetuating
Personality	Situational	Conditioning
Sleep–wake cycle	Environmental	Substance abuse
Circadian rhythm	Medical	Performance anxiety
Coping mechanisms	Psychiatric	Poor sleep hygiene
Aging	Medications	

insomnia than a low-predisposition individual. Further, insomnia experienced over a period of time can change a person's cognitive and behavioral approach to sleep, perpetuating the sleep disturbance.

PREDISPOSING FACTORS

The concept of predisposing factors is intuitive. Patients predisposed to developing insomnia are thought to have increased physiologic, cognitive, and emotional arousal (Table 4) (15). Indeed, patients with insomnia exhibit a higher basal heart rate, metabolic rate, and temperature than normal sleepers (16,17). This increased physiologic arousal is considered secondary to increased sympathetic nervous system activity. Theories of cognitive arousal have focused on two beliefs commonly observed in patients with insomnia. First, patients with insomnia worry over their poor sleep and the impact it has on daytime functioning. These fears result in performance anxiety when preparing for sleep. Second, their inability to sleep causes the sleep environment to become negatively conditioned. For example, the individual may feel sleepy while lying on the sofa but upon entering the bedroom become fully awake. Emotional arousal refers to the concept that arousal vulnerability is related to emotional factors. This notion is supported by several studies using psychometric methods in which insomnia patients had abnormal scores on tests measuring anxiety, depression, and other aspects of personality.

Another factor predisposing to insomnia is a deficient homeostatic sleep drive. Indeed, many insomnia patients are devoid of daytime sleepiness. Normal sleepers, when sleep restricted, reveal increased sleepiness on the multiple sleep latency test. In contrast, those with insomnia exhibit no sleepiness on this test, despite obtaining significantly less sleep per night than average.

PRECIPITATING FACTORS

Precipitating factors trigger the onset of insomnia (Table 4). These factors are varied, including medical and psychiatric illness and primary sleep disorders. Even subtle events such as fever, dietary changes, and alterations

in the sleep setting can initiate insomnia. Medications and substances are common precipitating factors. Some with chronic insomnia have clear precipitating events while others cannot recall a specific trigger. Precipitating events are not necessarily due to diagnostic conditions or negative situations. For example, patients may have difficulty sleeping prior to travel, in anticipation of special events, or before important evaluations at school or work. In these instances, the insomnia begins episodically and over time becomes chronic.

PERPETUATING FACTORS

Patients predisposed to insomnia with a precipitating event may develop transient sleep difficulties. Whether the insomnia persists and becomes chronic is related to cognitive and behavioral factors regarding sleep that perpetuate the disorder (Table 4). In many patients, these predisposing, precipitating, and perpetuating factors evolve over time (Fig. 1).

In an attempt to improve their sleep, many patients adopt behaviors that perpetuate their insomnia. These behaviors include changing their sleep schedule, becoming reliant on somnogenic substances, and developing secondary medical or psychological issues. Many of these behaviors conflict with proper sleep hygiene practices. Such maladaptive habits may occur during the day or night and include heavy caffeine or alcohol use or eating or exercising during the usual sleep period. Many patients with insomnia spend too much time in bed and therefore start performing activities other than sleep in bed. For example, the patient may get into bed earlier than usual attempting to

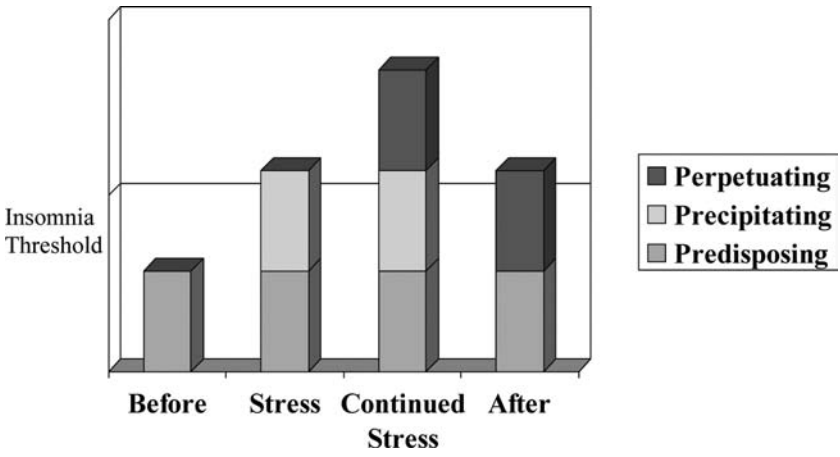


Figure 1 Spielman's model of predisposing, precipitating, and perpetuating factors in the development of chronic insomnia. *Source*: From Ref. 14.

sleep. If unable to sleep, he or she may keep a book or TV remote control on the nightstand. These behaviors generally lead to more wake time in bed serving to condition the bed as a place to be awake. Some patients actually fear going to bed or have anxiety over the oncoming sleep period. Individuals with insomnia often become focused on their sleep and daytime functioning. They spend time during the day preoccupied about not sleeping well and have performance anxiety regarding their ability to sleep. This loss of confidence regarding sleep perpetuates insomnia by promoting apprehension toward sleep and producing counterproductive sleep rituals. These maladaptive behaviors become the predominate feature of psychophysiological insomnia.

PSYCHIATRIC DISORDERS AND INSOMNIA

Patients with psychiatric disorders often complain of trouble sleeping and insomnia is a diagnostic symptom for mood and anxiety disorders. However, the absence of insomnia does not preclude a psychiatric diagnosis and many patients with insomnia deny mood or anxiety symptoms. Determining the cause and relationship between insomnia and psychiatric illness is important for several reasons. First, sleep disturbance may be an early sign or cause of psychiatric disorders. Second, early treatment can halt the progression or full manifestation of the disorder, and third, insomnia recognition can alter psychiatric management (18,19).

A National Institute of Mental Health epidemiologic study by Ford and Kramerow (10) questioned 7954 respondents regarding sleep complaints and psychiatric symptoms. A baseline questionnaire was completed and repeated one year later. Insomnia was defined as sleep difficulties lasting two weeks in the previous six months. Thus, most respondents with insomnia had severe symptoms. Of the 10% (811) reporting insomnia at the first interview, 40% had one or more psychiatric disorders, compared to 16% of subjects without an insomnia complaint (Table 5). A year later, an additional 17% of those with insomnia were found to have a psychiatric disorder. The respondents with continuing insomnia had significantly higher rates of

Table 5 Insomnia and Psychiatric Disorders

Respondents with insomnia	Respondents without insomnia
40% had one or more psychiatric disorders:	*16% with one or more psychiatric disorders*:
• Anxiety disorder 24%	• Anxiety disorder 10%
• Depressive disorder 22.6%	• Depressive disorder 3%
• Alcohol abuse 7%	• Alcohol abuse 3.8%
• Drug abuse 4.3%	• Drug abuse 1.4%

Table 6 Insomnia as a Risk Factor for Later Emergence of Psychiatric Disorders

	Prior history of insomnia (%)	No prior history of insomnia (%)
New cases of psychiatric illness at the 3.5 year follow-up:		
• Major depression	15.9	4.6
• Any anxiety disorder	13.7	7.1
• Alcohol dependence	7.1	4.7
• Drug dependence	4.1	0.6

new onset major depression and anxiety disorders than those whose insomnia had resolved.

Another longitudinal study by Breslau and colleagues examined insomnia as a risk factor for later emergence of psychiatric disorders. In this study, 1007 adults between the ages of 21 and 30 were interviewed, with 16.6% reporting insomnia of at least 2 weeks duration. A follow-up interview 3.5 years later revealed a threefold increase in major depression and a twofold increase in anxiety disorders among the subjects with insomnia (Table 6). Prior insomnia was a significant independent predictor of subsequent major depression. At least six studies have indicated that patients with insomnia devoid of mood disorders are at increased risk of developing major depression, even up to a decade following the onset of the sleep disturbance. Ohayon and Roth (13) interviewed 14,915 individuals from four European countries to establish the order of symptom development in people with insomnia and comorbid psychiatric disorders. They found that insomnia tended to precede or simultaneously appear with mood disorders and follow or simultaneously appear with anxiety disorders.

Studies examining psychiatric disorders and insomnia have revealed several consistent findings. Anxiety disorders and insomnia frequently occur together. In fact, a higher percentage of persons with insomnia meet the criteria for anxiety disorders than for depressive disorders. A prior history of insomnia is associated with a greater risk for the future onset of an anxiety disorder. Insomnia is a risk factor for the subsequent development of depression and depression is a prominent cause of insomnia. Determining whether the insomnia is primary or secondary to a psychiatric disorder guides the treatment plan. Whether treatment of primary insomnia will prevent subsequent development of psychiatric disorders is unclear.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The clinician must remember that ''insomnia'' is a patient complaint with many potential etiologies. Therefore, the clinical approach should be similar to that of other symptoms such as chest pain or shortness of breath. The

insomnia complaint requires a history, physical exam, and diagnostic studies to elucidate the diagnosis. Frequently, clinicians proceed to treatment without pursuing a diagnosis, thus failing to identify the primary medical, psychiatric, or sleep-related cause.

Clinical Definitions of Insomnia

Insomnia duration helps establish the diagnosis and treatment plan. Several different bodies have established insomnia duration criteria outlined in Table 7. In these definitions, all three organizations distinguish shorter from longer lasting insomnia. The unique feature between these conditions is that transient (adjustment) insomnia occurs in people with normal sleep that returns to normal with resolution of precipitating events (20). This distinction is clinically important as successful treatment of transient insomnia can prevent formation of perpetuating factors of insomnia, which can become entrenched.

Sleep and psychiatric organizations use different diagnoses for insomnia (Tables 8 and 9) (21,22). Psychophysiological insomnia is the most equivalent diagnosis of psychiatric ''primary insomnia'' provided by the International Classification of Sleep Disorders-2. This disorder involves insomnia combined with decreased functioning during wakefulness along with a number of learned sleep-preventing associations. These patients try too hard to sleep as evidenced by an inability to fall asleep when desired despite easily falling asleep during monotonous pursuits such as watching TV or reading. They exhibit conditioned arousal to bedroom or sleep-related activities indicated by sleeping poorly at home and better away from home or when not carrying out bedtime routines. Many of these individuals have increased somatized tension (e.g., agitation, muscle tension, or increased vasoconstriction). Polysomnographic monitoring demonstrates an increased sleep latency, reduced sleep efficiency, and increased number and duration of awakenings. This

Table 7 Clinical Definitions of Insomnia Based on Time

NIH consensus
• Transient insomnia: lasting several days
• Short-term insomnia: 1–3 weeks
• Long-term insomnia: more than 3 weeks
International Classification of Sleep Disorders
• Acute insomnia: less than 1 month
• Subacute insomnia: 1–6 months
• Chronic insomnia: greater than 6 months
The Diagnostic and Statistical Manual of Mental Disorders (DSM–IV)
• Primary insomnia: greater than 1 month, thus excluding shorter lasting conditions from diagnostic consideration

Table 8 The Psychiatric Primary Definition of Insomnia

A. The predominant complaint is difficulty initiating or maintaining sleep, or nonrestorative sleep, for at least 1 month
B. The sleep disturbance (or associated daytime fatigue) causes clinically significant distress or impairment in social, occupational, or other important areas of functioning
C. The sleep disturbance does not occur exclusively during the course of narcolepsy, breathing-related sleep disorder, circadian rhythm sleep disorder, or a parasomnia
D. The disturbance does not occur exclusively during the course of another mental disorder (e.g., major depressive disorder, generalized anxiety disorder, or delirium)
E. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition

Source: From Ref. 21.

disorder can coexist with other sleep disorders, such as inadequate sleep hygiene or obstructive sleep apnea syndrome.

The International Classification of Sleep Disorders-2 includes several other insomnia diagnoses including sleep state misperception (now called paradoxical insomnia), insomnia due to mental disorder, inadequate sleep hygiene, and idiopathic insomnia (Table 9). Paradoxical insomnia is characterized by the inability of a patient to recognize when they are asleep. Patients with disrupted sleep due to inadequate sleep hygiene consistently demonstrate poor sleep habits. Individuals with no clear explanation for long-standing sleep problems have idiopathic insomnia, a persistent form of the disorder starting in childhood or adolescence. In addition to these

Table 9 The International Classification of Sleep Disorders-2 Diagnostic Conditions Characterized by Sustained Insomnia

• Psychophysiological insomnia
• Paradoxical insomnia (formerly sleep state misperception)
• Idiopathic insomnia
• Insomnia due to mental disorder
• Inadequate sleep hygiene
• Behavioral insomnia of childhood
• Insomnia due to drug or substance
• Insomnia due to medical condition
• Insomnia not due to substance or known physiological condition, unspecified (nonorganic insomnia, NOS)
• Physiological (organic) insomnia, unspecified

Source: From Ref. 22.

specific insomnia diagnoses, the disorder can be classified as due to medical illness or drug or substance abuse. As is often true in medicine, few patients fit neatly into these categories, with many exhibiting multiple features from each of these different insomnia types.

The Clinical Approach to Insomnia

The differential diagnosis of insomnia is broad, making the accurate diagnosis challenging. A good initial approach is to ascertain whether insomnia is the primary or secondary condition. By carefully considering the secondary medical, psychiatric, and medication-related causes of insomnia, the clinician may uncover a treatable primary condition with subsequent improvement of the sleep complaint (Table 10). The treatment plan will be guided by findings from a well-done sleep history and physical examination [Table 11; also see Chap. 1 (23)].

Some aspects of the history are particularly helpful in elucidating perpetuating factors of insomnia. Questions regarding behaviors around bedtime and the sleeping environment may provide clues. Maladaptive behaviors are often revealed by obtaining detailed descriptions of day and nighttime activities including sleep preparation and the act of going to sleep (24,25). Assessment for somatized tension such as agitation, clenching, or reactivity to stressors is helpful. Direct questions are most effective, including duration of time spent in bed and duration of time spent sleeping. Other helpful questions focus on learned sleep preventing associations. A few examples of these types of questions are provided below:

- Do you feel sleepy during the day and if so, are you able to nap?
- Do you sleep better when away from your own bed?
- If not trying to sleep (watching TV or reading), does sleep come more easily?
- Are you unable to turn off thoughts when laying in bed?
- Do you get anxious when thinking about going to sleep?
- Do you avoid overnight travel because you are afraid of insomnia?

These aspects of the history help elucidate whether the insomnia is primary or secondary, transient or chronic. In primary insomnia, the patient frequently relates learned sleep preventing associations and somatized tension. The interaction between clinician and patient provided below demonstrates how to learn if these factors are present:

Clinician: "What do you think keeps you awake?"
Patient: "I don't know. I just cannot sleep."
Clinician: "Do you feel like you have difficulty turning off thoughts?"
Patient: "Not really."

Table 10 Medical Disorders, Medications, and Substances Associated with Insomnia

Medical diagnosis	Psychiatric diagnosis	Neurological diagnosis	Sleep disorders	Medications and substances
Gastroesophageal reflux disease	Mood disorders (depression)	Parkinsonism	Restless legs syndrome	CNS stimulants
Pulmonary conditions (COPD, asthma)	Anxiety disorders (generalized anxiety disorder, panic disorder)	Dementia	Obstructive sleep apnea	Antidepressants
Cardiovascular conditions (CAD, CHF)	Alcoholism	Cerebrovascular disease	Central sleep apnea	Antihypertensives
Benign prostatic hyperplasia		Epilepsy	Delayed sleep phase syndrome	Anticholinergics
Hyperthyroidism		Multiple sclerosis		Sympathomimetic amines
Chronic pain syndromes (fibromyalgia, rheumatoid arthritis)				Caffeine
Autoimmune disorders (SLE)				Alcohol
Chronic renal failure				

Abbreviations: COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; CHF, congestive heart failure; SLE, systemic lupus erythematosis; CNS, central nervous system.

Table 11 Sleep History in Patients with Insomnia

Type of insomnia
• Transient, short term, or acute
• Persistent, long term, or chronic
• Intermittent
Sleep pattern
• Sleep-onset insomnia
• Difficulty maintaining sleep
• Early morning awakening
• Nonrestorative sleep
Associated events
• Medical illness, medications
• Psychosocial stress
• Mood changes
• Immediate precipitants
Previous sleep history
• Previous sleep quality
• Previous episodes of insomnia
• Similarity to present problem
• Response to treatment
Sleep hygiene history
• Bedtime and arising time
• Variation on days off and workdays
• Shift-work or circadian changes
• Napping behavior
• Exercise, lifestyle
• Caffeine, alcohol, substance use
History from bedpartner
• Snoring, irregular breathing
• Movements during sleep
• Estimates of patient's sleep quality and length
• Changes in mood and performance of patient

Clinician: "What do you think about when you are laying in bed?"
Patient: "I am thinking that I would like to be asleep."
Clinician: "Are you feeling sleepy at that time?"
Patient: "I thought I was. Just a few minutes before I got into bed I was watching TV on the sofa and I could barely keep my eyes open. Then I got into bed and I felt wide awake. In fact, sometimes when I'm in bed, I am very aware of my heartbeat. At times, I really need to sleep, and I let myself fall asleep on the sofa because I have more success sleeping there."

In this example, the patient describes sleepiness that is overcome when "trying" to sleep. This suggests paradoxically that the act of going to sleep is

a learned sleep preventing association. The patient is aware of frequent difficulty falling asleep. In this case, somatized tension is manifested by awareness of the heartbeat.

Correct identification of the underlying disorder is often difficult. Differentiating primary insomnia from generalized anxiety disorder is the most challenging differential diagnosis in insomnia. When anxiety is pervasive, generalized anxiety disorder is the more likely diagnosis. Primary insomnia is more likely when the individual is focused on the inability to sleep. Differentiating depression from primary insomnia is also difficult as patients often describe insomnia symptoms more accurately than their mood disturbance. Indeed, depressed patients often seek treatment for insomnia while failing to acknowledge their depressive symptomatology. Adding to this challenge is the notion of "masked" depression in which symptoms of decreased energy and appetite predominate.

Medical or neurological disorders can cause insomnia, as discombobulation of almost any system in the body disrupts sleep. Indeed, patients with diseases affecting the nervous system, heart, liver, kidneys, gastrointestinal tract, lungs, and skin may complain of insomnia. Pain disturbs sleep, promoting insomnia. Furthermore, musculoskeletal discomfort may worsen during periods of rest. Pain from entrapment neuropathies such as carpal tunnel syndrome are typically worse at night, and headaches such as cluster headache and pain related to increased intracranial pressure or brain mass lesions can become more intense during sleep. Restless legs syndrome produces discomfort that is worse in the evening prior to sleep onset. Arthritis and other rheumatologic disorders frequently disrupt sleep by increasing nighttime pain and stiffness.

The clinician may uncover physical exam findings in patients with insomnia. Hyperalert individuals demonstrate mild tachycardia, a rapid respiratory rate, or cold hands. These individuals are easily distracted or startled and may seem anxious during the interview. The clinician should recognize signs of obstructive sleep apnea, such as a narrow airway or obesity, since these too can present as insomnia. Signs of Cushing's syndrome (a round face and buffalo hump) or hyperthyroidism (tachycardia and excessive sweating) are important clues to an endocrinological contribution. A thorough neurological examination is important to rule out sleep-disrupting lesions. This exam should assess cognition, mood, and affect as well as motor and sensory systems. Clinicians can utilize the Mini Mental Status Exam and Minnesota Multiphasic Personality Inventory to identify cognitive, personality, or affective issues.

Further diagnostic testing is sometimes necessary to rule out endocrine disorders such as thyroid or adrenal disease. Occasionally, low iron or B12 levels contribute to the patient's complaints. A sleep diary is helpful as it provides a more uniform and dynamic collection of information regarding the patient's sleep. A sample diary is shown in Table 12. One to two weeks

Table 12 Sample Sleep Diary

Complete in the morning for the previous night		
Date	2/14	2/15
Bedtime	11 PM	10 PM
Rise time	7 AM	7 AM
Estimated time to fall asleep	1 hr	2 hr
Estimated number of awakenings and total time awake	4 times, 3 hr	5 times, 2 hr
Estimated amount of sleep obtained	4 hr	5 hr
Naps	None	None
Medications	None	None
Rate how you feel today 1 = very tired 2 = somewhat tired 3 = somewhat alert 4 = wide awake	1	2

of daily sleep diaries help reveal the patient's sleep pattern, providing a snapshot of the patient's interpretation of his or her sleep and guiding treatment. Be advised that the sleep diary is subjective and that patients may not accurately estimate the amount of time awake during the night. This common occurrence is not a deliberate attempt to mislead the clinician but rather a result of insomnia patients underestimating their total sleep time. Polysomnography is not routinely recommended by the American Academy of Sleep Medicine for the evaluation of insomnia. Indeed, most of the relevant information is obtained in the history. However, polysomnography is recommended when patients are suspected of having obstructive sleep apnea or medically intractable insomnia (Table 13).

Distinguishing primary insomnia from other sleep disorders is often challenging. For example, consider the case of a 50-year-old female who presented with the complaint of sleep maintenance insomnia. Her symptoms were present for 10 years and she was unable to recall a precipitating event.

Table 13 Indications for Polysomnography in the Evaluation of Insomnia

- Clinical suspicion for another sleep disorder that requires polysomnography for diagnosis
  - Obstructive sleep apnea
  - Periodic limb movement disorder
  - Narcolepsy
  - Abnormal behaviors during sleep
- Treatment refractory insomnia (failed three medication trials)

She had seen several clinicians and specifically denied depression and anxiousness. She described herself as a "Type A personality," feeling this contributed to her career success. She felt that she had lost control of her sleep and her symptoms of insomnia resulted in daytime fatigue. She denied daytime sleepiness and was unable to fall asleep during attempted daytime naps. The history was negative for psychiatric or medical conditions that contribute to insomnia. She was divorced and did not have a bed partner. She denied snoring and the history did not suggest other sleep disorders. She described learned sleep preventing associations and somatized tension.

At subsequent appointments, she presented several weeks of sleep logs and enrolled in a cognitive–behavioral insomnia program. By the end of the 7-week course, she experienced a dramatic improvement in her sleep maintenance insomnia, although she still complained of daytime fatigue and unrefreshing sleep. A polysomnogram revealed severe obstructive sleep apnea without snoring. Continuous positive airway pressure (CPAP) therapy provided dramatic improvement in her daytime fatigue.

In retrospect, obstructive sleep apnea may have been the patient's precipitating event with the resulting insomnia leading to behavioral and cognitive changes regarding her sleep. She started spending more time in bed trying to get additional sleep and was taking multiple over-the-counter medications without success. These changes along with her untreated obstructive sleep apnea likely perpetuated her insomnia. She felt that the insomnia program was valuable, as it reduced her sleep-related anxiety. Also, she indicated that CPAP tolerance might have been difficult had she not addressed the insomnia issue first. This example reveals the challenging aspects of evaluating and managing insomnia patients. The clinician should use the history and appropriate studies to arrive at the diagnosis. Since there are many causes of insomnia, it is incumbent upon the physician to diligently identify the underlying etiology.

TREATMENT AND MANAGEMENT OF INSOMNIA

The treatment of insomnia is always guided by the underlying etiology. For example, a patient with depression and insomnia must be treated for depression first, as this may resolve the insomnia complaint. Insomnia duration also affects the approach to treatment. Because most treatment efficacy studies of insomnia were performed on patients with chronic insomnia, the following discussion will pertain to this patient population.

There are three main insomnia treatment methods: sleep hygiene improvement, cognitive–behavioral therapy, and sedative-hypnotic medications. The term "sleep hygiene" was first used by Peter Hauri (26) to provide recommendations for patients with insomnia. These guidelines were developed from his clinical observations that patients with insomnia exhibited sleep-interfering behaviors. He published the original sleep hygiene rules in

Table 14 Sleep Hygiene

- Reducing and limiting intake of caffeine, tobacco, and other stimulants to the early part of the day
- Avoiding alcohol close to bedtime
- Maintain consistent life routines, including the sleep–wake schedule, meal times, and exercise times
- Avoiding strenuous physical activity or work-related activities close to bedtime

1977, and since that time countless sleep hygiene recommendations have been developed. Table 14 provides typical sleep hygiene recommendations (27).

Core sleep hygiene rules generally address alcohol, caffeine, and exercise. Beyond this, there exists a lack of consensus as to what constitutes good hygiene. As a result, the efficacy of improved sleep hygiene on insomnia is difficult to study systematically. In fact, one is hard pressed to find two studies with the same sleep hygiene definition. Despite this lack of consensus, clinicians commonly recommend improving sleep hygiene to their insomnia patients even though this is not effective as a sole treatment for persistent insomnia (28). Indeed, the American Academy of Sleep Medicine practice parameters state that insufficient evidence is available to recommend sleep hygiene as a single therapy for chronic insomnia. Furthermore, they were unable to determine whether sleep hygiene is effective when added to other approaches. The logical question is whether clinicians should discuss and recommend sleep hygiene with their patients at all. Poor sleep hygiene is not a causal factor in the development in chronic insomnia. Rather, it likely perpetuates the disorder. Adhering to good sleep hygiene is unlikely to resolve insomnia but should be addressed as part of a comprehensive approach to the patient with chronic insomnia.

COGNITIVE–BEHAVIORAL THERAPY

In 1999, the American Academy of Sleep Medicine reviewed the published insomnia literature and found that 70% to 80% of patients improved following nonpharmacological interventions (29). Indeed, these treatments significantly reduced both sleep onset latency and wake time after sleep onset. Total sleep duration was also increased by a modest 30 minutes. Perhaps, the most important finding was the sustained improvement in sleep at six months after treatment completion. Therefore, cognitive–behavioral therapy is an indispensable aspect of successful insomnia treatment.

The Stimulus Control Method

In their work with insomnia patients, Bootzin and Nicassio (30) noted a maladaptive relationship between the sleep environment and wakefulness.

For these individuals, the bedroom became a wakeful place rather than a place to sleep. Thus, they developed the stimulus control behavioral technique to break the association between the bedroom and not sleeping (Table 15). The instructions are based on the principle of classical conditioning, which attempts to strengthen the bed as a cue for sleep. Stimulus control teaches the patient not to engage in sleep-incompatible behavior in the bedroom, thus weakening the association of the bedroom with wakefulness.

Stimulus control is somewhat counterintuitive, as many patients with insomnia gradually increase their total time in bed. Although stimulus control instructions are fairly straightforward, they are difficult to follow. Several aspects of this method are critical to success. Patients must be instructed that stimulus control will take some time to be effective. Indeed, the first several days of treatment can increase anxiety and negatively impact sleep quality. Treatment must continue consistently for one to two weeks before significant improvement will be noted. Therefore, this treatment modality should only be implemented when patients can comply consistently for two weeks. Treatment efficacy is reduced if stimulus control is attempted only on certain days or if the work schedule interferes. In these instances, therapy may actually perpetuate insomnia. Sleep diaries are helpful to monitor treatment progress.

Compliance is improved by explaining the rationale for each stimulus control instruction (Table 15). The first rule, go to bed only when sleepy, is designed to refamiliarize the patient with the concept of sleepiness. Interestingly, insomnia patients complain of fatigue rather than sleepiness. Therefore, the first rule helps the patient distinguish fatigue and other somatic complaints from sleepiness. The presence of sleepiness increases the likelihood of falling asleep and provides confidence that the patient's sleep drive is functional. The second and third rules strengthen the cue between the bed and sleep. The goal of these rules is elimination of frustration associated with lying awake in bed. They also encourage the patient to perform relaxing activities outside the bedroom, which can further reduce frustration and anxiety. The fourth rule is designed to entrain the circadian rhythm,

Table 15 Stimulus Control Instructions

- Go to bed only when sleepy
- Use the bed only for sleep and avoid other activity in bed (sexual activity being the only exception)
- Get out of bed and leave the bedroom when unable to fall asleep easily (usually within 15 to 20 min). When out of bed, engage in relaxing and pleasant activities. Return to bed only when sleepy. Repeat as often as necessary
- Set an alarm and wake up at the same time regardless of how much you slept
- Avoid daytime naps unless you take them regularly, in which case do not nap for more than 1 hr

strengthening the daily pattern of wakefulness and sleepiness. The final rule prevents a diminution of the homeostatic sleep drive and promotes a regular sleep–wake rhythm (31). Most patients with insomnia are unable to nap, but daytime sleepiness may become more significant once stimulus control is initiated. Short regular naps can improve performance and are unlikely to impact sleep–wake rhythms.

The effectiveness of stimulus control is well established. Multiple studies have evaluated this method as a single treatment or in combination with other interventions. These studies reveal that stimulus control improves sleep in patients with insomnia by established criteria when compared to controls.

Sleep Restriction Technique

Sleep restriction is another behavioral therapy originally developed by Spielman et al. (32) (Table 16). This technique increases homeostatic sleep drive and consolidates sleep. Patients reduce their time in bed to equal the amount of time they sleep as established by a sleep diary. For example, if a patient sleeps 5 hours and spends 7.5 hours in bed, the prescribed length of time in bed will be 5 hours. Time in bed should not be limited to less than 4.5 hours, even if the patient reports less sleep. Daily sleep diaries are completed and adjustments to the sleep schedule are based on the calculated sleep efficiency. Some clinicians use a sleep efficiency of 85% as a decision point to increase time in bed, while others use 90%. When the sleep efficiency is less than 85%, some advocate reducing time in bed. Regardless of the exact regimen, the key to success is a consistent total sleep time duration.

Sleep restriction has typically been evaluated in combination with other cognitive–behavioral therapy techniques, although two studies have investigated this method as a sole treatment. In these studies, this method

Table 16 Sleep Restriction Technique

Technique	Example
Determine the average amount of sleep based on a 1-week sleep log	5 hr
Restrict time in bed to equal this duration for the following week (avoid restricting to less than 4.5 hr)	2–7 A.M.
At weekly intervals, calculate sleep efficiency (SE)	SE = (total sleep time/time in bed) × 100 If SE < 90% continue current schedule If SE > 90% add 15 min to time in bed

increased sleep efficiency and decreased both sleep latency and time awake after sleep onset. As with stimulus control, sleep restriction is a challenging therapeutic modality, being both counterintuitive and anxiety provoking. The patient must be counseled that insomnia may exacerbate initially, with sleep improving in one to two weeks.

Sleep restriction is based on the theory that partial sleep deprivation increases the homeostatic sleep drive. Another factor may be at play as well. Patients with insomnia tend to underestimate their total sleep time. Thus, sleep restriction based on a patient's subjective sleep diary causes the patient to spend less time in bed than their usual total sleep time. This further increases the homeostatic sleep drive and consolidates sleep.

Relaxation Techniques

Relaxation techniques have great utility in treating insomnia (Table 17). Progressive muscle relaxation focuses the patient on sensations associated with relaxation, actively involving them in the process of reducing somatized tension. These techniques provide a positive sleep promoting behavior and reduce the focus on insomnia. For the first few weeks, individuals should practise these methods outside of bedtime. Once mastered, these techniques are implemented as part of a presleep ritual. Immediate benefit may not be apparent, but continued practice provides an important component of a comprehensive insomnia treatment regimen.

Combined Cognitive–Behavioral Treatment Programs

Cognitive therapy alone is not effective for insomnia but is useful when combined with behavioral treatments. Cognitive treatment addresses unrealistic beliefs and attitudes regarding sleep and sleep loss. For example, patients may wish to obtain a certain amount of sleep, believing they will not be rested unless they obtain this sleep. This amount may be arbitrarily determined based on the sleep of other family members or on population norms. Interestingly, patients often report never achieving this amount of sleep, even prior to the history of insomnia. Nevertheless, in efforts to obtain this

Table 17 Relaxation Techniques

- Progressive muscle relaxation: involves tensing and relaxing a series of muscles
- Biofeedback: frontalis muscle tension is recorded while the patient is given visual or auditory feedback. Patients are taught relaxation techniques and immediate feedback indicates degree of success
- Guided imagery: techniques providing a neutral or pleasant target on which to focus the thought process
- Diaphragmatic breathing: abdominal breathing that induces a state of relaxation

Table 18 Model 7-Week Cognitive–Behavioral Insomnia Program

Session 1:	Course introduction, sleep architecture, and physiology
Session 2:	Circadian rhythm and homeostatic sleep drive, discussion of Spielman model of insomnia, medication and substance effects on sleep, primary versus secondary insomnia
Session 3:	Insomnia and heightened physical and psychological arousal, relaxation techniques and the concept of scheduled worry time
Session 4:	Stimulus control and sleep restriction, hypnotic medication taper
Session 5:	Cognitive restructuring including case examples of patients with insomnia. Identify cognitive changes that occur
Session 6:	Mindfulness practice that involves being an impartial witness to one's experience
Session 7:	Course summary and relapse prevention

increased amount of sleep, they perpetuate their insomnia by spending increased amounts of time in bed. Cognitive restructuring identifies and changes maladaptive beliefs regarding sleep. Combined cognitive and behavioral treatments for insomnia are administered in weekly sessions over six to eight weeks. A model program is outlined in Table 18. Studies examining the effectiveness of cognitive–behavioral therapy reveal positive outcomes, although the relative effect of each intervention has not been established.

PHARMACOLOGICAL TREATMENT OF INSOMNIA

The pharmacological treatment of insomnia is challenging. Many patients present with chronic insomnia and until recently there have been no FDA-approved medications for this form of insomnia (eszopiclone was recently approved for the treatment of chronic insomnia). Establishing the diagnosis is important when considering the pharmacological treatment of insomnia. In secondary insomnia, the clinician should treat the underlying condition and then re-evaluate the insomnia symptoms. For example, a patient with sleep-onset insomnia and a history of restless legs syndrome should be treated for restless legs with the hope of resolving the insomnia complaint. This is also the case for medical conditions such as congestive heart failure, depression, and chronic pain.

Persistent secondary insomnia or primary insomnia should be approached with a combination of pharmacological treatments and cognitive–behavioral therapy. General guidelines regarding medications are listed in Table 19. Medication selection is guided by the clinical scenario, with the primary focus on treating specific causes and the secondary focus on treating symptoms (33). Table 20 outlines the pros and cons of medications commonly used for insomnia (34).

Table 19 General Guidelines for Insomnia Medications

- Use lowest effective dose
- Use intermittent dosing if clinically effective
- Prescribe medications for short-term use, then re-evaluate
- Discontinue medications gradually if long-term use is present
- Medications with shorter elimination half-lives are less likely to result in sedation the following day

Regarding combination treatment for insomnia, a recent study in the elderly found that pharmacological therapy and cognitive–behavioral therapy, either alone or in combination, were more effective than placebo at the 8-week post-treatment assessment (Fig. 2) (35). Interestingly, subjects treated with cognitive–behavioral therapy alone reported the most sustained improvement in insomnia symptoms over time. The combined pharmacotherapy/cognitive–behavioral therapy group also had sustained improvement, although less than cognitive–behavioral therapy alone. Subjects treated with pharmacotherapy alone demonstrated less sustained improvement than the placebo group. Overall, cognitive–behavioral treatment, singly or combined, was rated by subjects, significant others, and clinicians as more effective than drug therapy alone, and subjects were more satisfied with the cognitive–behavioral approach.

This study demonstrated the importance of cognitive–behavioral therapy for insomnia in the elderly. One would expect this finding to be applicable to younger populations. Although medications still play an important role, the optimal timing and duration of therapy has not been established.

CLINICAL FOLLOW-UP OF INSOMNIA PATIENTS

The clinical follow-up of patients with insomnia is best determined on a case-by-case basis. Patients with severe nighttime symptoms or daytime dysfunction should be followed regularly until a stable treatment regimen has been implemented. A reasonable approach is presented in Table 21.

CONCLUSION

Insomnia is a common patient complaint that challenges even the most experienced clinicians. A thorough history and physical exam is crucial to arriving at an accurate diagnosis. Only after the correct diagnosis has been established should treatment be initiated. Cognitive–behavioral therapy results in significant, sustained symptom improvement. The non-benzodiazepine sedative-hypnotic medications (zolpidem, zaleplon, eszopiclone) have greatly

Table 20 Current Medication Options for Insomnia

Medication™	Mechanism of action	Pros	Cons
Trazodone (Desyrel)	Sedating antidepressant	Improves subjective and objective measures of insomnia in patients with major depression and insomnia	Lack of data to support use for insomnia in nondepressed patients
		Treats insomnia secondary to antidepressant medications	Risks of priapism and cardiotoxicity
		Low cost	May cause residual sedation
Diphenhydramine (Benadryl)	Sedating H1 antihistamines	Available over the counter	Lack of data to support its use for insomnia
Hydroxyzine (Atarax, Vistaril)		Low cost	Adverse effects include cognitive impairment, anticholinergic effects, and daytime sedation
			Tolerance may develop with repeated use
			Medication interactions
Melatonin	Pineal hormone	Low incidence of side effects other than sedation	Not well studied in clinical trials
		Effective in jet lag and circadian rhythm disorders	Effect of chronic usage unknown
		Significantly greater sleep efficacy versus placebo in a single study of chronic insomnia in the elderly	

Benzodiazepines Clonazepam (Klonopin) Diazepam (Valium) Lorazepam (Ativan) Temazepam (Restoril) Triazolam (Halcion)	Binds to benzodiazepine (BZ) receptors Modulates GABA activity at GABA A receptors Nonselective affinity for BZ1, BZ2, and BZ3 subtypes	Decreases sleep latency and decreases frequency and duration of awakenings Increases total sleep time Low cost Elimination half-life varies allowing clinician to pick appropriate medication for individual patient. For example: Triazolam: rapid onset, short elimination half-life Temazepam: intermediate onset of action and elimination half life	Residual sedation (hangover effect), sleepiness, and impaired daytime performance are related to higher dose and longer elimination half-life Decrease slow-wave sleep and REM sleep Anterograde amnesia and cognitive impairment related to higher dose Rebound insomnia Dependence (withdrawal syndrome) Muscle relaxation, anxiolytic, and anticonvulsant properties of benzodiazepines are not desired in the treatment of primary insomnia Schedule IV controlled substances Data supporting use as hypnotic is from short-term studies (at most 5 weeks duration)

(*Continued*)

Table 20 Current Medication Options for Insomnia (*Continued*)

Medication™	Mechanism of action	Pros	Cons
Non-benzodiazepine hypnotics Zolpidem (Ambien) Zaleplon (Sonata) Eszopiclone (Lunesta)	Preferential binding to BZ1 receptor	Effective treatment of insomnia Reduced sleep latency and number of awakenings Increased total sleep time Preservation of sleep architecture Low incidence of rebound insomnia Low incidence of tolerance and withdrawal symptoms Low abuse potential Esczopiclone has indication for long-term use in patients with chronic insomnia Can be taken at the beginning of the night or in the middle of the night depending on the elimination half-life Can be coadministered in depressed patients on SSRIs with secondary insomnia Intermittent dosing is effective	May cause following day sedation Duration may not be long enough in some patients Schedule IV controlled substance Higher cost Longest placebo-controlled study was only 5 weeks for currently approved medications (Zolpidem and Zaleplon)

Note: Published data for six months of therapy available for eszopiclone.
Abbreviations: SSRI, selective serotonin reuptake inhibitors; REM, rapid eye movement; GABA, gamma amino butyric acid.

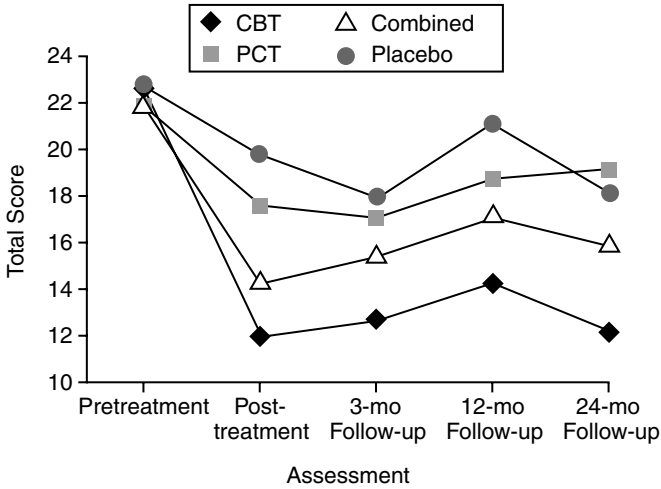


Figure 2 Pretreatment, post-treatment, and follow-up changes in total scores for the Sleep Impairment Index, a seven-item scale that yields a quantitative index of insomnia severity. Higher scores indicate more severe insomnia. *Abbreviations*: CBT, cognitive–behavioral therapy; PCT, pharmacotherapy. *Source*: From Ref. 35.

improved insomnia treatment due to their improved safety and low side-effect profiles. The ideal duration of use of these medications has yet to be established. Combination therapy can be utilized in patients who are refractory to a single treatment modality.

Table 21 The Clinical Approach and Follow-Up of the Insomnia Patient

- Always treat the primary condition first in cases of secondary insomnia
- Use a similar approach to insomnia complaints in treatment refractory secondary insomnia patients and primary insomnia patients
- Utilize sleep restriction and stimulus control methods in appropriate patients. In apprehensive patients, use these methods only during cognitive–behavioral therapy
- Use sedative-hypnotic medications when appropriate, such as with severe insomnia
- Discuss cognitive–behavioral therapy and enroll the patient in a 7-week program, taper hypnotics if possible during this program and determine follow-up at the end of the program
- Use sleep diaries to track treatment efficacy
- Long-term follow-up is dictated by symptom severity, severe insomnia patients should be seen 1 to 2 weeks after initiation of treatment

REFERENCES

1. Leger D, Guilleminault C, Bader G, Levy E, Paillard M. Medical and socio-professional impact of insomnia. Sleep 2002; 25(6):625–629.
2. Benca RM. Consequences of insomnia and its therapies. J Clin Psychiatry 2001; 62(suppl 10):33–38.
3. Walsh JK, Engelhardt CL. The direct economic costs of insomnia in the United States for 1995. Sleep 1999; 22(suppl 2):S386–S393.
4. Stoller MK. Economic effects of insomnia. Clin Ther 1994; 16:873–897.
5. Chilcott LA, Shapiro CM. The socioeconomic impact of insomnia. An overview. Pharmacoeconomics 1996; 10(suppl 1):1–14.
6. Ancoli-Israel S, Roth T. Characteristics of insomnia in the United States: results of the 1991 National Sleep Foundation survey. I. Sleep 1999; 22(suppl 2):S347–S353.
7. Simon GE, Vonkorff M. Prevalence, burden, and treatment of insomnia in primary care. Am J Psychiatry 1997; 154:1417–1423.
8. Smith MT, Perlis ML, Park A, et al. Comparative meta-analysis of pharmacotherapy and behavior therapy for persistent insomnia. Am J Psychiatry 2002; 159:5–11.
9. Shochat T, Umphress J, Israel AG, Ancoli-Israel S. Insomnia in primary care patients. Sleep 1999; 22(suppl 2):S359–S365.
10. Ford DE, Kramerow DB. Epidemiologic study of sleep disturbances and psychiatric disorders: an opportunity for prevention? JAMA 1989; 262:1479–1484.
11. Ishigooka J, Suzuki M, Isawa S, Muraoka H, Murasaki M, Okawa M. Epidemiological study on sleep habits and insomnia of new outpatients visiting general hospitals in Japan. Psychiatry Clin Neurosci 1999; 53:515–522.
12. Ohayon MM, Cualet M, Lemoine P. Comorbidity of mental and insomnia disorders in the general population. Compr Psychiatry 1998; 39:185–197.
13. Ohayon MM, Roth T. What are the contributing factors for insomnia in the general population? J Psychosom Res 2001; 51:745–755.
14. Spielman AJ, Caruso LS, Glovinsky PB. A behavioral perspective on insomnia treatment. Psychiatr Clin North Am 1987; 10:541–553.
15. Stepanski E. Etiology of insomnia. In: Lee-Chiong TL, Sateia M, Carskadon M, eds. Sleep Medicine. Philadelphia: Lippincot Williams & Wilkins, 2002:161–168.
16. Bonnet MH, Arand D. Hyperarousal and insomnia. Sleep Med Rev 1997; 1: 97–108.
17. Bonnet M, Arand D. 24-Hour metabolic rate in insomniacs and matched normal sleepers. Sleep 1995; 18:581–588.
18. Breslau N, Roth T, Rosenthal L, Andreski P. Sleep disturbance and psychiatric disorders: a longitudinal epidemiological study of young adults. Biol Psychiatry 1996; 39:411–418.
19. Ford DE, Cooper-Patrick L. Sleep disturbances and mood disorders: an epidemiologic perspective. Depress Anxiety 2001; 14:3–6.
20. Roehrs T. Transient and short-term insomnias. In: Kryger MH, Roth T, Dement WC, eds. Principles and Practices of Sleep Medicine. 3rd ed. Philadelphia, PA: W. B. Saunders Company, 2000:624–632.
21. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Text Revision. Washington, D.C.: American Psychiatric Association, 2000.

22. American Sleep Disorders Association. The International Classification of Sleep Disorders, Revised: Diagnostic and Coding Manual. Rochester, MN: American Sleep Disorders Association, 1997.
23. Zorich F, Walsh J. Evaluation and management of insomnia: an overview. In: Kryger MH, Roth T, Dement WC, eds. Principles and Practices of Sleep Medicine. 3rd ed. Philadelphia, PA: W. B. Saunders Company, 2000:615–623.
24. Chesson A, Hartse K, Anderson WM, et al. Practice parameters for the evaluation of chronic insomnia. An American Academy of Sleep Medicine report. Standards of Practice Committee of the American Academy of Sleep Medicine. Sleep 2000; 23(2):237–241.
25. National Heart, Lung, and Blood Institute Working Group on Insomnia. Insomnia: Assessment and Management in Primary Care. Bethesda, MD: National Heart, Lung and Blood Institute; September 1998. NIH Publication No. 98–4088.
26. Hauri P. Primary insomnia. In: Kryger MH, Roth T, Dement WC, eds. Principles and Practices of Sleep Medicine. 3rd ed. Philadelphia, PA: W. B. Saunders Company, 2000:633–639.
27. Hauri P. Current Concepts: the Sleep Disorders. Kalamazoo, MI: The Upjohn Company, 1977.
28. Stepanski E, Wyatt J. Use of sleep hygiene in the treatment of insomnia. Sleep Med Rev 2003; 7:215–225.
29. Chesson A, Anderson WM, Littner M, et al. Practice parameters for the nonpharmacologic treatment of chronic insomnia. An American Academy of Sleep Medicine report. Standards of Practice Committee of the American Academy of Sleep Medicine. Sleep 1999; 22(8):1128–1133.
30. Bootzin RR, Nicassio PM. Behavioral treatments for insomnia. In: Hersen M, Eissler R, Miller P, eds. Progress in Behavior Modification. Vol. 6. New York, NY: Academic Press, 1978:1–45.
31. Manber R, Kuo T. Cognitive–behavioral therapies for insomnia. In: Lee-Chiong TL, Sateia M, Carskadon M, eds. Sleep Medicine. Philadelphia: Lippincot Williams & Wilkins, 2002:177–186.
32. Spielman AJ, Saskin P, Thorpy MJ. Treatment of chronic insomnia by restriction of time in bed. Sleep 1987; 10:45–56.
33. Kupfer D, Reynolds C. Current concepts: management of insomnia. N Engl J Med 1997; 336(5):341–346.
34. Mendelson W. The treatment of chronic insomnia: drug indications, chronic use and abuse liability. Summary of a 2001 New Clinical Drug Evaluation Unit Meeting Symposium. Sleep Med Rev 2004; 8:7–17.
35. Morin CM, Colechhi C, Stone R, Brink D. Behavioral and pharmacological therapies for late life insomnia. JAMA 1999; 281:991–999.

4

Restless Legs Syndrome and Periodic Limb Movement Disorder: Nightwalkers

Richard P. Allen

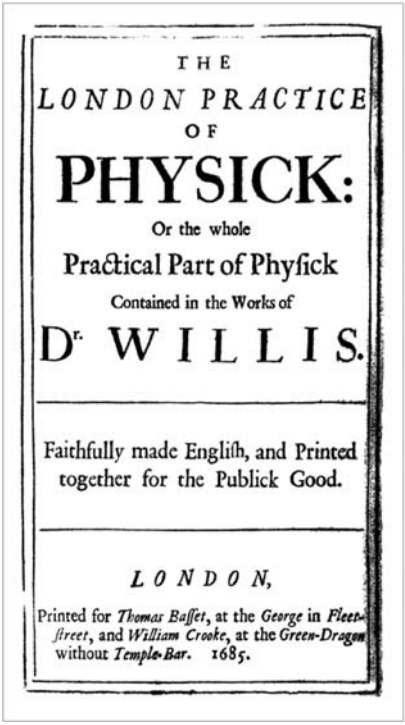
Department of Neurology, Johns Hopkins University School of Medicine,
Johns Hopkins Center for RLS,
Baltimore, Maryland, U.S.A.

Symptoms	***Diagnoses***
Urge to move the legs: • *Usually associated with uncomfortable or unpleasant sensations* • *Occurring when resting or sedentary* • *Worse at night* • *Relieved by movement* *RLS and PLMD do not produce sleepiness per se; rather, fatigue and lack of energy* *Nocturnal movements noticed by a bed partner*	*Restless legs syndrome* *Periodic limb movement disorder*

INTRODUCTION

The restless legs syndrome (RLS) was first described in the medical literature by Willis (1) in classical Latin over 300 years ago. His account of an RLS case was included in the posthumous publication of an English translation of his works (2) and aptly details the basic clinical features of the disease (Fig. 1). Despite this early recognition, the illness received little attention and was regarded a psychiatric disorder (3) until the seminal work by Ekbom (4) reviewing 127 cases and providing 53 case reports. Ekbom struggled to name the condition, and after trying "irritable legs," he settled on the term "restless legs," which is now the accepted term for this condition. While Willis emphasized the observed movements, Ekbom emphasized the peculiar sensations accompanying these movements. Both describe a condition brought on by rest, not occurring during movement, and worse at night.

Following Ekbom, there was little attention paid to RLS. In contrast, the discovery of periodic limb movements during sleep (PLMS) garnered considerable attention during the initial development of sleep medicine. These movements, initially misnamed "nocturnal myclonus" by Symonds (5)



THE
LONDON PRACTICE
OF
PHYSICK:
Or the whole
Practical Part of Phyſick
Contained in the Works of
Dr. WILLIS.

Faithfully made Engliſh, and Printed together for the Publick Good.

LONDON,
Printed for Thomas Baſſet, at the George in Fleet-ſtreet, and William Crooke, at the Green-Dragon without Temple-Bar. 1685.

Wherefore to some, on being a bed, they **betake themselves to sleep**, presently in the **arms and legs**, leaping and contractions of the tendons, and so great a restlessness and tossings of their members ensue that the diseased are **no more able to sleep than if they were in the place of the greatest torture.**

The Lady Of Quality in the night was hindered from sleep by reason of those spasmodic affects which came upon her as she was upon the point of rest; nor indeed was she able to sleep all Night, unless she took first a pretty good dose of Laudanum.

Willis 1685

Willis is noted for describing the circle of Willis blood vessels in the base of the brain and also the first to find sugar in urine of diabetics. He was a Don at Oxford and had a very successful practice in London.

Figure 1 The first known medical description of restless legs syndrome.

and identified by Lugaresi et al. (6) as occurring with RLS, were so pronounced on many sleep recordings that they were viewed as a separate disorder. Thus, the diagnosis of a periodic limb movement disorder (PLMD), characterized as PLMS occurring with insomnia or daytime sleepiness, became common in the sleep community while RLS was underappreciated (7). This situation changed dramatically with the discovery of dopamine treatment for RLS (8) and the development of the international restless legs syndrome study group. This group made the first effort to produce a modern consensus diagnostic standard for RLS (9), which has subsequently been updated and revised at a National Institutes of Health consensus workshop providing the current diagnostic criteria for RLS (10). The modern diagnostic criteria emphasizes the sensori-motor aspects of the disorder, noting the cardinal symptom as a strong urge to move the legs usually, but not always, accompanied by other sensory feelings in the legs. In this chapter, we define and discuss in detail the diagnosis and treatment of RLS and PLMD.

DISEASE DEFINITIONS

Confusion exists regarding commonly used terms in RLS and PLMD. Table 1 provides the current definitions for each of the basic terms used in working with these disorders. A number of common mistakes are made with these definitions. First, the PLM period length is measured from movement onset-to-onset as opposed to the intermovement interval from movement offset-to-onset. Always record the period or onset-to-onset duration. Second, the definition of PLMD requires that the PLMS do not occur due to other

Table 1 Basic Definitions in RLS and PLMD

- SIT: the subject sits upright (45° angle) in bed with legs stretched out staying awake in a lighted room with no external stimulation and is instructed to try not to move the legs. The test lasts 60 min. Electroencephalography and leg movements are recorded
- PLM: characteristic limb movements (0.5–5 or 10 sec duration) recurring periodically (every 5–90 sec) in a series (four or more) in any sleep or wake state
- PLMS: PLM in sleep with a duration of 0.5–5 sec
- PLMW: PLM in wake with durations of 0.5–10 sec (either part of a nocturnal polysomnogram or during the SIT)
- RLS: a clinical syndrome diagnosed by history based on the clinical presentation. Both PLMS and PLMW are nonspecific motor signs of RLS
- PLMD: a sleep disorder in which PLMS (usually >5/hr of sleep) are associated with a sleep dysfunction that cannot be otherwise explained

Abbreviations: SIT, suggested immobilization test; PLM, periodic limb movements; RLS, restless legs syndrome; PLMD, periodic limb movement disorder.

sleep disorders including RLS. Therefore, RLS includes PLMS but excludes PLMD, and a patient with RLS and coexistent PLMS cannot be diagnosed with PLMD.

The suggested immobilization test (SIT, Table 1) is a diagnostic test that should last 60 minutes. Quickly awaken any patient who falls asleep, but do not extend the time of the test. The periodic limb movements in wake (PLMW) data should be taken from the wake portion of the SIT excluding any, hopefully brief, sleep periods. PLMW from the nocturnal polysomnogram should include the movements prior to sleep onset as well as those during wake after sleep onset.

RESTLESS LEGS SYNDROME

Diagnosis

The International Classification of Sleep Disorders-2 (ICSD-2) diagnostic criteria for RLS mirror those developed by consensus at a recent National Institutes of Health RLS workshop (10). All four defining features (Table 2) must be present to diagnose RLS. The first diagnostic criterion describes the basic symptom of RLS as an urge to move focused on the legs. Other simultaneous sensations may involve a sense of moving or dynamic unpleasant disturbance deep within the leg. Since these feelings and urges have no common reference in normal experience, the subject often describes it by analogy with some examples including a ''creepy, crawly feeling'' or a sensation of ''soda pop in the veins.'' Most patients do not, report pain with their RLS, although some do experience this sensation. Indeed, Ekbom reported pain in 15 out of 127 cases, and recent studies of clinical populations report pain occurring in a third to 56% of cases (11). The report of pain complicates the differential diagnosis (Table 3).

Table 2 RLS Diagnosis: Essential Criteria

1. An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs (focal akathisia of the legs)
2. The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity, such as lying or sitting (quiescegenic)
3. The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues (movement responsive)
4. The urge to move or unpleasant sensations are worse in the evening or night than during the day, or only occur in the evening or night (nocturnal).

Source: From International Classification of Sleep Disorders-2 and Ref. 10.
Abbreviation: RLS, restless legs syndrome.

Table 3 Differential Diagnosis of RLS

Alternate diagnosis	Critical feature not consistent with RLS
Positional discomfort	Does not occur in all rest positions Relief by a single position change, not activity
Drug (neuroleptic) induced akathisia	Not focal on legs Starts after drug use
Painful legs and moving toes	Not nocturnal or quiescegenic
Pain syndromes	Not quickly relieved by movement
Sleep starts	Not quiescegenic Limited to sleep onset
Nocturnal leg cramps	Not quickly relieved by movement
Anxiety/psychiatric states	Not relieved by movement Related to stress

Abbreviation: RLS, restless legs syndrome.

The other three diagnostic criteria define conditions that alter the expression of the RLS symptoms. The quiescegenic aspect of RLS involves symptom onset not only when resting with decreased motor activity but also resting with decreased mental activity. Indeed, the greater the sense of confinement and the greater the degree of ennui reducing mental activity, the more likely RLS symptoms will occur. A good clinical question to ask patient, is how they would react to being confined and unable to move when they have the symptoms.

Immediate relief with movement persisting as long as the movement continues is a required feature of the diagnosis. Responding to the urge to move, rather than the exercise of movement, relieves the symptoms. Thus, patients get relief from mentally engrossing tasks such as knitting, intense work efforts, computer activities, and arguments. The more mentally engrossing a task, the more likely symptoms will be relieved. Eating can also resolve RLS symptoms. For example, slowly eating popcorn one kernel at a time has been reported to benefit patients when attending a film.

Restless legs symptoms generally start in the afternoon or evening and become progressively worse, reaching a maximum severity around the nadir of the circadian variation in core temperature. After this low point (between 2 and 5 A.M.) a rapid relief of symptoms occurs. Even the most severely affected RLS patients report great relief from symptoms in the morning (Fig. 2). Assessing the circadian pattern often confuses the quiescegenic and circadian effects, as they tend to occur simultaneously. A way to separate the two involves asking patients how long they can sit still symptom free at various times during the day. Sitting at breakfast is almost always minimally distressing, while sitting in the evening is often difficult. Some patients find relief with sleep, as they either do not experience the sensory symptoms

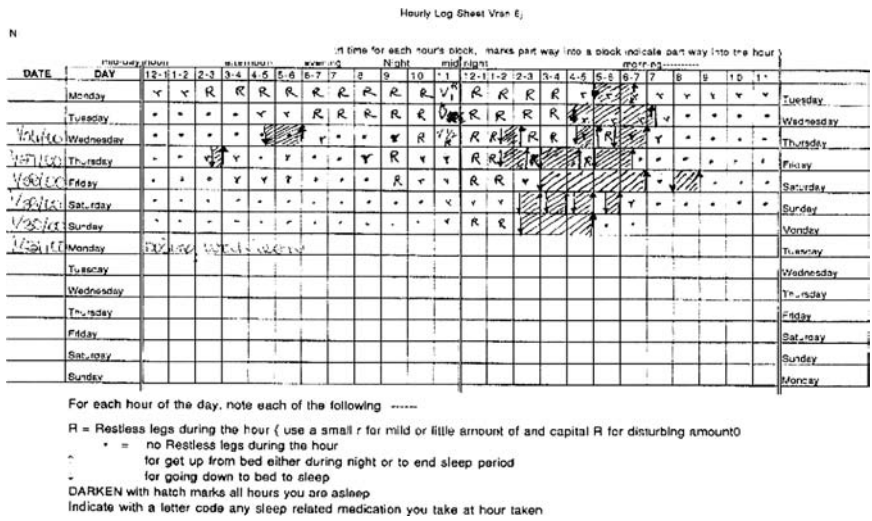


Figure 2 A week in the life of a restless legs syndrome patient. R, a disturbing urge to move; r, a milder annoying urge to move; ↓, down to bed; ↑, out of bed; darkened hatch marks indicate sleep time. Note the very short sleep times and the marked absence of symptoms in the morning (*right side of the sheet*).

or the symptoms are so mild they do not awaken. Therefore, mild patients may only experience RLS symptoms when sitting at length in the late afternoon or evening.

Differential Diagnosis

The differential diagnosis of RLS includes several medical disorders and some mimics. Medical disorders confused with RLS include painful legs and moving toes, peripheral neuropathy, arthritis, and various pain syndromes (Table 3). The neuropathies can be difficult to separate from RLS since the sensory experiences of this disorder overlap with those occurring with neuropathy. For example, Ekbom described the classic neuropathic symptom of burning feet as occurring in some RLS patients devoid of neuropathy. RLS patients can also have a comorbid neuropathy that makes separation of the RLS and neuropathic symptoms difficult, complicating diagnosis and treatment. Fortunately, there are two features of RLS that separate these conditions. First, RLS is immediately relieved by movement. Second, RLS does not involve numbness or a loss of sensation. Indeed, these latter symptoms indicate a disorder other than RLS, presumably a neuropathy.

Most medical conditions confused with RLS do not produce a true urge to move the legs. Similarly, the common "mimics" of RLS, including positional discomfort, fidgets, and leg cramps, cause conditions in which leg

movements relieve the symptoms without producing a primary urge to move. In these conditions, patients discover their legs moving rather than noting a compelling need for leg movement, a critical distinction separating most mimics from RLS. Leg cramps are often confused with RLS, although most patients can make this distinction. Cramping involves a painful hardening of the muscles relieved by stretching the involved muscle rather than simple movement. Positional discomfort may be more difficult to differentiate. The clinician should be aware that RLS occurs with rest, usually in the evening, regardless of body position. Symptoms occurring only with a fixed body position such as leg crossing are not RLS.

Phenotypes and Genetics

Restless legs syndrome occurs as both a primary and secondary condition with the secondary form of the disease occurring as a result of another medical condition. Seven percent to 60% of patients with renal failure on dialysis (12–15) have RLS, which can completely resolve following transplantation (16). Similarly, RLS occurred in 36% of pregnant women in an Italian study (17) and in 32% of patients with iron deficiency anemia (18). The RLS usually resolves when the secondary cause is corrected. RLS has been associated with some types of neuropathy, particularly Charcot-Marie-Tooth disease (CMT) type 2 but not in CMT type 1 (19), and cryoglobulinemic neuropathy. This suggests that the sensory more than motor disturbances occurring with neuropathy contributes to the occurrence of RLS (20). Interestingly, surveys of clinical patients with neuropathy failed to show an elevated prevalence of RLS (21), suggesting that while sensory neuropathy may precipitate or exacerbate RLS, it is not a true secondary cause of the disorder.

Primary RLS starts at any age but tends to have two patterns of onset, early and late in life. Statistical analyses of RLS age-of-onset distributions suggest a combination of two normal distribution patterns with different means (Fig. 3). This observation led to establishing two phenotypes of RLS based on age-of-onset of symptoms. *Early-onset RLS* with symptoms starting before age 45 demonstrates a high frequency of familial occurrence and a slow progression of symptoms. *Late-onset RLS* starting after age 45 includes more sporadic cases involving rapid symptom worsening over 1–5 years followed by symptom stability (22). First-degree relatives of RLS patients have a greater risk of developing the disorder than the general population. In one study, this risk was 6.7 times greater for relatives of an early-onset RLS patient and 2.9 times greater for relatives of late-onset patients. The critical age-of-onset of symptoms for separating the early and late onset phenotypes remains uncertain. One analysis suggested that 30 years provided the best separation (23), but that study used the average age-of-onset for all affected members in a family. The age-of-onset should

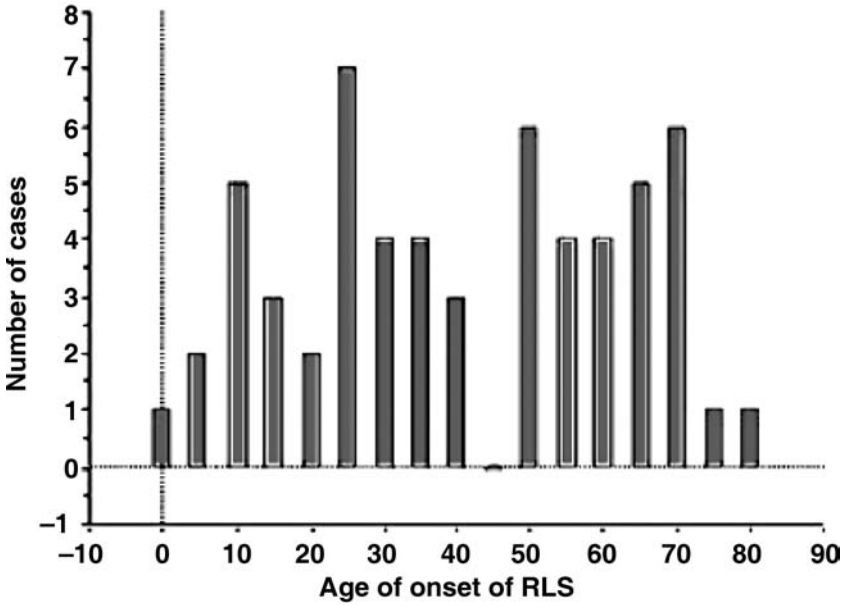


Figure 3 RLS sage-of-onset distribution for a sample of patients diagnosed at a major sleep center. The pattern is best described as the combination of two normal distributions, one for the earlier onset of RLS symptoms and the other for later onset with a break between the two occurring at about age 45. *Abbreviation*: RLS, restless legs syndrome. *Source*: From Allen et al., Sleep Med 2002; 3:S3–S7.

be considered a marker helping identify two different disease conditions. The earlier the onset the more likely the condition represents the early-onset form of RLS.

Three linkage studies looking at families with a large number of affected members have now reported significant LOD scores (>3.0) on three different chromosomes. A French Canadian family demonstrated a linkage on chromosome 12q (D12S1044-D12578), pointing to an autosomal recessive mode of inheritance (24). Evaluation of an Italian family found a linkage on chromosome 14q (D14S70-D14S1068) with an autosomal dominant mode of inheritance (25). Lastly, a model-free evaluation of 15 large U.S. families identified a susceptibility locus on chromosome 9p24–22, which also revealed an autosomal dominant inheritance pattern. Several candidate genes have been evaluated, including those associated with dopamine, and none has been found to be related to RLS (26). Indeed, despite these and other efforts, to date no specific gene has been linked to RLS. Although RLS has a high familial occurrence, the genetic picture indicates a complex disorder involving multiple genes interacting with each other and environmental factors (27). Environmental factors are likely significant determinants of the disorder.

Pathophysiology

Transcranial magnetic stimulation (28,29) as well as reflex (30–32) and electrophysiological studies (33,34) all demonstrate a subcortical pathology for RLS that increases spinal cord excitability by both reducing nighttime inhibition and disinhibiting the motor cortex (29). The subcortical abnormality was assumed to involve dopaminergic systems since levodopa produces an initial dramatic clinical reduction in symptoms in virtually all cases (35). Moreover, dopamine antagonists exacerbate RLS symptoms. However, little data aside from pharmacological studies support a primary dopaminergic abnormality in RLS. A cerebrospinal fluid (CSF) study was negative (36) and striatal dopamine imagining studies have produced mixed results. A positron emission tomography (PET) study of RLS patients and controls reported decreased striatal D2 receptor binding (37) not observed in a similar smaller study (38). A single photon emission computed tomography (SPECT) study demonstrated decreased striatal D2 binding in RLS (39), although two other SPECT studies failed to find this decrease (40,41). The most consistent finding has been a decrease in striatal fluoro-L-dopa uptake found in two separate studies of RLS patients compared to controls (37,42). Whatever the dopamine abnormality, it has been difficult to demonstrate. Some believe that it involves the dopamine cell bodies in A11 that serve the spinal column. Lesions of A11 have been reported to change the activity level of rats, causing increased standing time (43). The relation of this to RLS is unclear.

An alternate view of RLS pathology comes from secondary causes of the disorder including pregnancy, end-stage renal disease, and iron deficiency. These conditions share an association with compromised iron status, suggesting that brain iron insufficiency is a primary pathology in RLS. Peripheral iron status as indicated by serum ferritin levels demonstrate an inverse relationship with RLS severity (44,45). A study of morning CSF samples found all 16 patients with RLS had either abnormally reduced ferritin or abnormally high transferrin levels or both (46). Neuroimaging for regional iron content showed reduced iron in the substantia nigra correlating with RLS symptom severity (Fig. 4) (47). Substantia nigra autopsy tissue from RLS patients compared to controls shows a decrease not only in iron content but also in H-ferritin levels (the type more common in the brain) along with increased transferrin levels. These results match those from the CSF, indicating significant iron deficiency in the substantia nigra of RLS patients (48). Further work using microlaser capture and isolation of substantia nigra dopamine cells demonstrates that these cell bodies have reduced levels of iron, H-ferritin, and the major iron transporters. A surprising finding has been decreased transferrin receptors, which should increase with iron deficiency. This decrease is thought to occur because of an unexpected but critical decrease in IRP1, one of two major iron

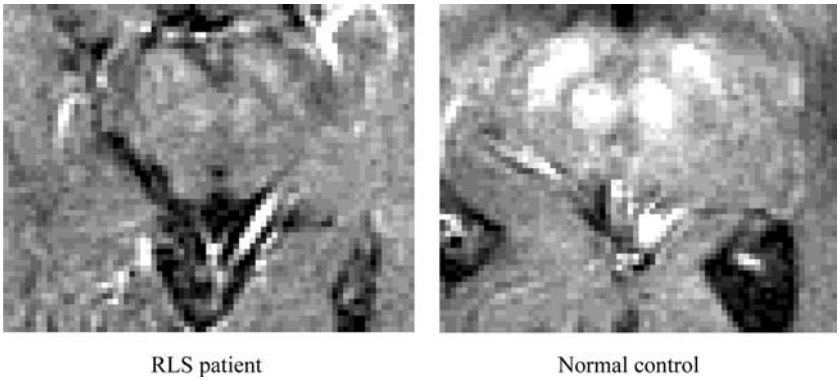


Figure 4 Magnetic resonance imaging R2* images in a 70-year-old RLS patient and a 71-year-old control subject. Much lower R2* relaxation rates are apparent in the RLS case in both red nucleus and substantia nigra. The R2* relaxation rate indicates tissue iron content. *Abbreviation*: RLS, restless legs syndrome. *Source*: From Ref. 47.

regulatory proteins in these cells. Therefore, a possible primary pathology producing brain iron deficiency, and thus RLS, may be abnormally reduced IRP1 (49).

The relationship between reduced iron and dopamine system abnormalities remains unclear. One possibility is the recently discovered relationship between iron status and THY1, a protein that stabilizes dopamine receptors. Autopsy studies show that THY1 is reduced in RLS patients as expected given the brain iron deficiency. It seems likely that brain iron deficiency affects other aspects of brain functioning and possibly other neurotransmitter systems. More research is needed in this area.

Autopsy evaluations of RLS patients found that none of the pathologies were attributed to nigral cell death, including Parkinson's disease or Lewy body dementia (48,50). However, there was an increase in tyrosine hydoxylase (TH) staining, indicating increased efforts at dopaminergic production, possibly attempting to compensate for an iron-poor environment or perhaps producing more dopamine than normal.

Iron deficiency might be a compensatory response to another dopaminergic abnormality. One way to evaluate this is by reversing the brain iron deficiency by giving large doses of intravenous (IV) iron, an approach that has provided effective treatment lasting several months in a number of RLS patients (51,52). The IV iron treatment has not yet been evaluated using double-blind, placebo-controlled methods and is only experimental at this point. This treatment has potential adverse effects that need to be carefully evaluated. Nonetheless, the excellent response to iron treatment for some patients further supports the view that brain iron deficiency represents a primary pathology for RLS.

Epidemiology: Prevalence, Risk Factors, and Comorbid Conditions

Most of the initial population-based prevalence studies of RLS failed to use the full diagnostic criteria for the disorder. Recent studies using appropriate diagnostic criteria and population-based samples (Table 4) indicate that RLS prevalence in most European or European descendant populations is 7–10%, with females affected twice as often as males. Indeed, a primary care prevalence study revealed a female-to-male ratio of two to one for early-onset RLS, with slightly more males than females among the late-onset RLS patients (53). A survey from Turkey using established techniques found a lower prevalence of about 3.2%. RLS may be primarily a northwestern European disorder, and in those populations it is one of the most common neurological disorders.

Restless legs syndrome demonstrates wide symptom variability, with some patients experiencing only mild intermittent symptoms while others have severe daily restlessness. The prevalence of clinically significant cases is about 7%. In one large population-based sample in five European countries and the United States, the prevalence of RLS occurring at least once a week was 5%, and that of clinically significant illness (defined as occurring at least twice a week and being reported as at least moderately distressing) was 2.7%. In the clinically significant cases, the prevalence remained about twice as high for females than males (3.7% vs. 1.7%) (54).

Two major environmental risk factors have been identified for RLS. First, child birth increases the risk of developing the disorder later in life, with nulliparous women believed to have no greater risk of RLS than men (55). Second, any condition producing iron deficiency increases the risk of RLS. Thus, frequent blood donating (56,57), rheumatoid arthritis (58), low-density lipoprotein apheresis (59), and gastric surgery (60) all produce significant iron deficiency and are all associated with a higher risk of RLS. Hypertension, chronic headaches, and anxiety/depression are all epidemiologically associated with RLS as well (61,62).

Table 4 Prevalence of RLS in Population-Based Studies

Study/year	Location	Method	All (%)	Men (%)	Women (%)
Berger (2004)	German	Interview	10.6	7.6	13.4
REST (2004)	Five EU countries and the USA	Questionnaire	7.2	—	—
Ulfberg (2001)	Sweden	Questionnaire	—	6.1	13.9
Sevn (2003)	Turkey	Interview	3.2	3.9	2.5

Abbreviations: RLS, restless legs syndrome; EU, European Union; USA, United States of America.

Medical Assessment—Tests and Measurements for Restless Legs Syndrome

The diagnosis of RLS is derived from subjective reports of symptoms. A carefully obtained clinical history must review in detail each of the diagnostic features and attention must be paid to the differential diagnoses (Table 3). The urge to move must be primary and not an afterthought. The quiescegenic nature of the disorder must be clear and not related to one particular body position. The relief with movement should occur fairly quickly with the start of the movement and should persist as long as the movement continues and should not be a matter of exercise or removing stiffness. The circadian pattern should be evident independent of activity level and in particular should include reduced or absent symptoms for some part of the morning. Typically, the patient describes the best sleep as occurring in the morning. Features helping confirm a diagnosis include a positive family history, a description of periodic leg movements while awake/asleep, a history of sleep disturbance, and a positive therapeutic response to a dopamine agonists or levodopa.

All RLS patients should have a serum evaluation of ferritin, % transferrin saturation, and total iron binding capacity. Iron deficiency is indicated by either a serum ferritin $>17\,\mu g/L$ or a percent transferrin saturation >20, but these values may vary depending on laboratory standards. RLS may be the only indication of iron deficiency in patients with a normal hemoglobin level. While uncommon, this will happen in a significant number of RLS cases presenting for treatment. Correcting the iron deficiency will in many cases reduce or even eliminate the RLS symptoms. A general neurological examination is recommended to identify any neuropathies. Similarly, sleep complaints should be assessed with a full sleep history to search for comorbid sleep disorders.

Restless legs syndrome severity is assessed with two validated scales. The Johns Hopkins Restless Legs Severity Scale (JHRLSS; Table 5) is a simple single-item evaluation that can be filled out retrospectively. This scale ranges from 0 to 4 and relates to the time of day that RLS symptoms usually start. It has been validated against periodic limb movements severity and sleep efficiency on polysomnography (63). Severity can also be evaluated on the International Restless Legs Syndrome Study Group scale (IRLS), which has 10 items each scored from 0 to 4, giving a range of scores from 0 to 40 (Table 6). This scale can be obtained from the Restless Legs Syndrome Foundation web site (RLS.org). Please register with MAPI research coordinator C. Anfray at Canfray@mapi.fr prior to using the instrument for research. The scores on this scale are interpreted as follows: 0–10, minimal; 10–20, mild; 20–30, moderate; and >30, severe RLS (64).

The suggested immobilization test (SIT) can help support the diagnosis or assess severity of disease (Table 7). Also helpful is a standard all-night polysomnogram with anterior tibialis and leg activity meters that record body position and periodic leg movements. For the SIT, the most accepted

Table 5 Johns Hopkins Restless Legs Syndrome Severity Scale (JHRLSS)

Score	Usual time of day when RLS symptoms start (after 12 noon)
0 (never)	No symptoms
0.5 (infrequent)	Symptoms less than daily or almost daily
1 (mild)	At bedtime and/or during the sleep period (symptoms may occur within 60 min before the usual bedtime or simply at the time of going to bed or during the night after in bed)
2 (moderate)	In the evening (6 P.M. or later). Symptoms may start at anytime between 6 P.M. and the usual bedtime (the definition of evening may need to be adjusted for patients who routinely have much later bedtimes, such as those who have an afternoon siesta)
3 (severe)	Afternoon (before 6 P.M.). Symptoms start in the afternoon and persist into the evening and night
4 (very severe)	Morning (before noon). Symptoms may start in the morning or they may be present virtually all day. There is usually a "protected period" in the mid-morning (8–10 A.M.) with few if any symptoms. Even the protected period may have symptoms for the most severe RLS, often occurring with significant RLS augmentation

Sample Standard Questions:

1. How many days in a week or month do you have RLS symptoms?
   ___per week ___ per month
2. On a usual day, what is the earliest time after 12 noon that these sensations or movements are likely to occur if you were to sit down or rest?
   ___ P.M. or ___ A.M.
   (pick any time from 12 noon in the day through the night to the early morning)

Note: Since RLS symptoms (once started) tend to persist until morning, the number of hours in the day with RLS will be about 1–6 for mild, 7–12 for moderate, and 13 or more for severe RLS on this scale.
Abbreviation: RLS, restless legs syndrome.

measure is the PLMW/hr, although a sensory score can also be obtained by asking the patient to rate at five-minute intervals the amount of discomfort over the past five minutes. Normal values for the PLMW/hr on the SIT done before the normal bedtime have not been established, but a PLMW/hr >40 on the SIT has been suggested as a standard for supporting the diagnosis of RLS (65). The best measure for RLS diagnosis from the nocturnal polysomnogram is not the PLMS but rather the PLMW during the sleep period. The PLMW/hr >15 on a standard all-night polysomnogram had the best diagnostic value of any single measure, giving about 85% accuracy

Table 6 International Restless Legs Syndrome Study Group RLS Rating Scale

Ask the patient to rate his/her symptoms for the following 10 questions. The patient and not the examiner should make the ratings; however, the examiner should be available to clarify any misunderstandings the patient may have about the questions. The examiner should mark the patient's answers on the form.

In the past week . . .
(1) *Overall*, how would you rate the *RLS discomfort in your legs or arms*?
[4]☐ Very severe
[3]☐ Severe
[2]☐ Moderate
[1]☐ Mild
[0]☐ None

In the past week . . .
(2) *Overall*, how would you rate the *need to move* around because of your RLS symptoms?
[4]☐ Very severe
[3]☐ Severe
[2]☐ Moderate
[1]☐ Mild
[0]☐ None

In the past week . . .
(3) *Overall*, how much *relief* from your RLS arm or leg discomfort did you get from moving around?
[4]☐ No relief
[3]☐ Mild relief
[2]☐ Moderate relief
[1]☐ Either complete or almost complete relief
[0]☐ No RLS symptoms to be relieved

In the past week . . .
(4) How severe was your *sleep disturbance* due to your RLS symptoms?
[4]☐ Very severe
[3]☐ Severe
[2]☐ Moderate
[1]☐ Mild
[0]☐ None

In the past week . . .
(5) How severe was your *tiredness* or *sleepiness during the day* due to your RLS symptoms?
[4]☐ Very severe
[3]☐ Severe
[2]☐ Moderate
[1]☐ Mild
[0]☐ None

In the past week . . .

(*Continued*)

Table 6 International Restless Legs Syndrome Study Group RLS Rating Scale (*Continued*)

(6) How severe was *your RLS on the whole*?
- [4]☐ Very severe
- [3]☐ Severe
- [2]☐ Moderate
- [1]☐ Mild
- [0]☐ None

In the past week . . .
(7) How *often* did you get RLS symptoms?
- [4]☐ Very often (this means 6–7 days per week)
- [3]☐ Often (this means 4–5 days per week)
- [2]☐ Sometimes (this means 2–3 days per week)
- [1]☐ Occasionally (this means 1 day a week)
- [0]☐ Never

In the past week . . .
(8) When you had RLS symptoms, how severe were they on average?
- [4]☐ Very severe (this means 8 hr or more per 24-hr day)
- [3]☐ Severe (this means 3–8 hr per 24-hr day)
- [2]☐ Moderate (this means 1–3 hr per 24-hr day)
- [1]☐ Mild (this means less than 1 hr per 24-hr day)
- [0]☐ None

In the past week . . .
(9) *Overall*, how severe was the impact of your RLS symptoms on your ability to carry out your *daily activities*, for example having a satisfactory family, home, social, school, or work life?
- [4]☐ Very severe
- [3]☐ Severe
- [2]☐ Moderate
- [1]☐ Mild
- [0]☐ None

In the past week . . .
(10) How severe was your *mood disturbance* due to your RLS symptoms—for example being angry, depressed, sad, anxious, or irritable?
- [4]☐ Very severe
- [3]☐ Severe
- [2]☐ Moderate
- [1]☐ Mild
- [0]☐ None

Source: IRLS, Investigator Version 2.2.

Table 7 Suggested Immobilization Test for RLS

- Patient instructions:
  - Lie still and avoid all voluntary movements, particularly movements of the legs and arms
- Test conditions:
  - Patients remain in bed reclined at a 45° angle with their legs outstretched
  - No external stimuli are provided
  - All time cues are removed
  - No noises are allowed during the test
  - If the patient falls asleep (30 sec epoch of any sleep stage), the technician is to immediately wake the patient
- Test duration:
  - 60 min
- Test time:
  - Usually, the hour before the normal bedtime to start sleep
  - A 10–15 min break is recommended between the end of the suggested immobilization test and the start of the polysomnography

Abbreviation: RLS, restless legs syndrome.

in making the diagnosis (Table 8). It is strongly recommended that all polysomnography recordings include an assessment of the PLMW as well as the PLMS. It should be noted that the sensitivity and specificity of these tests was evaluated against normal controls and not patients with other sleep disorders such as insomnia or narcolepsy.

Since PLMs are a primary motor sign of RLS, they are helpful for assessing changes in severity, particularly in regards to treatment. Specialized activity meters PAM-RL (IM Systems, Baltimore, Maryland, U.S.A.) provide a better assessment, given the cost and inconvenience of polysomnography or

Table 8 Sensitivity and Specificity of Sleep Laboratory Tests for RLS (100 Idiopathic RLS Patients Compared with 50 Healthy Age-Matched Controls)

Test	Measure	Sensitivity (%)	Specificity (%)
Suggested immobilization test	MDS[a] >11	82	84
Suggested immobilization test	PLMW/hr >12	62	84
Polysomnography	PLMS/hr >7	78	76
Polysomnography	PLMW/hr >15	85	91

[a]MDS refers to the average of the subjective rating of discomfort made every 5 min based on placing a marker on a 100 mm analog horizontal scale ranging from 0 (no discomfort) to 100 (extreme discomfort) (39).

Abbreviations: RLS, restless legs syndrome; PLMW, periodic limb movements during wakefulness; PLMS, periodic limb movements of sleep.

the SIT. These meters can be sent and returned by mail with instructions on how and when to wear them. They record up to five nights of data and provide movement graphs for inspection if desired (Fig. 5). This meter allows the clinician to know if the movements have resolved during sleep. Effective treatment should reduce the PLM rate in the sleep period to below 20.

Treatment Options—Algorithms

Treatment recommendations for RLS have been advanced either as evidenced-based practice parameters developed by the American Academy of Sleep Medicine (66,67), expert opinion (68), or as a consensus opinion, including one put forth by the medical advisory board of the RLS foundation (69). The recommendations here expand on the latter two approaches.

Medication Choices

As of May 2005, only the dopamine agonist ropinirole has FDA approval for RLS treatment limited to moderate to severe RLS. Therefore, all other treatment recommendations are ''off-label.'' The medicines used in RLS are divided into four classes: dopaminergic medications, opioids, antidepressants, and hypnotics. Most clinical treatment trials have focused on dopaminergic

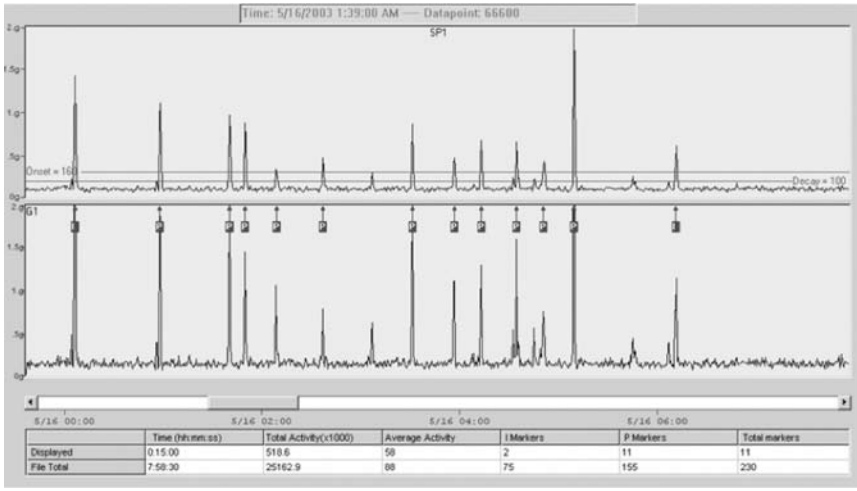


Figure 5 Leg activity meter record of leg activity data from the PAM-RL (IM Systems, Baltimore, Maryland, U.S.A.). The bottom shows the raw activity data, and the top line gives the data filtered to aid movement detection. The white P flag indicates a periodic leg movement, and the 'i' flag indicates an isolated movement. The movement amplitude is well calibrated to exclude the smaller movements, but the thresholds can be adjusted from the defaults if desired. Statistics are at the bottom for this time period and the entire night's recording.

medications (particularly levodopa, pergolide, ropinirole, and pramipexole). These medications are safe and effective for RLS and are currently considered first-line treatment. Table 9 provides the typical dose ranges for these medications. Pergolide is an ergotamine associated with rare but severe cardiac complications (70), limiting its use.

Willis (2) reported using opiates to treat RLS. Despite this long history of use, these medications have not been evaluated for safety or efficacy in RLS. Because of their abuse potential, they are considered second-line treatment for RLS. All opioids work to some degree, although there is wide interindividual variability in treatment response among the various preparations. Generally speaking, treatment response is highest for methadone and lowest for

Table 9 Usual Starting and Maximum Daily Doses of Medications Used to Treat RLS

Medication	Daily dose range (mg)	Augmentation risk
Dopamine agonists		
Pergolide (Permax®)	0.05–0.75	Mild
Pramipexole (Mirapex®)	0.125–1.5	Mild
Ropinirole (Requip®)	0.5–6	Mild
Bromocriptine (Parlodel®)	5–20	Mild
Dopamine		
Levodopa/carbidopa (Sinemet®)	25/100–75/300	Very high
Levodopa/carbidopa-CR (Sinemet CR®)	50/200	Very high
Opioids		
Propoxyphene hydrochloride (Darvocet®)	130–520	Minimal
Codeine (Tylenol #3®)	15–120	Minimal
Oxycodone	2.5–20	Minimal
Hydrocodone	5–20	Minimal
Methadone	5–30	Minimal
Tramadol (Ultram®)	50–200	High
Other: levorphanol, pentazocine, sustained release morphine (dosing uncertain)		
Anticonvulsants		
Gabapentin (Neurontin®)	300–3600	?
Carbamazepine (Tegretol®)	200–800	?
Other: valproate, lamotrigine (dosing uncertain)		
Benzodiazepines and other gaba-active hypnotics		
Clonazepam (Klonopin®)	0.5–4.0	?
Temazepam (Restoril®)	15–30	?
Triazolam (Halcion®)	0.125–0.5	?
Zolpidem (Ambien®)	5–10	?
Zaleplon (Sonata®)	5–20	?
Other: diazepam, alprazolam, nitrazepam (dosing uncertain)		

Abbreviation: RLS, restless legs syndrome.

propoxyphene. Tramadol fits loosely into the opioid class of medications and, unlike other opioids, can cause significant RLS augmentation.

The gaba-active sedative hypnotics including the benzodiazepines have not been extensively studied for the treatment of RLS. One small clinical trial of clonazepam showed efficacy equivalent to placebo (71). Although these medications improve sleep, they do not reduce the PLMS of RLS patients (72). Thus, these medications should be reserved for mild RLS patients with a chief complaint of sleep onset difficulties. The goal of these medications is not to reduce the RLS, but rather to help the patient sleep. Some RLS patients develop insomnia secondary to either dopaminergic treatment or RLS-induced sleep disruption.

In these cases, hypnotics are helpful adjunctive treatment. Generally speaking, the clinician should choose the hypnotic with the shortest half-life to mitigate unwanted residual daytime sleepiness. These medications should be used with caution in the frail elderly due to the increased fall risk they produce.

Some anticonvulsants can reduce RLS symptoms. Unlike the other medications discussed, this is a drug-specific effect not true for all medications in this class. In particular, two have been shown to be effective in double-blind trials. Carbamazepine (Tegretol®) was evaluated in the first ever large RLS treatment placebo-controlled trial (73). Despite reasonable efficacy, concern regarding adverse effects limits use of this medication. Gabapentin (Neurontin®) has demonstrated efficacy in small samples of patients with mild RLS, but it remains to be shown how well it treats severe forms of the disease. In addition, the efficacy of long-term treatment is unknown (74,75). Nevertheless, this treatment option is particularly appealing in the RLS patient with a comorbid neuropathy as it can treat both conditions. The mechanisms by which the nondopaminergic medications produce relief remain unknown. They may all depend on activation of the dopaminergic system in some manner.

Augmentation and Rebound

While all of these medications have specific adverse effects, there is one side effect that is specific for RLS. All or nearly all dopaminergic medications can worsen the underlying condition, also known as augmentation. This phenomenon has four features (Table 10), with the primary elements being onset of RLS symptoms earlier in the evening or afternoon than prior to treatment, resulting in a longer duration of symptoms. This often requires dosing the medication earlier and adding doses to cover the longer symptom duration. Severe augmentation can cause RLS symptoms to spread to the arms, trunk, shoulders, and neck and occur around the clock. In this instance, adding more dopaminergic medication can worsen the augmentation. Fortunately, the condition is reversible by discontinuing the medication. After 4–8 days off medication, the symptoms revert to their prior level of severity. Therefore, although milder augmentation can be managed by adding an earlier medication dose, the clinician must be careful to ensure that the augmentation does not worsen.

Table 10 Rebound and Augmentation from Dopaminergic Treatment of RLS

- Rebound is an end of dose effect
  - The re-emergence of symptoms at the end of a dose, typically during the night or in the morning
  - This is not dopamine specific
- Augmentation is a paradoxical worsening of symptoms during treatment when drug coverage is not in effect. Patients experience symptoms that
  - Start earlier in the day
  - Increase in severity
  - Are provoked more easily (with shorter periods of rest)
  - Spread to the arms and other parts of the body
- PLMS patients may experience their first RLS symptoms in the context of augmentation

Abbreviation: RLS, restless legs syndrome.

Augmentation occurs in up to 85% of patients on levodopa and 15–30% of patients on dopamine agonists. Indeed, severe augmentation requiring a medication change occurred in over half of patients on carbidopa/levodopa as opposed to a very small percentage of patients on dopamine agonists (76,77). Given the importance of augmentation avoidance, Table 9 provides the risk of augmentation for most of the more common medications used for RLS. The augmentation risk is so high with carbidopa/levodopa that daily use is not recommended, although intermittent use no more than four days a week is considered safe. Augmentation is not seen with opioids, although it has been observed with tramadol even at low to normal doses.

As opposed to augmentation, dopaminergic rebound involves new onset morning RLS symptoms, occurring as the therapeutic effect of the medication wears off. This "end-of-dose" or "withdrawal phenomenon" occurs with other RLS treatments as well and is rarely a significant problem. The exception is the short acting carbidopa/levodopa, which can produce rebound symptoms that disturb that last portion of the sleep period.

Iron Treatment

Oral iron treatment is indicated whenever there is iron deficiency, as indicated by either a serum ferritin >17 mcg/L or a percent transferrin saturation $>20\%$. Iron can be given orally as ferrous sulfate 325 mg taken with 200 mg Vitamin C to aid absorption. If possible, it should be given on an empty stomach three times a day. Serum iron evaluations should be repeated 6 to 8 weeks after starting therapy and at regular 6- to 12-month intervals thereafter. Once the serum ferritin reaches 50 μg/L and the percent transferrin saturation exceeds 20%, the iron should be stopped. Please note that iron repletion should be immediately stopped if the percent transferrin saturation ever exceeds 50%. Patients on iron treatment may also be started on other

medications while they wait for the iron to take effect. Doses of other medications may be reduced once the iron levels have normalized.

Intravenous (IV) iron treatment can be considered for patients with iron deficiency not corrected by oral iron treatment (at least six months) or who cannot take oral iron. These patients should be carefully evaluated to rule out sources of blood loss maintaining the iron deficiency before starting the treatment. Intravenous iron is given as a series of two or three treatments over a week. One option includes administering 125 mg of elemental iron as 10 mL of ferric gluconate (Ferrlicit®) (two packages of 62.5 mg each) by a slow IV push over 10–15 minutes for each treatment. Another option is administration of 100 mg of elemental iron as 5 mL of iron sucrose (Venofer®) by a slow IV push over 5–10 minutes for each treatment (78). The series of treatments may be repeated if the serum ferritin or percent transferrin saturation remains abnormal. This treatment should not be started or continued if either the serum ferritin exceeds 50 μg/L or the percent transferrin saturation exceeds 40%. While IV iron is now being evaluated for treatment of RLS in patients without iron deficiency, this is not considered an effective or safe treatment for RLS outside the context of iron deficiency. Indeed, in this context it is an experimental treatment and should only be done with the standard approval process for research involving human subjects.

Behavioral Treatments

Lifestyle adjustments can reduce RLS symptoms. A later bed- and waking time can allow subjects to be active during the evening when they would be prone to symptoms and sleep later in the morning when they are less likely to be symptomatic. In general, anything that wakes a patient up or stimulates brain activity reduces RLS symptoms, while anything that makes the patient sleepy exacerbates the symptoms. Thus, very hot or very cold baths, hard rubbing of the legs or other body parts, stimulating games or social interactions, and engrossing demanding hobbies such as complicated needle work or drawings all serve to alert the patient and reduce their symptoms. Alcohol in low doses appears to exacerbate RLS, possibly because of sedation. Table 11 lists medications that can cause or exacerbate RLS. Close attention should be paid to the relationship between a subject's symptoms and medication changes. In particular, over-the-counter sedating antihistamines can significantly affect RLS symptoms.

Choosing a Treatment

When choosing a treatment, it must be determined whether the RLS is primary or secondary. Treating secondary RLS should address the secondary cause in addition to the RLS symptoms. Special consideration should be given when choosing medications for pregnant women and dialysis patients. Primary RLS treatment depends largely upon the severity, timing, and

Table 11 Medications to Avoid in RLS

- Dopamine blockers that cross blood brain barrier
  - Neuroleptics
  - Metoclopramide
  - Many anti-emetics
- Antihistamines—sedating, cross blood brain barrier
- Antidepressants—use cautiously, avoid if possible
  - Selective serotonin reuptake inhibitors
  - Tricyclic antidepressants
  - Burproprion (Wellbutrin®) may be used and may help restless legs syndrome

Abbreviation: RLS, restless legs syndrome.

Table 12 RLS Treatment Guidelines: Sequence of Options

RLS symptoms	First choice	Second choice	Third choice
Mild			
Intermittent	Behavioral treatment, sedative hypnotic	PRN carbidopa/levodopa 25/100, PRN low-dose DA	PRN opiates
Most days	Behavioral treatment, daily low-dose DA	Daily opiates	Daily sedative hypnotics
Moderate or severe			
Intermittent	PRN carbidopa/levodopa, PRN or PRN DA	PRN or daily opiates	Daily gabapentin
Most days	Daily DA	Daily opiates	Daily gabapentin
Special considerations			
Mostly painful symptoms	DA, gabapentin, opiates	Combine other RLS treatments with hypnotics	*****
Break-through symptoms	If on DA then PRN added lowest DA dose, if not on DA then PRN carbidopa/levodopa 25/100 or lowest DA dose if tolerated	*****	Nonpharmacological treatment

Abbreviations: RLS, restless legs syndrome; DA, dopamine agonist; intermittent, averages no mores than two times a week; PRN, as needed.

frequency of the symptoms. Table 12 outlines an approach to RLS treatment. Infrequent RLS symptoms can sometimes be managed with behavioral treatments and life-style changes. They also are likely to respond to as needed (PRN) use of hypnotics, carbidopa/levodopa 25/100, or low-dose dopamine agonists. Dopamine agonists have the advantage of a long half-life, allowing them to last throughout the night. The major disadvantages of these medications are cost and adverse effects. When symptoms are moderate to severe but still no more than two times a week, hypnotics and behavioral treatments are unlikely to suffice. In this instance, dopamine medications and PRN opiates are the treatment of choice. If symptom severity is disturbing, then daily doses of dopamine agonists, opioids, or gabapentin can be considered.

Dosage timing depends on symptom onset, with most patients taking medications before bed to permit sleep. Some patients require medications earlier in the day for symptom relief.

The dopamine agonists pergolide and ropinirole take effect within an hour, while pramipexole takes two hours to provide relief. Severe RLS patients with evening symptoms typically require both an afternoon and bedtime dose. Dose titration to efficacy is necessary for all RLS medications, particularly dopamine agonists and gabapentin. Dopamine agonists can be administered either as a single dose at bedtime or in divided doses, with one in the evening and the other at bedtime. The dose should start low, gradually increasing every 3–7 days until symptoms abate, side effects are seen, or a maximum dose is achieved.

Follow-Up Evaluations

Initial follow-up should occur within 4 to 6 weeks to facilitate medication adjustments. Once a stable dose is achieved, yearly follow-up is adequate. At these visits, clinicians should query patients regarding augmentation as indicated by symptom onset earlier in the day. Indeed, rapid development of earlier symptoms within a 2-year period of treatment is likely due to augmentation. The current diagnostic criteria for augmentation require a symptom advance of at least two hours (10). A slower advance of RLS symptoms over several years more likely reflects progressive worsening of the disorder over time. If an abrupt worsening of symptoms occurs, evaluate the patient for blood loss or medication changes and order serum iron tests (ferritin and percent transferrin saturation).

PERIODIC LIMB MOVEMENT DISORDER

Diagnosis

There is considerable controversy regarding the significance or even existence of periodic limb movement disorder (PLMD, definition Table 1). Many feel that PLMS does not cause enough sleep disruption in and of

Table 13 Diagnostic Criteria for PLMD

A. Repetitive, highly stereotyped limb movements are present, confirmed by polysomnography. Polysomnographic monitoring demonstrates muscle movements during sleep that are
i. 0.5–5 sec in duration
ii. Of amplitude greater than or equal to 25% of toe dorsiflexion during calibration
iii. In a sequence of four or more movements, and
iv. Separated by an interval of more than five seconds (from limb movement onset to limb movement onset) and less than 90 sec (typically there is an interval of 20–40 sec)
B. The PLMS index exceeds five per hour in children and in most adult cases exceeds 15/hr
C. There is clinical sleep disturbance
D. Criteria are not met for another primary sleep disorder known to be associated with PLMS
Supportive features:
A. There is a sustained clinical response to dopaminergic therapy
B. The limb movements are not caused by a medication or substance known to induce or aggravate PLMS

Abbreviations: PLMD, periodic limb movement disorder; PLMS, periodic limb movements in sleep.

itself to justify treatment. An alternate view is that PLMS indicates an episodic arousal. Indeed, these phenomena are often preceded by cardiac and electroencephalographic changes consistent with a sleep disrupting arousal. Thus, in this paradigm, PLMS either represents a sign of a sleep-disrupting disorder or is part of a complex leading to sleep disruption. In any event, it is appropriate to diagnose and treat this condition.

The latest International Classification of Sleep Disorders includes revised PLMD diagnostic criteria (Table 13). These revisions emphasize the exclusion of other sleep disorders that produce PLMS and make the minimum PLMS criteria less rigid but should be at least 15/hr for adults. PLMS/hr disturbing sleep may differ by subject age and sleep depth. Thus, the diagnosis depends on clinical judgment that the observed rate suffices to disturb the patient's sleep–wake functioning. Ultimately, a patient's sleep pattern, medications, and age should all be considered before deciding that PLMS represents a significant primary disorder.

Differential Diagnosis

Many sleep-related conditions produce PLMS, thus accounting for the sleep disturbance associated with these movements, particularly sleep-disordered breathing. Indeed, limb movements often occur coincident with apneas, hypopneas, and inspiratory flow limitation associated with upper-airway resistance

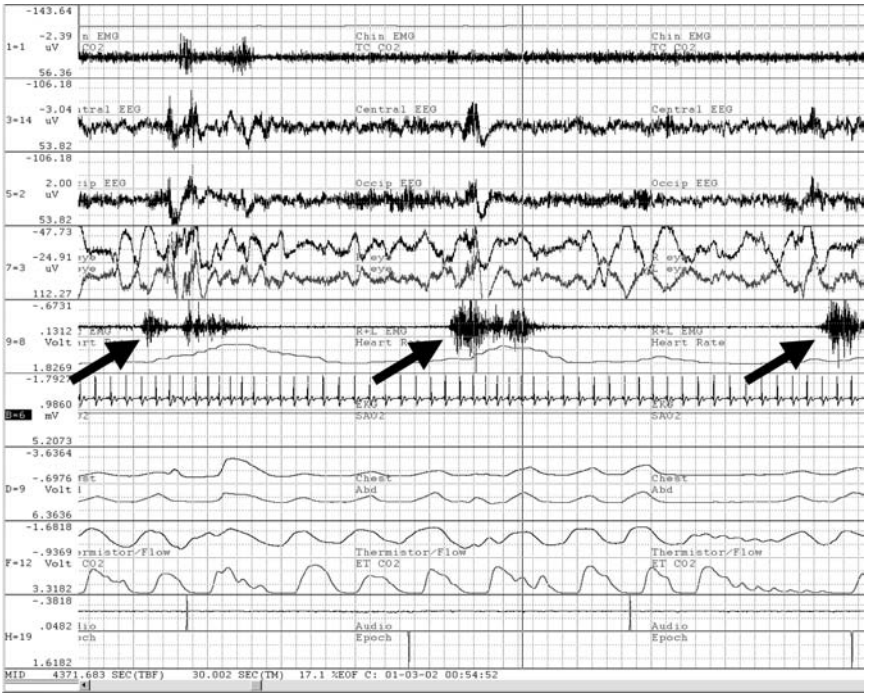


Figure 6 Periodic limb movements in sleep produced by regular sleep-disordered breathing events (*black arrows*). *Source*: Courtesy of Wayne Thompson Health Sciences Centre Sleep Disorders Clinic, Winnipeg, Manitoba, Canada.

syndrome. Detecting these respiratory events and separating them from PLMS not related to respiratory disturbances requires sophisticated airflow measures. Figure 6 provides an example of PLMS occurring as part of arousals associated with sleep-disordered breathing. Other disorders commonly comorbid with PLMS include RLS, REM sleep behavior disorder, narcolepsy, and Parkinson's disease. The presence of these conditions excludes the diagnosis of PLMD.

Treatments

Many cases of PLMD can be treated without medications by improving sleep hygiene. When using medications the treatment goal should be clear. If sleep improvement is the objective, then benzodiazepines and other gaba-active hypnotics should be considered. These medications provide little or no benefit in reducing the movements during sleep (72). If the goal is both movement reduction and sleep improvement, then low-dose dopamine agonists or opiates are the medications of choice (79). There is no evidence that gabapentin reduces PLMS occurring with PLMD. Dopamine agonists are effective at similar doses as those used for RLS, with the maximum dose typically less

for PLMD than RLS. Whether or not augmentation occurs in PLMD, leading to evening RLS symptoms, is unknown. If this occurs, the offending medication should be discontinued and an alternate medication should be initiated.

Current literature evaluating adult PLMD fails to reveal statistically significant relationships between PLMS severity and arousals and nighttime and daytime symptoms. Similarly, these reports have not established that treatments for PLMD improve daytime functioning. Nonetheless, there are individual case reports of improved daytime functioning with treatment. This issue may relate to interindividual response differences to brief repetitive awakenings. Considerable controversy exists whether or not to treat PLMD. Clearly, the rate of PLMS/hr alone cannot determine the need for treatment, but this rate and the number of arousals must be evaluated in the context of the clinical picture when making this decision. The existing literature does not provide clear treatment guidelines.

REFERENCES

1. Willis T. De Animae Brutorum. London: Wells and Scott, 1672.
2. Willis T. The London Practice of Physics. London: Bassett and Crooke, 1685.
3. Wittmaack T. Pathologie und therapie der sensibilitat neurosen. Liepzig: Schafer, 1861.
4. Ekbom KA. Restless legs: a clinical study. Acta Med Scand 1945; 158(suppl): 1–122.
5. Symonds CP. Nocturnal myoclonus. J Neurol Neurosurg Psychiatr 1953; (16): 166–171.
6. Lugaresi G, Coccagna G, Berti Ceroni G, Ambrosetto C. Restless legs syndrome and nocturnal myoclonus. In: Gastaut H, Lugaresi E, Berti Ceroni G, eds. The Abnormalities of Sleep in Man. Bologna: Aulo Gaggi Editore, 1968;:285–294.
7. Coleman RM, Roffwarg HP, Kennedy SJ, Guilleminault C, Cinque J, Cohn MA, et al. Sleep–wake disorders based on a polysomnographic diagnosis. A national cooperative study. JAMA 1982; 247(7):997–1003.
8. Akpinar S. Treatment of restless legs syndrome with levodopa plus benserazide [letter]. Arch Neurol 1982; 39(11):739.
9. International Restless Legs Syndrome Study Group. Toward a better definition of restless legs syndrome. Mov Disord 1995; 10:634–642.
10. Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisi J. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. Sleep Med 2003; 4(2):101–119.
11. Bassetti CL, Mauerhofer D, Gugger M, Mathis J, Hess CW. Restless legs syndrome: a clinical study of 55 patients. Eur Neurol 2001; 45(2):67–74.
12. Kutner N, Bliwise D. Restless legs complaint in African-American and Caucasian hemodialysis patients. Sleep Med 2002; 3(6):497–500.
13. Hui D, Wong T, Li T, Ko F, Choy D, Szeto C, et al. Prevalence of sleep disturbances in Chinese patients with end stage renal failure on maintenance hemodialysis. Med Sci Monit 2002; 8(5):CR331–CR336.

14. Huiqi Q, Shan L, Mingcai Q. Restless legs syndrome (RLS) in uremic patients is related to the frequency of hemodialysis sessions. Nephron 2000; 86(4):540.
15. Winkelman JW, Chertow GM, Lazarus JM. Restless legs syndrome in end-stage renal disease. Am J Kidney Dis 1996; 28(3):372–378.
16. Winkelmann J, Stautner A, Samtleben W, Trenkwalder C. Long-term course of restless legs syndrome in dialysis patients after kidney transplantation. Mov Disord 2002; 17(5):1072–1076.
17. Manconi M, Govoni V, Cesnik E, De Vito A, Zucconi M, Ferini-Strambi L, et al. Epidemiology of restless legs syndrome in a population of 606 pregnant women. Sleep 2003; 26:A330–A331.
18. Akyol A, Kiylioglu N, Kadikoylu G, Bolaman AZ, Ozgel N. Iron deficiency anemia and restless legs syndrome: is there an electrophysiological abnormality? Clin Neurol Neurosurg 2003; 106(1):23–27.
19. Gemignani F, Marbini A, Di Giovanni G, Salih S, Terzano MG. Charcot-Marie-Tooth disease type 2 with restless legs syndrome. Neurology 1999; 52(5): 1064–1066.
20. Gemignani F, Marbini A, Di Giovanni G, Salih S, Margarito FP, Pavesi G, et al. Cryoglobulinaemic neuropathy manifesting with restless legs syndrome. J Neurol Sci 1997; 152(2):218–223.
21. Rutkove S, Matheson J, Logigian E. Restless legs syndrome in patients with polyneuropathy. Muscle Nerve 1996; 19:670–672.
22. Allen RP, Earley CJ. Defining the phenotype of the restless legs syndrome (RLS) using age-of-symptom-onset. Sleep Med 2000; 1:11–19.
23. Winkelmann J, Muller-Myhsok B, Wittchen HU, Hock B, Prager M, Pfister H, et al. Complex segregation analysis of restless legs syndrome provides evidence for an autosomal dominant mode of inheritance in early age at onset families. Ann Neurol 2002; 52(3):297–302.
24. Desautels A, Turecki G, Montplaisir J, Sequeira A, Verner A, Rouleau GA. Identification of a major susceptibility locus for restless legs syndrome on chromosome 12q. Am J Hum Genet 2001; 69(6):1266–1270.
25. Bonati MT, Ferini-Strambi L, Aridon P, Oldani A, Zucconi M, Casari G. Autosomal dominant restless legs syndrome maps on chromosome 14q. Brain 2003; 126(Pt 6):1485–1492.
26. Li J, Hu LD, Wang WJ, Chen YG, Kong XY. Linkage analysis of the candidate genes of familial restless legs syndrome. Yi Chuan Xue Bao 2003; 30(4): 325–329.
27. Brooks DG. The first genetic locus mapped for RLS is unlikely to be the last: Article Reviewed: 'Identification of a major susceptibility locus for restless legs syndrome on chromosome 12q'. Sleep Med 2002; 3(3):285–286.
28. Quatrale R, Manconi M, Gastaldo E, Eleopra R, Tugnoli V, Tola MR, et al. Neurophysiological study of corticomotor pathways in restless legs syndrome. Clin Neurophysiol 2003; 114(9):1638–1645.
29. Tergau F, Wischer S, Paulus W. Motor system excitability in patients with restless legs syndrome. Neurology 1999; 52(5):1060–1063.
30. Rijsman RM, Stam CJ, Weerd AWd. Abnormal H-reflexes in periodic limb movement disorder; impact on understanding the pathophysiology of the disorder. Clin Neurophysiol 2004. In press.

31. Aksu M, Bara-Jimenez W. State dependent excitability changes of spinal flexor reflex in patients with restless legs syndrome secondary to chronic renal failure. Sleep Med 2002; 3(5):427–430.
32. Bara-Jimenez W, Aksu M, Graham B, Sato S, Hallett M. Periodic limb movements in sleep: state-dependent excitability of the spinal flexor reflex. Neurology 2000; 54(8):1609–1616.
33. Entezari-Taher M, Singleton JR, Jones CR, Meekins G, Petajan JH, Smith AG. Changes in excitability of motor cortical circuitry in primary restless legs syndrome. Neurology 1999; 53(6):1201–1205.
34. Trenkwalder C, Bucher SF, Oertel WH. Electrophysiological pattern of involuntary limb movements in the restless legs syndrome. Muscle Nerve 1996; 19(2): 155–162.
35. Montplaisir J, Lorrain D, Godbout R. Restless legs syndrome and periodic leg movements in sleep: the primary role of dopaminergic mechanism. Eur Neurol 1991; 31(1):41–43.
36. Earley CJ, Hyland K, Allen RP. CSF dopamine, serotonin, and biopterin metabolites in patients with restless legs syndrome. Mov Disord 2001; 16(1):144–149.
37. Turjanski N, Lees AJ, Brooks DJ. Striatal dopaminergic function in restless legs syndrome: 18F-dopa and 11C-raclopride PET studies. Neurology 1999; 52(5): 932–937.
38. Trenkwalder C, Walters AS, Hening WA, Chokroverty S, Antonini A, Dhawan V, et al. Positron emission tomographic studies in restless legs syndrome. Mov Disord 1999; 14(1):141–145.
39. Michaud M, Soucy JP, Chabli A, Lavigne G, Montplaisir J. SPECT imaging of striatal pre- and post-synaptic dopaminergic status in restless legs syndrome with periodic leg movements in sleep. J Neurol 2002; 249(2):164–170.
40. Eisensehr I, Wetter TC, Linke R, Noachtar S, von Lindeiner H, Gildehaus FJ, et al. Normal IPT and IBZM SPECT in drug-naive and levodopa-treated idiopathic restless legs syndrome. Neurology 2001; 57(7):1307–1309.
41. Tribl GG, Asenbaum S, Klosch G, Mayer K, Bonelli RM, Auff E, et al. Normal IPT and IBZM SPECT in drug naive and levodopa-treated idiopathic restless legs syndrome [letter to editor]. Neurology 2002; 59(4):649–650.
42. Ruottinen HM, Partinen M, Hublin C, Bergman J, Haaparanta M, Solin O, et al. An FDOPA PET study in patients with periodic limb movement disorder and restless legs syndrome. Neurology 2000; 54(2):502–504.
43. Ondo WG, He Y, Rajasekaran S, Le WD. Clinical correlates of 6-hydroxydopamine injections into A11 dopaminergic neurons in rats: a possible model for restless legs syndrome. Mov Disord 2000; 15(1):154–158.
44. O'Keeffe ST, Gavin K, Lavan JN. Iron status and restless legs syndrome in the elderly. Age 1994; 23(3):200–203.
45. Sun ER, Chen CA, Ho G, Earley CJ, Allen RP. Iron and the restless legs syndrome. Sleep 1998; 21(4):371–377.
46. Earley CJ, Connor JR, Beard JL, Malecki EA, Epstein DK, Allen RP. Abnormalities in CSF concentrations of ferritin and transferrin in restless legs syndrome. Neurology 2000; 54(8):1698–1700.
47. Allen RP, Barker PB, Wehrl F, Song HK, Earley CJ. MRI measurement of brain iron in patients with restless legs syndrome. Neurology 2001; 56(2):263–265.

48. Connor JR, Boyer PJ, Menzies SL, Dellinger B, Allen RP, Earley CJ. Neuropathological examination suggests impaired brain iron acquisition in restless legs syndrome. Neurology 2003; 61:304–309.
49. Connor JR, Wang X, Patton S, Menzies SL, Troncoso JC, Earley CJ, et al. Decreased transferrin receptor expression in restless legs syndrome: a putative mechanism. Neurology 2004; 62(9):1563–1567.
50. Pittock SJ, Parrett T, Adler CH, Parisi JE, Dickson DW, Ahlskog JE. Neuropathology of primary restless leg syndrome: absence of specific tau- and alpha-synuclein pathology. Mov Disord 2004; 19(6):695–699.
51. Earley CJ, Heckler D, Horská A, Barker PB, Allen RP. The treatment of restless legs syndrome with intravenous iron dextran. Sleep Med 2004; 5(3): 231–235.
52. Nordlander NB. Therapy in restless legs. Acta Med Scand 1953; 145:453–457.
53. Nichols DA, Allen RP, Grauke JH, Brown JB, Rice ML, Hyde PR, et al. Restless legs syndrome symptoms in primary care: a prevalence study. Arch Intern Med 2003; 163(19):2323–2329.
54. Allen RP, Montplaisir J, Myers A. Profile of RLS in a large multinational population and characterization of a group likely warranting treatment: the REST (RLS Epidemiology, Symptoms and Treatment) General Population Study [abstr]. Neurology 2004. In press.
55. Berger K, Luedemann J, Trenkwalder C, John U, Kessler C. Sex and the risk of restless legs syndrome in the general population. Arch Intern Med 2004; 164(2): 196–202.
56. Ulfberg J, Nystrom B. Restless legs syndrome in blood donors. Sleep Med 2004; 5(2):115–118.
57. Silber MH, Richardson JW. Multiple blood donations associated with iron deficiency in patients with restless legs syndrome. Mayo Clin Proc 2003; 78(1): 52–54.
58. Györfi M, Szakács Z, Koumlves P. Restless legs syndrome and serum transferrin receptor and ferritin levels in patients with rheumatoid arthritis. Sleep 2003; 26:A334.
59. Happe S, Tings T, Schettler V, M C, Paulus W, Trenkwalder C. Low-density lipoprotein apheresis and restless legs syndrome. Sleep 2003; 26: A335–A336.
60. Banerji N, Hurwitz L. Restless legs syndrome, with particular reference to its occurrence after gastric surgery. Br Med J 1970 (or 1989?); 4:774–775.
61. Rothdach AJ, Trenkwalder C, Haberstock J, Keil U, Berger K. Prevalence and risk factors of RLS in an elderly population: the MEMO study. Memory and morbidity in Augsburg elderly. Neurology 2000; 54(5):1064–1068.
62. Ulfberg J, Nystrom B, Carter N, Edling C. Prevalence of restless legs syndrome among men aged 18 to 64 years: an association with somatic disease and neuropsychiatric symptoms. Mov Disord 2001; 16(6):1159–1163.
63. Allen RP, Earley CJ. Validation of the Johns Hopkins restless legs severity scale. Sleep Med 2001; 2(3):239–242.
64. The International Restless Legs Syndrome Study Group. Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. Sleep Med 2003; 4(2):121–132.

65. Montplaisir J, Boucher S, Nicolas A, Lesperance P, Gosselin A, Rompre P, et al. Immobilization tests and periodic leg movements in sleep for the diagnosis of restless leg syndrome. Mov Disord 1998; 13(2):324–329.
66. Littner MR, Kushida C, Anderson WM, Bailey D, Berry RB, Hirshkowitz M, et al. Practice parameters for the dopaminergic treatment of restless legs syndrome and periodic limb movement disorder. Sleep 2004; 27(3):557–559.
67. Chesson AL Jr, Wise M, Davila D, Johnson S, Littner M, Anderson WM, et al. Practice parameters for the treatment of restless legs syndrome and periodic limb movement disorder. An American Academy of Sleep Medicine report. Standards of Practice Committee of the American Academy of Sleep Medicine. Sleep 1999; 22(7):961–968.
68. Earley CJ. Clinical practice. Restless legs syndrome. N Engl J Med 2003; 348(21): 2103–2109.
69. Silber MH, Ehrenberg BL, Allen RP, Buchfuhrer MJ, Earley CJ, Hening WA, et al. An algorithm for the management of restless legs syndrome. Mayo Clin Proc 2004; 79(7):916–922.
70. Horvath J, Fross RD, Kleiner-Fisman G, Lerch R, Stalder H, Liaudat S, et al. Severe multivalvular heart disease: a new complication of the ergot derivative dopamine agonists. Mov Disord 2004; 19(6):656–662.
71. Boghen D, Lamothe L, Elie R, Godbout R, Montplaisir J. The treatment of the restless legs syndrome with clonazepam: a prospective controlled study. Can J Neurol Sci 1986; 13(3):245–247.
72. Saletu M, Anderer P, Saletu-Zyhlarz G, Prause W, Semler B, Zoghlami A, et al. Restless legs syndrome (RLS) and periodic limb movement disorder (PLMD): acute placebo-controlled sleep laboratory studies with clonazepam. Eur Neuropsychopharmacol 2001; 11(2):153–161.
73. Telstad W, Sorensen O, Larsen S, Lillevold PE, Stensrud P, Nyberg-Hansen R. Treatment of the restless legs syndrome with carbamazepine: a double blind study. BMJ 1984; 288(6415):444–446.
74. Burchell BJ. Treatment of restless legs syndrome with gabapentin: a double-blind, cross-over study. Neurology 2003; 60(9):1558.
75. Garcia-Borreguero D, Larrosa O, de la Llave Y, Verger K, Masramon X, Hernandez G. Treatment of restless legs syndrome with gabapentin: a double-blind, cross-over study. Neurology 2002; 59(10):1573–1579.
76. Allen RP, Earley CJ. Augmentation of the restless legs syndrome with carbidopa/levodopa. Sleep 1996; 19(3):205–213.
77. Earley CJ, Allen RP. Pergolide and carbidopa/levodopa treatment of the restless legs syndrome and periodic leg movements in sleep in a consecutive series of patients. Sleep 1996; 19:801–810.
78. Silverstein SB, Rodgers GM. Parenteral iron therapy options. Am J Hematol 2004; 76(1):74–78.
79. Kaplan PW, Allen RP, Buchholz DW, Walters JK. A double-blind, placebo-controlled study of the treatment of periodic limb movements in sleep using carbidopa/levodopa and propoxyphene. Sleep 1993; 16:717–723.

5

Snoring, Snorting, and Gasping: Sleep-Disordered Breathing Syndromes

William J. DePaso

Sleep Disorders Center at Virginia Mason Medical Center, Seattle, Washington, U.S.A.

Symptoms

Snoring
Apneas
Gasping/choking
Cough
Wheezing
Orthopnea
Paroxysmal nocturnal dyspnea
Stridor
Sleepiness
Insomnia
Frequent nocturnal awakenings

Diagnosis

Obstructive sleep apnea
Central sleep apnea/Cheyne–Stokes respirations
Nocturnal hypoventilation syndromes
Sleep apnea in children

INTRODUCTION

Obstructive sleep apnea is second only to asthma among prevalent respiratory diseases. As a result, primary care physicians must be comfortable working up and managing these patients. Respiration varies across the three sleep–wake states (wake, rapid eye movement, and nonrapid eye movement sleep). Obstructive sleep apnea is state dependent, occurring only during sleep. Although diurnal, obstructive lung diseases, congestive heart failure, and neuromuscular diseases are profoundly affected by the sleep state. Sleep-disordered breathing encompasses the full spectrum of respiratory ailments occurring during sleep. This chapter provides a practical approach to the sleep apnea syndromes (obstructive and central), disorders of nocturnal hypoventilation (obesity-hypoventilation and neuromuscular diseases), and cardiorespiratory illnesses exacerbated by sleep (congestive heart failure and chronic obstructive pulmonary diseases). Management strategies will be discussed in a subsequent chapter.

Breathing problems during sleep are usually first noticed by a vigilant bed partner, with snoring and apneas often going unrecognized by the patient. Snoring is best defined as an intrusive breathing noise occurring while asleep with variable intensity and patterns. It can be soft or loud, low or high frequency, constant or intermittent, and melodious or choppy. The lower the frequency, the more likely the noise is to penetrate barriers such as walls or doors. The impact of snoring on the bed partner is just as variable. A bed partner with impaired hearing may be unfazed by noises up to 100 dB, while a bedmate with sensitive hearing and insomnia may complain of barely discernable sounds. Patients are usually unaware of their snoring frequency or intensity. Occasionally, nocturnal gasps or snorts persisting into wakefulness provide evidence of nocturnal breathing difficulties to the patient. Most patients with obstructive sleep apnea snore, but not all patients who snore have sleep apnea.

Apneas may or may not be observed by a bed partner. Apneas that present as pauses in loud snoring followed by a gasp or a snort with resumption of snoring are indicative of obstructive sleep apnea. The gasp and snort result from pooled oropharyngeal secretions and airway edema occurring during the apnea. The term *obstructive sleep apnea syndrome* is often used to describe this full spectrum of disease related to upper airway closure during sleep. Other commonly used terms include *sleep-disordered breathing* and *sleep apnea*. These terms will be used interchangeably in this chapter. In contrast, pauses in breathing not associated with snoring followed by rapid but quiet breathing are indicative of central sleep apnea or periodic breathing.

Orthopnea is dyspnea in the supine position improving with upright posture. It results from fluid shifts, as with congestive heart failure, or from mechanically disadvantaged respiratory muscles, as with chronic obstructive pulmonary disease and neuromuscular illnesses. Paroxysmal nocturnal

Table 1 Common Symptoms of Sleep Disordered Breathing

- Snoring
- Apneas
- Gasping/choking
- Cough
- Wheezing
- Orthopnea
- Paroxysmal nocturnal dyspnea
- Stridor

dyspnea is orthopnea occurring at night that awakens the patient. Here the supine position and sleep state combine to stress the respiratory system. Symptoms improve with wakefulness and assumption of an upright posture. Although commonly associated with congestive heart failure exacerbations, paroxysmal nocturnal dyspnea may also occur in diseases requiring accessory muscles for respiration such as neuromuscular diseases and chronic obstructive pulmonary disease.

Stridor is a high-pitched noise, representing obstruction to inspiratory airflow in the extra-thoracic airway such as the vocal cords. Nocturnal stridor often results from acid reflux, leading to laryngospasm, which causes extreme and sometimes prolonged respiratory distress. Wheezing is an expiratory musical noise resulting from intrathoracic airway narrowing. Common causes include circadian exacerbations of asthma, congestive heart failure, chronic obstructive pulmonary disease, and nocturnal aspiration. Nocturnal coughing results from pooled secretions, airway narrowing, or edema. Nocturnal aspiration, drainage from infected sinuses, or other gravity-dependent processes cause nocturnal coughing. Please see Table 1 for a list of common symptoms of sleep-disordered breathing.

OBSTRUCTIVE SLEEP APNEA

Clinical Features

Obstructive sleep apnea results from closure of the pharyngeal airway during sleep, resulting in snoring and asphyxia. The breathing pause often causes varying degrees of hypercarbia and hypoxemia. If vigorous inspiratory efforts continue against the obstructed airway (“Mueller maneuver”), large swings in negative intrathoracic pressure occur, stressing the cardiovascular system and causing brief cortical arousals. These arousals result in sleepiness by fragmenting sleep.

Normal persons will experience a few episodes of airway collapse during sleep. Therefore, a single obstructive apnea does not make a syndrome. The clinical syndrome becomes apparent when the number and severity of repetitive apneas rises above a threshold. Variability is common in gas exchange

abnormalities and the degree, length, and repetition of airway obstruction. The spectrum of clinical illness depends on the nature of the apneas and the biological susceptibility of the patient, including cardiopulmonary integrity and susceptibility to sleep fragmentation. Sometimes patients with mild sleep apnea are very sleepy while those with severe disease are asymptomatic. Simple snoring can be the only manifestation of sleep-disordered breathing. Although bothersome to a bed partner, this has no measurable effect on the patient. As disease severity worsens, the syndrome proceeds along a continuum from upper airway resistance syndrome, to mild, moderate, and severe sleep apnea. Figure 1 graphically demonstrates this point.

Snoring is a bothersome breathing noise made while asleep and the most common sign of sleep apnea. It is caused by turbulent airflow from vibration of redundant tissues in the upper airway and is highly variable in intensity and frequency. It is experienced by up to 46% of men over the age of 40 (1). It is less common and likely under-reported in women. Snoring indicative of sleep apnea is choppy, snorty, interruptive, loud, frequent, continuous, and low frequency such that even at low volumes the sound can penetrate bedroom walls and doors. It often terminates with an abrupt snort or gasp that may be recognized by the patients themselves. Patients who awaken rapidly return to sleep without a prolonged awakening or feelings of anxiety. Patients who awaken gasping with persistent respiratory distress either have central sleep apnea or some other respiratory disorder.

Nocturnal drooling and mouth dryness are signs of oral breathing occurring as patients try to relieve oropharyngeal obstruction by rotating their mandible downward and forward. Nocturia is common in obstructive sleep apnea resulting from release of atrial naturetic peptide by apnea-induced increases in right heart preload. Unusual movements or behaviors during sleep are common, ranging from small twitches and kicking to violent thrashing as the body struggles to open the obstructed airway. Arousals from sleep last up

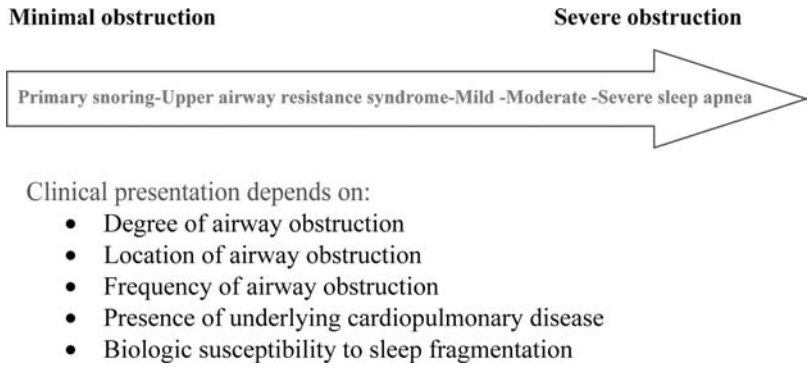


Figure 1 The clinical spectrum of obstructive sleep apnea.

to 30 seconds before the patient becomes conscious. Arousals can lead to sleep walking or talking in predisposed individuals. Occasional injury to the patient or bed partner may occur. Sleep apnea can cause sleep-onset or sleep-maintenance insomnia (2). Some patients have primary insomnia in addition to sleep apnea. In these instances, the insomnia should be addressed separately.

There are many of diurnal symptoms associated with sleep apnea. Most patients with sleep apnea report unrefreshing sleep and difficulty staying awake, but the absence of these symptoms does not exclude the diagnosis. Up to 30% of patients with severe sleep apnea experience no sleepiness. Fatigue is a complex symptom and patients may not be able to distinguish it from sleepiness. This is particularly true in sleep apneics with comorbid fibromyalgia and chronic fatigue syndrome. Sleepiness is defined as the intrusion of sleep or sleep-like processes into wakeful activity. This process is useful when facilitating sleep onset at bedtime and harmful when causing unwanted sleep intrusion into wakefulness. There are many aspects to sleepiness, and a failure to recognize this can cause a clinician to underestimate the extent of hypersomnia in a given patient.

Subjective sleepiness implies that patients feel sleepier than they desire. *Paroxysmal sleepiness* describes episodes of sleep occurring without warning. Patients are unprepared for sleep and therefore awaken perplexed they were sleeping. *Active sleepiness* is a form of paroxysmal sleepiness that occurs while patients are performing an activity requiring their attention. Common circumstances include talking, or driving. Sleepiness in the context of such a high level of alertness implies a severe problem. Examples of extreme sleepiness include a police officer falling asleep while directing traffic and a Las Vegas card dealer dozing off while dealing black jack. *Passive sleepiness* is another common form of paroxysmal sleepiness. This occurs in situations that do not require constant vigilance and interaction. Listening to a lecture, attending church or the theatre, watching television, reading, and using the computer are examples of situations in which patients with mild to moderate forms of sleepiness might find themselves dozing unexpectedly.

Napping is a form of *compensatory behavior* that masks a patient's sleepiness. Caffeine consumption is a *masking behavior* that hides sleepiness. Certain personality types mask sleepiness. Highly driven people tend to underrecognize the presence of sleepiness, while patients with sedentary lifestyles might easily give into their drowsiness. Some patients do *rousing behaviors* to keep themselves awake. Playing the radio, opening the windows, turning on the air conditioning, or eating are examples of behaviors that drivers use to stay alert. Finally, sleepiness may only be recognized by its consequences, such as avoiding pleasurable activities due to low energy. These aspects of sleepiness are listed in Table 2.

Evaluating subjective sleepiness in a given patient can be time consuming. It is most important to ask whether the patient has ever experienced

Table 2 Aspects of Sleepiness

Aspect	Example
Subjective sleepiness	Sleepier than you want to be
Paroxysmal sleepiness	Sleepiness that occurs without warning
Active sleepiness	Sleepiness while driving, talking
Passive sleepiness	Sleepiness while reading, watching television
Compensatory behaviors	Increased frequency and length of naps
Masking behaviors	Caffeine ingestion
Rousing behaviors	Playing radio or open window while driving
Consequences of sleepiness	Avoid social activities or poor work performance

sleepiness or performed rousing behaviors while driving. Patients who fall asleep while driving are likely to be repeated offenders. All patients being evaluated for a sleep disorder should be warned about the dangers of driving or operating dangerous equipment when drowsy. The Epworth Sleepiness Scale (Table 3) is a validated survey that asks patients to rate on a scale of 0–3 their recent propensity to fall asleep in eight theoretical circumstances. A score ≤ 10 is normal. This is an epidemiologic tool that correlates nicely with various consequences of sleep apnea such as traffic accidents. It has no diagnostic value for sleep apnea. The Stanford sleepiness scale asks patient, to rate their present ability to fall asleep (e.g., how sleepy are you right now?). It is helpful when assessment of instantaneous sleepiness is needed, such as during a multiple sleep latency test.

Table 3 The Epworth Sleepiness Scale

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently, try to work out how they would have affected you. Use the following scale to choose the most appropriate number for each situation: 0, would never doze; 1, slight chance of dozing; 2, moderate chance of dozing; 3, high chance of dosing

Situation	Chance of dozing
Sitting and reading	
Watching TV	
Sitting inactive in a public place (e.g., a theater or meeting)	
As a passenger in a car for an hour without a break	
Lying down in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car, while stopped for a few minutes in traffic	

Other symptoms include erectile dysfunction, peripheral edema, and chronic headaches. Headaches due to sleep apnea are prominent upon awakening and resolve during the day. The exact mechanism is unknown, but carbon dioxide retention and vascular hyper-reactivity is one hypothesis. A host of neuropsychological abnormalities are associated with sleep apnea, such as impaired cognition (mental clouding, poor memory and concentration, impaired hand–eye coordination) and mood disorders (personality changes, mood swings, poor anger control, anxiety, and depression). Poor work performance, social withdrawal, and driving impairment are also encountered. Sadly, many patients with unrecognized sleep apnea who complain of fatigue and moodiness are diagnosed with depression and empirically placed on antidepressants. Although many patients with sleep apnea have concomitant depression, most are not depressed but rather sleep deprived.

Epidemiology

Sleep disorder breathing is common. A population-based study of Wisconsin state employees demonstrated that 24% of men and 9% of women had an apnea–hypopnea index >5 (1). Furthermore, sleepiness was associated with an abnormal apnea–hypopnea index in 4% of men and 2% of women, representing a 2:1 male to female preponderance. Obesity, male sex, advancing age, and the presence of craniofacial abnormalities are the major risk factors for sleep-disordered breathing (3). All measures of obesity including neck/waist girth, body mass index, skin fold measurement, and total body weight correlate with increased risk of developing the disease. An increase in body mass index of 1 kg/m^2 is associated with a 30% increase in the odds of obstructive sleep apnea and a 9% change in the apnea–hypopnea index.

Sleep apnea worsens with age until the age of 65, when disease severity levels out. Current estimates suggest 60% of adults over the age of 65 have an apnea–hypopnea index greater than 10. The prevalence of sleep apnea also increases with age, particularly for adults over the age of 65. Up to 90% of adults >85 years old have an apnea–hypopnea index >10. Many are asymptomatic, raising the question of clinical significance. All patients with inherited or acquired craniofacial abnormalities causing reduced cross-sectional upper airway size are at risk of developing the disease. Other sleep apnea risk factors include menopause, tobacco smoking, chronic nasal obstruction, and a positive family history of disease (4). Please see Table 4 for a review of the major risk factors for obstructive sleep apnea.

Sleep apnea is associated with increased morbidity and mortality. In 1988, He et al. (5) followed patients with severe sleep apnea for nine years. The cumulative survival for untreated patients with an apnea index less than 20 was 96%, as compared to 63% for those with apnea indices greater

Table 4 Risk Factors for Obstructive Sleep Apnea

Strong evidence:
- Obesity
- Male sex (2:1)
- Advancing age
- Craniofacial abnormalities

Some evidence:
- Menopause
- Family member with the disorder
- Smoking
- Nasal obstruction

than 20. Patients with an apnea index >20 who were successfully treated with continuous positive airway pressure had a five year survival of 100%, as compared to 85% for the untreated group. Cardiovascular disease was considered the cause of the excess mortality.

Obstructive Sleep Apnea and Cardiovascular Disease

The association between sleep-disordered breathing and cardiovascular disease is demonstrated by the Sleep Heart Health Study. This population-based study used in-home polysomnography in 6132 patients over the age of 40 (47% were men, 47% over the age of 65) (6). The odds ratio of any self-reported cardiovascular disease was 1.42 for an apnea–hypopnea index >11, as compared to an apnea–hypopnea index of <1.4. Similarly, odds ratios for self-reported congestive heart failure was 2.38, stroke 1.58, and coronary disease 1.27.

A group of 182 disease-free Swedish men aged 30–69 were evaluated for obstructive sleep apnea and followed for seven years. Sleep apnea was defined as >5/hr of nocturnal oxygen desaturations. A cardiovascular event (myocardial infarction, cerebrovascular accident, or death) occurred in 36.7% of the patients with sleep apnea versus 6.6% of patients without the disease ($p < 0.001$). Further follow-up revealed that 56.8% of the untreated group developed cardiovascular disease versus 6.7% of the successfully treated group (7). Table 5 summarizes the association between obstructive sleep apnea and cardiovascular disease.

Obstructive Sleep Apnea and Hypertension

There is a well-defined association between hypertension and obstructive sleep apnea (10). Animal models of sleep apnea demonstrate that 1–3 months of induced obstructive apneas lead to sustained daytime hypertension (11,12). Obstructive sleep apnea is found in up to 35% of patients

Table 5 Summary of the Association Between Obstructive Sleep Apnea and Cardiovascular Disease

- The acute effects of sleep apnea on the cardiovascular system are profound and well documented
- There is a modest, but definite, dose–response association between chronic sleep apnea and the development of hypertension
- Patients with established coronary disease have a markedly worse outcome if they have untreated sleep apnea
- Sleep apnea is very common in patients with congestive heart failure and is likely a cause of idiopathic cardiomyopathy
- Continuous positive airway pressure therapy improves heart failure
- Central sleep apnea/Cheyne–Stokes respirations in patients with heart failure is associated with a poor prognosis that is improved with continuous positive airway pressure
- Patients with hypertension, heart failure, or documented coronary artery disease should be screened for sleep apnea

Source: From Refs. 8, 9.

in hypertension clinics (13). The Wisconsin cohort study consisted of 1069 randomly selected state employees (56% men, mean age 47 ± 8 years, range 30–60) who underwent laboratory-based polysomnography. Repeated studies were performed in 709 of these patients at four years and 184 patients after eight years (14,15). This study demonstrated a dose–response relationship between the apnea–hypopnea index and the prevalence of hypertension. The odds ratio for hypertension (blood pressure $\geq 140/90$ or taking antihypertensive medications) was 1.21 for an apnea–hypopnea index of 5, 1.75 for an index of 15, and 3.07 for an index >30 (14). A similar analysis in the Sleep Heart Health Study revealed an odds ratio for hypertension of 1.37 in patients with an AHI >30 as compared to normal individuals (16). In the subgroup of patients with significant oxygen desaturations, the odds ratio increased to 1.46. Patients with sleep apnea also have an increased incidence of hypertension. Four-year follow-up of patients in the Wisconsin cohort with an apnea–hypopnea index >15 revealed an odds ratio of 2.89 for developing new hypertension (15).

Patients with essential hypertension exhibit a 15% reduction in their blood pressure during sleep. Patients with sleep apnea devoid of this drop are deemed ''nondippers'' and display high risk of developing cardiovascular disease (17). These patients often have treatment-refractory hypertension. A study of 41 patients with persistent hypertension despite treatment with three or more drugs revealed that 83% had obstructive sleep apnea, including 96% of male patients (18). There are now several randomized, controlled clinical trials demonstrating the efficacy of continuous positive airway

pressure in reducing nocturnal as well as diurnal blood pressure in patients with obstructive sleep apnea (19–22).

Obstructive Sleep Apnea and Cardiac Disease

A case control study in Sweden showed that patients with comorbid coronary artery disease and obstructive sleep apnea had a worse long-term prognosis. When the apnea–hypopnea index was >10, the odds ratio for death, stroke, or myocardial infarction was 1.62 (23). Another Swedish study followed patients admitted to the coronary care unit with coronary artery disease for five years. Sleep apnea was an independent predictor of mortality due to a cardiovascular event. An apnea–hypopnea index ≥ 10 increased the chance of a fatal cardiovascular event from 9.3% to 37.5% (24).

There is wide variation in rates of arrhythmias in obstructive sleep apnea patients, with 18–50% exhibiting rhythm disturbances (25). Bradycardia and heart block predominate, and tachycardia occurs infrequently. Varying degrees of heart block were seen in 17 of 239 patients with an apnea–hypopnea index >10. Most patients had underlying congestive heart failure or pulmonary hypertension, and 80–90% showed improvement following treatment with continuous positive airway pressure (26). Some patients with sleep apnea with bradycardia experienced improvement in their symptoms following placement of a pacemaker (27). Patients with sleep apnea and congestive heart failure have increased premature ventricular contractions. Central sleep apnea with Cheyne–Stokes respirations can result in more complex ventricular ectopy. Continuous positive airway pressure reduces premature ventricular contractions in these patients (28). Patients with obstructive sleep apnea who had a prophylactic automatic cardiac defibrillator for congestive heart failure were found to exhibit increased risk for significant ventricular arrhythmias (29). Patients with sleep apnea and atrial fibrillation are more likely to remain in sinus rhythm if they are treated (30).

The prevalence of sleep apnea in patients followed in heart failure clinics is approximately 60% (31–33). Although many of these patients had central sleep apnea with Cheyne–Stokes respirations, a significant number had obstructive sleep apnea. Considering congestive heart failure prevalence in patients with obstructive sleep apnea, 7.7% have an ejection fraction $<50\%$ and 36.8% have evidence of diastolic dysfunction by echocardiogram (34,35). In those with depressed ejection fractions, continuous positive airway pressure normalized function (36). In fact, continuous positive airway pressure is very heart friendly. Positive intrathoracic pressures reduce preload and afterload. Increased intra-alveolar pressure reduces pulmonary capillary wedge pressure and improves oxygenation. In addition, sympathetic surges are tempered by reduced arousals from sleep. The beneficial effect of positive pressure therapy on outcomes in patients with sleep apnea and congestive heart failure are well documented (37–39).

Obstructive Sleep Apnea and Cerebrovascular Disease

The association between sleep apnea and cerebrovascular disease is less clear. The odds ratio for self-reported cerebrovascular disease in patients with sleep apnea was 1.58 in the Sleep Heart Health Study (6). Seventy to ninety percent of stroke patients have obstructive sleep apnea following their acute event. Central sleep apnea may also be seen. Increased fibrinogen levels, enhanced platelet aggregation, and shunting through a patent foramen ovale are a few of the potential physiologic mechanisms linking chronic obstructive sleep apnea with cerebrovascular disease (40). The Swedish cohort with sleep apnea and coronary artery disease demonstrated an odds ratio of stroke of 2.98 at five years (23).

Obstructive Sleep Apnea: Genetics

Obstructive sleep apnea is a genetically complex disease that does not demonstrate any classical Mendelian patterns (41,42). The phenotypic expression of sleep apnea is diverse. Environmental factors, as well as age, gender, race and ethnicity influence the variable penetrance of multiple genes. Epidemiologic research using segregation analyses demonstrates that a family history of sleep apnea explains about 30% to 40% of the variability of the disease in a general population. Genetic factors likely explain the higher prevalence of obstructive sleep apnea in Asians and young African-American males as compared to Caucasians, even after controlling for obesity.

The families of patients with sleep apnea have an increased risk of developing the disease. One first-degree relative with obstructive sleep apnea confers a 50–75% higher risk of having the disorder for family members as compared to someone with no known affected relatives. Two obstructive sleep apnea-affected first-degree relatives are associated with a 2–2.5-fold higher risk, and three affected first-degree relatives raise the relative risk 3–4-fold higher.

The phenotypic definition of obstructive sleep apnea in genetic research is problematic. The use of a threshold level of respiratory events per hour of sleep oversimplifies the disorder, which is better represented by a continuum of phenotypes. The study of intermediate phenotypes has proven useful. Obesity, metabolic syndromes, disproportionate craniofacial anatomy, ventilatory control, and sleep–wake regulation are intermediate phenotypes that are highly associated with sleep apnea. In a general population, 60–90% of the variability of these traits is explained by genetic factors.

There is a growing list of plausible candidate genes for obstructive sleep apnea, but the identification of specific genes will probably not occur until a reliable biochemical marker that identifies a specific sleep apnea phenotype is found.

Obstructive Sleep Apnea: Pathophysiology

The pharynx is a complex structure used for respiration, glutition, and speech. Patency is maintained through coordination of a number of muscle groups. Pharyngeal obstruction occurs when forces favoring collapse are greater than forces favoring patency. Although most patients with obstructive sleep apnea have a demonstrable reduction in the cross-sectional area of their upper airway, the sleep state dependence of airway collapse suggests a functional component to the pathophysiology of apnea (43). The force necessary to close the airway depends on many factors, including airway anatomy, strength of the central neural reflex, and corresponding level of anatomic response. The portion of the collapsible airway with the greatest degree of obstruction at baseline will likely be the region of earliest and greatest collapse. The velo-pharynx and the oro-pharynx are the most vulnerable to obstruction. Collapse typically originates from the lateral pharyngeal walls rather than antero-posteriorally behind the tongue base. Obstruction of the nasal passages can lead to turbulent airflow and snoring but does not directly result in apneas.

Many factors tip the balance of forces in favor of pharyngeal collapse. The baseline airway cross-sectional area may be reduced by enlarged tonsils, para-pharyngeal fat pads, the tongue base, soft palate, and/or uvula. Obesity is associated with enlargement of the tongue and para-pharyngeal fat pads. Nasal obstruction leads to increased nasal resistance during inspiration, causing the negative pressures required for respiration to exceed the forces maintaining airway patency. Alterations in craniofacial bony structures can also narrow the airway, particularly in nonobese patients.

Gravitational forces during supine positioning favor retro-lingual collapse. Immediately prior to inspiration, a reflex-mediated increase in upper airway tone braces the airway for the negative pressures required for lung air movement. If this reflex is weak or the timing is wrong, the airway will not recover from the initial collapse and completely close. Advancing age, drugs, and alcohol can blunt this sleep-state-dependent airway protective reflex. Table 6 provides a list of factors that favor pharyngeal collapse

Table 6 Factors that Favor Pharyngeal Collapse

- Anatomic narrowing of the upper airway
- Supine position
- Advancing age
- Obesity
- Sleep state
- Drugs
- Alcohol
- Altered consciousness

Table 7 Anatomic Abnormalities Associated with Obstructive Sleep Apnea

Soft tissues:
- Enlarged tonsils, tongue, and para-pharyngeal fat pads
- Elongated soft palate and uvula
- Narrowed nasal airway
- Enlarged and shortened neck

Bony structures:
- Small, retro-posed mandible
- Narrowed, retro-posed maxilla
- Inferiorly positioned hyoid bone

and Table 7 lists specific anatomic abnormalities associated with obstructive sleep apnea.

Patients with sleep apnea have increased sympathetic activation (44). Increased circulating catecholamines cause vasoconstriction and tachycardia, impairing cardiovascular variability. Sleep apneics exhibit endothelial dysfunction characterized by increased endothelin levels and free radical release. Elevation of inflammatory mediators (e.g., c-reactive protein), abnormalities of coagulation (e.g., platelet aggregation and fibrinogen levels), and evidence of metabolic dysfunction (e.g., leptin and insulin resistance) have all been described in patients with sleep apnea (45–49). These aberrations provide a pathophysiologic rationale for the link between sleep apnea and cardiovascular diseases. Table 8 lists the pathophysiologic consequences of sleep apnea, while Table 9 describes the associated cardiovascular diseases.

Control of the cardiovascular system varies across sleep–wake states. Compared to wakefulness, nonrapid eye movement sleep (NREM) is associated with a mild increase in parasympathetic tone and a mild reduction in sympathetic tone leading to a mild decrease in heart rate, blood pressure, stroke volume, cardiac output, and myocardial work. From a cardiovascular perspective, tonic rapid eye movement sleep (REM) is similar to the wake state. Phasic REM sleep, during which rapid saccadic eye movements occur, is associated with a mild increase in sympathetic tone and a similar

Table 8 Pathophysiologic Consequences of Sleep Apnea

- Increased sympathetic tone
- Endothelial dysfunction
- Oxidative vascular stress
- Elevated inflammatory mediators (e.g., c-reactive protein)
- Coagulation abnormalities (e.g., increased platelet aggregation and fibrinogen levels)
- Metabolic dysfunction (e.g., increased leptin and insulin resistance)

Table 9 Cardiovascular Diseases Associated with Sleep Apnea

- Congestive heart failure
- Stroke
- Hypertension
- Coronary artery disease
- Arrhythmias

magnitude decrease in parasympathetic tone. This leads to increases in the heart rate, blood pressure, and myocardial work. Brief arousals from sleep, defined as 3–5-second periods of high-frequency EEG activity, lead to abrupt and profound activation of the sympathetic nervous system. This results in rapid and significant elevations of blood pressure, heart rate, and cardiac output. The cardiovascular changes observed during normal sleep are summarized in Table 10.

Given that most people spend 80% of their sleep in NREM and 20% in REM with few arousals, sleep is generally a period of cardiovascular quiescence. Therefore, anything disrupting this resting state could stress the cardiovascular system and lead to disease. Obstructive apneas have three distinct effects on the cardiovascular system. Airway closure leads to asphyxia and a Mueller maneuver followed by an arousal restoring airway patency. Asphyxia increases the $paCO_2$ and drops the paO_2, leading to increased pulmonary artery pressures. The degree of peripheral oxygen desaturation that follows depends on the oxygen content in the lung at the time of the apnea (functional residual capacity), the position of the patient on the oxy-hemoglobin dissociation curve (effected by altitude, underlying lung disease), and the length of the apnea. Oxygen desaturation in the presence of apnea leads to bradycardia (the dive reflex). Tachycardia and hypertension occur as the apnea resolves. Following a brief delay, oxygen saturation returns to normal.

Normally, the transpleural pressures are approximately -5 cm of water. Breathing against a closed airway leads to large swings in negative

Table 10 Cardiovascular Changes During Normal Sleep Compared to Wakefulness

	Wake	NREM	Tonic-REM	Phasic-REM	Arousal
Parasympathetic activity	—	Increased	=	Decreased	Decreased
Sympathetic activity	—	Decreased	=	Increased	Increased
Heart rate	—	Decreased	=	Increased	Increased
Blood pressure	—	Decreased	=	Increased	Increased
Stroke volume, cardiac output	—	Decreased	=	Increased	Increased
Myocardial work	—	Decreased	=	Increased	Increased

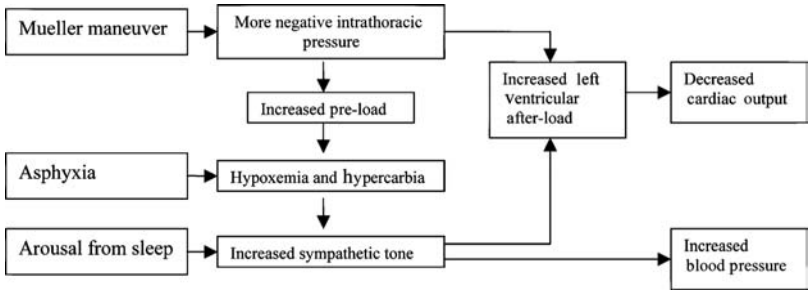


Figure 2 Adverse cardiovascular consequences of obstructive apneas.

intrathoracic pressure occasionally exceeding −60 cm of water. Intrathoracic venous pooling increases, causing an upsurge in right heart preload. The interventricular septum impinges on the left-ventricular cavity due to the resulting increased right-ventricular end diastolic volume, and pressure causes the interventricular septum to impinge on the left-ventricular cavity. Left-ventricular compliance decreases and filling is impaired. The increased negative intrathoracic pressure also causes increased left-ventricular after-load. This concept is far from intuitive. The aortic baro-receptor responds to the transmural aortic pressure. Transmural pressure is a function of the difference between the intra-aortic luminal pressure (blood pressure) and the periaortic tissue pressures (intrathoracic pressure). Mathematically, this is defined as the difference between intraluminal minus extraluminal pressure. Constant intraluminal pressure in the setting of increasingly negative extraluminal pressure increases the difference between the two. This pressure differential is sensed by the aortic baro-receptor as an increase in after-load. The post apnea arousal from sleep and oxygen saturation drop cause increased sympathetic activity, thus raising peripheral vascular tone and blood pressure, further increasing left-ventricular after-load.

In summary, reduced left-ventricular diastolic filling and increased after-load cause diminished stroke volume. Cardiac output is then reduced, increasing left atrial and pulmonary capillary wedge pressures. In this manner, obstructive sleep apnea places increased strain on the cardiovascular system. Please see Figure 2 for a schematic representation of this phenomenon.

OBSTRUCTIVE SLEEP APNEA: DIAGNOSIS

Screening for sleep disorders, particularly sleep apnea, should be performed routinely in all primary care practices. Questions should include snoring, nocturnal respiratory complaints, daytime fatigue or sleepiness, insomnia, or unusual behaviors during sleep. Special attention should be given to obese

patients and those with diabetes, hypertension, coronary artery disease, and congestive heart failure. Other patients meriting special consideration for sleep apnea include those with fatigue, headaches, chronic pain/fibromyalgia, mood disorders, impaired memory, and daytime sleepiness. All patients undergoing a procedure requiring sedation, analgesia, or anesthesia should be screened for sleep apnea.

Patients who snore regularly should be formally evaluated for sleep apnea if they have excessive daytime somnolence, regardless of their cardiovascular profile. Certain patients should also be evaluated—even if they do not report snoring (Table 11). Table 12 provides a useful sleep apnea screening tool combining a validated (Berlin) questionnaire with anthropomorphic data (50,51). Patients at high risk in two of three question categories should undergo evaluation for sleep apnea, regardless of their cardiovascular profile.

A general medical history should look for conditions that cause, mimic, or exacerbate sleep apnea (Table 13). Medications, chronic medical disease, or psychiatric illnesses that disturb sleep must be identified. A thorough cardiovascular risk profile is important to assist in treatment decisions. A complete review of nocturnal and diurnal symptoms associated with sleep apnea should be performed. It is important to review the patient's current sleep hygiene, as sleep apnea patients often develop bad sleep habits in attempts to compensate for poor sleep quality. Careful questioning is important regarding symptoms of concomitant sleep disorders such as restless legs syndrome, periodic limb movement disorder, circadian rhythm disorders, narcolepsy, and environmental issues. Identification of problems that interfere with treatment, such as claustrophobia, sinus infection, or chronic nasal congestion, is necessary. Bed partner observations are critical. However, those who snore, have hearing deficits, or otherwise sleep very soundly should not be relied upon to give accurate observational histories. The differential diagnosis of nocturnal respiratory distress includes sleep apnea, nocturnal

Table 11 Reasons to Screen for Sleep Apnea in Patients Not Reporting Snoring

- Morbid obesity with BMI >30
- Congestive heart failure
- Resistant hypertension
- Fibromyalgia
- Chronic fatigue syndrome
- Craniofacial abnormalities
- Depression
- Insomnia
- Daytime hypersomnia
- Chronic headaches

Table 12 Sleep Apnea Screening Tool

Please check all that apply.

Category I: Snoring (checking any two of statements 2–6 indicates high risk)

1. You have a bed partner who can reliably observe your sleep
2. You have been told that you snore
3. You snore more than 3 times per week
4. You snore as loud as someone talking
5. Your snoring bothers other people
6. You have been told that you have pauses in your breathing while sleeping and these occur more than 3 times per week

Category II: Daytime sleepiness or fatigue (checking one indicates high risk)

1. You are still tired after sleeping for 8 hr on more than 3 days per week
2. You are tired during the wake time more than 3 days per week
3. You have fallen asleep while driving
4. You do things to keep yourself from falling asleep during the day

Category III: Body measurements (checking one or more indicates high risk)

1. You have high blood pressure
2. Your shirt collar size is greater than 16 in or
3. Your dress size is larger than 14
4. You weigh more than 220 lb

DO NOT WRITE BELOW THIS LINE. FOR CLINIC PROVIDER USE ONLY.

Category IV: Physical examination

- Height: _____ in./cm Weight: _____ lb/kg
- Neck circumference: _____in./cm
- Body mass index: _____ kg./m^2

(If neck circumference is $\geq$41 cm or BMI $\geq 30\,kg/m^2$, patient is at high risk.)

reflux with aspiration, laryngospasm, congestive heart failure, asthma/chronic obstructive pulmonary disease, cardiac disease, and panic disorder (Table 14).

Sleep-related respiratory symptoms must be differentiated from orthopnea. Isolated obstructive sleep apnea is not associated with clinically significant diurnal pulmonary hypertension, daytime hypoxemia, or cor pulmonale. If these clinical entities are present in a patient with sleep apnea, look for associated underlying cardiopulmonary disease.

The physical examination in sleep apnea should focus on anthropomorphic features, the cardiovascular system, and the upper airway. Height and weight are measured to calculate the body mass index. Blood pressure, pulse, respiratory rate, and assessment of central venous pressure, heart tones, lung sounds, and peripheral edema should be performed. A detailed upper airway examination is necessary. Measurement of neck circumference

Table 13 Medical Conditions Associated with Sleep Apnea

- Congenital anatomic upper airway obstruction
- Acromegaly
- Achondroplastic dwarfism
- Diseases of the chest wall
- Arnold–Chiari malformation
- Micro- or retrognathia
- Trisomy 21
- Congestive heart failure
- Chronic obstructive pulmonary disease
- Polio and post-polio syndrome
- Myotonic dystrophy

is helpful in determining sleep apnea risk. The nose should be evaluated for external deformities, location of the nasal septum, size and character of the nasal turbinates, and patency of the anterior nasal valve. The size of the maxilla and mandible should be noted with attention to bite dynamics. Teeth crowding indicates small jaw structure. Tongue size and tongue base positioning in relation to the palate should be noted.

A Mallampati grading of the airway should be performed. Anesthesiologists use this rating scale to predict difficult oral translaryngeal intubations. Grade 1 signifies a normal airway, and grade 4 (base of the soft palate cannot be seen with a relaxed open mouth) is indicative of a markedly abnormal airway. The length of the soft palate, the width and length of the uvula, and the intertonsillar pillar distance should be noted. Generally speaking, the intertonsillar space should be two tongue blades in width and the length of both the soft palate and uvula one tongue blade in width. Tonsils are graded on a 1–4 scale, with 1 being normal and 4 indicating tonsils large enough to touch each other in the midline.

Table 14 Differential Diagnosis of Nocturnal Respiratory Distress

- Obstructive sleep apnea
- Central sleep apnea
- Nocturnal reflux with aspiration
- Laryngospasm
- Congestive heart failure
- Exacerbation of obstructive airways disease (chronic obstructive pulmonary disease and asthma)
- Coronary artery disease
- Sino-pulmonary infection with nocturnal pooling of secretions
- Neuromuscular weakness affecting the diaphragm
- Nocturnal panic disorder

The severity of sleep apnea is rated by tallying the total number of respiratory events captured during nocturnal polysomnography and dividing by the total sleep time. This approach has strengths and weaknesses. The correlation is good between respiratory events and the risk of developing cardiovascular complications, but the correlation is poor between the number of respiratory events and the presence of symptoms. Respiratory events must be at least 10 seconds in duration. Historically, the technology used to measure nocturnal breathing was insensitive, and only a complete cessation of airflow (apnea) was considered clinically significant. As technology advanced, hypopneas, defined as partial airflow limitation associated with incomplete airway collapse, were recognized as causing adverse consequences similar to apneas. Despite attempts to standardize the definition of hypopneas, variability remains, making comparisons between sleep laboratories difficult (52,53). The definition correlating best with sleep apnea's adverse cardiovascular complications requires an oxygen desaturation in association with airflow reduction. Most sleep laboratories have broadened the definition of a hypopnea to accept flow limitation in the absence of a desaturation given an arousal from sleep or a 50–70% reduction in flow.

Since apneas and hypopneas have similar adverse consequences, they are added together to make the apnea–hypopnea index. Using the apnea–hypopnea index, obstructive sleep apnea is defined as follows: (i) <5, not clinically significant; (ii) 5–14, mild; (iii) 15–29, moderate; and (iv) >30, severe. Up to 30% of patients, with an apnea–hypopnea index >30, are devoid of sleepiness, while some patients with apnea–hypopnea indices ≤ 5 can experience profound sleepiness that resolves with treatment.

Laboratory-based polysomnography is the gold standard diagnostic procedure (54,55). Ambulatory polysomnography technology is improving rapidly and may replace laboratory-based testing in the future (56,57).

Nocturnal oximetry studies are not sensitive or specific enough to be recommended as a useful screening test. The current diagnostic criteria for obstructive sleep apnea are listed in Table 15 (58). Table 16 describes the current American Academy of Sleep Medicine definition of apnea–hypopnea.

Diagnosis of upper airway resistance syndrome deserves special consideration. In this disorder, flow and oxygenation are maintained during a respiratory event as the increased work of breathing overcomes increased upper airway resistance (59). This is documented by esophageal balloon measurements of intrathoracic pressure. As upper airway resistance increases, intrathoracic pressure becomes increasingly negative. The extra work of breathing is terminated when arousal leads to a reduction in upper airway resistance and normal breathing returns. These events are called respiratory effort-related arousals and, when added to the apnea–hypopnea index, comprise the respiratory disturbance index. These respiratory events are subtle but can cause significant sleep disruption and sleepiness. Sensitive measures of airflow are now available and esophageal pressure monitors are no longer necessary (60).

Table 15 Diagnostic Criteria for Obstructive Sleep Apnea

Obstructive sleep apnea can be diagnosed by fulfilling the following criteria: A or B, plus C
(A) Unexplained daytime sleepiness
(B) Two or more of the following symptoms:
  (i) Choking or gasping during sleep
  (ii) Recurrent awakenings
  (iii) Un-refreshing sleep
  (iv) Daytime fatigue
  (v) Impaired concentration
(C) $\geq$5 obstructed breathing events/hr of sleep

Source: From Refs. 56, 58.

Sleepiness is a common symptom of sleep apnea. Objective sleepiness is measured by the multiple sleep latency test, which quantitates how easily a person falls asleep during the day. The patients are monitored for sleep staging during four 20-minute nap opportunities spaced throughout a day. The patients are instructed to sleep or not fight sleep while lying in a darkened room. If they fall asleep, they are allowed a 15-minute nap. The time to fall asleep on each nap is calculated and then averaged. Severe sleepiness is evident when the mean sleep latency is less than 5 minutes and abnormal if less than 12. There is poor correlation between the mean sleep latency and apnea–hypopnea index in sleep apneics. The maintenance of

Table 16 American Academy of Sleep Medicine Diagnostic Criteria for Determining an Obstructive Apnea–Hypopnea Event

An obstructive apena–hypopnea event can be diagnosed by fulfilling the following criteria: 1, 2, or 3, plus 4
1. A clear decrease (>50%) from baseline in the amplitude of a valid measure of breathing during sleep. Baseline is defined as the mean amplitude of stable breathing and oxygenation during the prior two minutes preceding the onset of the event (in patients with stable breathing) or the mean amplitude of the three largest breaths in the 2-min preceding the event (in patients without stable breathing)
2. A clear amplitude reduction of a validated measure of breathing during sleep that does not reach the above criterion but is associated with either an oxygen desaturation of >3% or an arousal
3. Pattern of progressively more negative esophageal pressure, terminated by a sudden change in pressure to a less negative level and an arousal
4. The event must last 10 sec or longer

Note: Nasal pressure transducer and respiratory inductance plethysmography are the only valid measures of breathing during sleep.
Source: From Ref. 53.

wakefulness test, on the other hand, measures a patient's ability to stay awake while sitting in a chair in a darkened room. The patient is given four 40-minute opportunities to stay awake.

CENTRAL SLEEP APNEA/CHEYNE–STOKES RESPIRATIONS

Central sleep apnea is sleep-disordered breathing caused by intermittent cessation of the central respiratory drive. The apneas occur with a patent upper airway, distinguishing it from obstructive apnea. Central sleep apnea is considered either hypercapnic or nonhypercapnic. Patients with the hypercapnic form exhibit prolonged pauses in respiratory drive, resulting in profound nocturnal hypoventilation. These patients often suffer from central nervous system disease to their brainstem respiratory centers. Patients with nonhypercapnic central sleep apnea have normal or low levels of carbon dioxide. These patients also have unstable, overly sensitive chemoreceptors, causing them to overcorrect abnormalities in their $paCO_2$. These factors combine with respiratory control changes occurring at sleep onset to cause central apneas, followed by hyperpnea or periodic breathing. The cycle time between apnea and hyperpnea is dependent on the transit time between the peripheral blood $paCO_2$ and feedback to the central nervous system.

Factors associated with periodic breathing include a low baseline $paCO_2$ (chronic hyperventilation), abrupt loss of the waking behavioral or cortical influence to breathing, and the elevated apnea threshold at sleep onset. Factors, causing perpetuation of periodic breathing beyond sleep onset include hyper-responsive chemoreceptors (peripheral greater than central), delayed feedback to the chemoreceptors (long circulation times), hypoxia (altitude), disease of the central nervous system, and instability of the upper airway. As the patient falls asleep, the apnea threshold rises while the respiratory controls become dependent on metabolic influences. If the $paCO_2$ is below this threshold (e.g., a person who hyperventilates), then an immediate cessation in respiratory pump function and a fall in alveolar ventilation occur.

This central apnea continues until the $paCO_2$ rises above the apnea threshold. At this point, an overly sensitive drive immediately identifies the need for increased ventilation, causing an abrupt increase in neural output to the respiratory pump and a sudden increase in ventilation with a corresponding drop in $paCO_2$. This change in ventilation, associated with a delayed drop in oxygen saturation, causes an arousal from sleep. Once awake, the apnea threshold rapidly drops. The arousal stimulates additional ventilation, and the $paCO_2$ reaches its prior subnormal level. The oxygen saturation rises and the patient falls back asleep while the process begins to repeat itself.

Nonhypercapnic central sleep apnea can be idiopathic or secondary to other diseases, such as congestive heart failure. Normal persons experience

periodic breathing when they ascend to high altitude. Patients with central apneas long enough to allow airway closure will occasionally snore and wake with a distressing sensation of choking. These apneas are often associated with profound oxygen desaturation. Although well-designed treatment trials for central sleep apnea are lacking, judicious use of continuous positive airway pressure, bi-level positive airway pressure with a back-up rate, sedatives, acetozolamide, and supplemental oxygen are effective therapies.

Cheyne–Stokes respiration is a pattern of periodic central apneas seen in congestive heart failure and central nervous system disease. The apneas alternate with hyperpnoea in a crescendo–decrescendo pattern. More common in men, it portends increased mortality in congestive heart failure patients (61). Thirty to forty percent of congestive heart failure patients display this respiratory pattern, particularly those who hyperventilate with a low $paCO_2$. Cheyne–Stokes respirations occur more in slow-wave sleep than REM due to the higher arousal threshold. In REM, reduced chemoreceptor sensitivity and minute ventilation and increased $paCO_2$ dampen periodic breathing by reducing the gain in respiratory control. Cardiac function and longevity are improved with continuous positive airway pressure therapy by decreasing preload and after-load. Reduced arousals decrease sympathetic tone.

Continuous positive airway pressure titrations are difficult in patients with Cheyne–Stokes respirations. A 4 to 8-week period of adaptation is necessary before undertaking a formal laboratory titration. The titration should correct mask issues and ensure that pressures are adequate to treat any concomitant obstructive apneas. Positive pressure typically improves sleep quality and oxygenation with little effect on periodic breathing. There is no documented advantage to using bi-level pressure. Head of bed elevation and supplemental oxygen may reduce periodic breathing. Optimal medical therapy should be employed to reduce the pulmonary capillary wedge pressure.

NOCTURNAL HYPOVENTILATION SYNDROMES

Hypoventilation means insufficient lung air movement to allow adequate oxygenation and elimination of carbon dioxide (62). There is an inverse relationship between alveolar ventilation and the arterial $paCO_2$. The partial pressure of carbon dioxide is proportional to the body's production and inversely related to alveolar ventilation. Alveolar ventilation is a function of both total ventilation measured at the mouth and functional airway dead space. Total ventilation equals tidal volume multiplied by the respiratory rate. Given that carbon dioxide production and dead space are constant, fluctuations in alveolar ventilation vary with changes in tidal volume and respiratory rate. Carbon dioxide rises when these variables decrease in relation to metabolic activity. Therefore, hypoventilation is defined by an increased $paCO_2$.

Hypoventilation syndromes occur when patients "can't breathe" (low tidal volume), as with airway obstruction, or when they "won't breathe"

(low respiratory rate), as with depressed respiratory drive. Normally, the central nervous system respiratory control center maintains a balance between workload and capacity. During wakefulness, ventilation is controlled by metabolic and behavioral inputs. Peripheral and brainstem chemoreceptors monitor the status of pH, $paCO_2$, and paO_2 on a continuous basis. Additional respiratory inputs from higher cortical regions allow respiratory variability independent of metabolic parameters, allowing us to speak and sing without apneas. Sometimes, anxiety-provoking situations cause over-breathing and $paCO_2$ reduction.

Metabolic control of breathing takes over at sleep onset. Mild hypoventilation is physiologically normal, indicated by a small increase in the $paCO_2$ apneic threshold. When we cycle into REM sleep, there is yet another change in the control of respiration. The behavioral drive remains silent and chemoreceptor sensitivity drops, resulting in further hypoventilation. Despite this, oxygen saturation is maintained.

Typical patients with severe nocturnal hypoventilation and hypoxemia include those who depend on skeletal muscles to breathe, have increased recumbent respiratory pump impedance (obesity), or have an abnormal respiratory drive. In REM sleep, accessory respiratory muscles are paralyzed. Hypoventilation becomes prominent when the diaphragm cannot overcome the increased impedance of the recumbent position. Morbid obesity is the classic scenario. Along with increased recumbent respiratory impedance, they exhibit a decreased functional residual capacity that shunts blood through their lungs. The increased shunt and reduced ventilation leads to profound oxygen desaturation during REM sleep.

Obesity-Hypoventilation Syndrome

Obesity-hypoventilation syndrome represents a heterogeneous group of patients with daytime hypoventilation associated with obesity. Obesity-associated hypoventilation is seen in patients with neuromuscular weakness, cardiopulmonary disease, and REM-associated hypoventilation during initiation of continuous positive airway pressure therapy. Improving ventilation with noninvasive positive pressure ventilation improves outcomes (63). Respiratory stimulants (acetazolamide, progesterone) may provide additional benefit.

Chronic Obstructive Lung Diseases/Asthma/Interstitial Lung Diseases

Changes in respiratory physiology during NREM and REM sleep profoundly affect patients with underlying lung diseases, even in the absence of obstructive sleep apnea. The respiratory pump is at a mechanical disadvantage when supine from gravitational effects on the diaphragm by the abdominal contents, requiring greater neuromuscular output to affect the same level of ventilation. Diaphragm elevation further decreases functional

residual volume, leading to decreased lung oxygen content at end expiration with increased shunting through atelectatic basal lung units. Nocturnal secretions pool in dependent areas of the airways and lungs, and circadian influences on airway tone exacerbate asthma and chronic obstructive pulmonary disease.

Those with advanced lung diseases recruit skeletal accessory respiratory muscles to assist their mechanically disadvantaged diaphragm. Supine positioning and REM atonia impair their effectiveness. Therefore, reversion to diaphragm breathing causes hypoventilation with profound hypercarbia and hypoxemia. Nocturnal cough, wheezing, and paroxysmal nocturnal dyspnea disrupt sleep. Bronchodilators and corticosteroids used for treatment are common causes of insomnia.

Patients with both obstructive sleep apnea and chronic obstructive pulmonary disease have the "overlap syndrome." Unlike most patients with sleep apnea, these patients often need noninvasive ventilation (bi-level positive pressure therapy) and supplemental oxygen to improve gas exchange and sleep quality. Bronchodilators should be used to treat their underlying lung disease. Interstitial lung diseases affect gas exchange. These patients exhibit reduced lung volumes, hypoxemia, and high baseline levels of ventilation. The reduced ventilation occurring in sleep causes large drops in oxygenation requiring supplemental oxygen.

Diseases of the Chest Wall and Respiratory Muscles

Diseases of the chest wall and respiratory muscles cause nocturnal respiratory difficulties. Because accessory skeletal muscles are the primary muscles of respiration, these patients develop hypercarbia and hypoxemia during REM hypotonia. Impaired cough mechanisms cause pooled secretions during sleep, leading to further gas exchange abnormalities. Increased nocturnal work of breathing and impaired sleep quality cause daytime fatigue and hypoventilation. Patients with post-polio syndrome have an increased risk of developing obstructive sleep apnea. Nocturnal oxygen therapy without augmentation of ventilation can worsen outcomes.

In general, augmenting ventilation occurs by either increasing the respiratory rate or tidal volume. Increasing the respiratory rate in patients with respiratory pump dysfunction rarely improves ventilation. Therefore, respiratory stimulants are not helpful. Conversely, increasing inspiratory flow with noninvasive nasal and/or oral ventilation markedly increases tidal volumes. This increased flow only occurs with a gradient between inspiratory pressures and expiratory pressures. The greater the gradient, the more ventilation is augmented. These bi-level pressure generators, unlike continuous positive airway pressure, can almost fully ventilate the patient. A fixed back-up rate can guarantee that a patient is delivered a minimum number of breaths. This is indicated in patients with respiratory drive abnormalities or

inspiratory muscle weakness who cannot trigger the noninvasive positive pressure ventilation device. Supplemental oxygen may be needed as well. When the forced vital capacity is reduced by $\geq$50%, use of nocturnal ventilatory support improves longevity.

SLEEP APNEA IN CHILDREN

All children should be screened for snoring. Snoring in children is always abnormal, though not necessarily pathologic. They should be evaluated for sleep apnea if they are sleepy, or if the parents are concerned after witnessing apneas. As with adults, polysomnography is the gold standard for diagnosis. Normative data are lacking in children, but for the most part, depending on the child's age, any apneas are considered abnormal. Tonsillectomy and adenoidectomy may be performed without polysomnography if other indications for the surgery are present or the parent observes repetitive apneas. Polysomnography should be performed if the diagnosis is uncertain or the patient is at high surgical risk.

REFERENCES

1. Young T, Palta M, Dempsey J, et al. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993; 328:1230–1235.
2. Krakow B, Melendrez D, Ferreira E, et al. Prevalence of insomnia symptoms in patients with sleep-disordered breathing. Chest 2001; 120:1923–1929.
3. Young T, Peppard PP, Gottlieb DJ. State of the art: epidemiology of obstructive sleep apnea; a population health perspective. Am J Respir Crit Care Med 2002; 165:1217–1239.
4. Stradling JR, Davies RJO. Obstructive sleep apnea/hypopnea syndrome: definitions, epidemiology and natural history. Thorax 2004; 59:73–78.
5. He J, Kryger MH, Zorick FJ, et al. Mortality and apnea index in obstructive sleep apnea; experience in 385 male patients. Chest 1988; 94(1):9–14.
6. Sahar E, Whitney CW, Redline S, et al. Sleep-disordered breathing and cardiovascular disease; cross-sectional analysis of the Sleep Heart Health Study. Am J Respir Crit Care Med 2001; 163:19–25.
7. Peker Y, Hedner J, Norum J, et al. Increased incidence of cardiovascular disease in middle-aged men with obstructive sleep apnea; a 7-year follow-up. Am J Respir Crit Care Med 2002; 166:159–165.
8. Shamsuzzaman ASM, Gersh BJ, Somers VK. Obstructive sleep apnea; implications for cardiac and vascular disease. JAMA 2003; 290:1906–1914.
9. Leung RST, Bradley TD. State of the art: Sleep apnea and cardiovascular disease. Am J Respir Crit Care Med 2001; 164:2147–2165.
10. Pepperell JCT, Davies RJO, Stradling JR. Systemic hypertension and obstructive sleep apnea. Sleep Med Rev 2002; 6(3):157–173.
11. Brooks D, Horner RL, Kozar LF, et al. Obstructive sleep apnea as a cause of systemic hypertension; evidence from a canine model. J Clin Invest 1997; 99(1): 106–109.

12. Bao G, Metreveli N, Fletcher EC. Acute and chronic blood pressure response to recurrent acoustic arousal in rats. Am J Hypertens 1999; 12(5):504–510.
13. Fletcher EC, DeBehnke RD, Lovoi MS, et al. Undiagnosed sleep apnea in patients with essential hypertension. Ann Int Med 1985; 103:190–195.
14. Young TB, Peppard PP, Palta M, et al. Population-based study of sleep-disordered breathing as a risk factor for hypertension. Arch Intern Med 1997; 157:1746–1752.
15. Peppard PE, Young TB, Palta M, et al. Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med 2000; 342: 1378–1384.
16. Nieto FJ, Young TB, Lind BK, et al. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. JAMA 2000; 283:1829–1836.
17. Ancoli-Israel S, Stepnowsky C, Dimsdale J, et al. The effect of race and sleep-disordered breathing on nocturnal BP "dipping"; analysis in an older population. Chest 2002; 122:1148–1155.
18. Logan AG, Perlikowski SM, Mente A, et al. High prevalence of unrecognized sleep apnoea in drug-resistant hypertension. J Hypertens 2001; 19(12):2271–2277.
19. Hla KM, Skatrud JB, Finn L, et al. The effect of correction of sleep-disordered breathing on BP in untreated hypertension. Chest 2002; 122:1125–1132.
20. Faccenda JF, Mackay TW, Boon NA, et al. Randomized placebo-controlled trial of continuous positive airway pressure on blood pressure in the sleep apnea–hypopnea syndrome. Am J Respir Crit Care Med 2001; 163:344–348.
21. Becker HF, Jerrentrup A, Ploch T, et al. Effect of nasal continuous positive airway pressure treatment on blood pressure in patients with obstructive sleep apnea. Circulation 2003; 107:68–73.
22. Pepperell JCT, Ramdassingh-Dow S, Crosthwaite N, et al. Ambulatory blood pressure after therapeutic and sub-therapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomized parallel trial. Lancet 2002; 359:204–210.
23. Mooe T, Franklin KA, Holmstrom K, et al. Sleep-disordered breathing and coronary artery disease; long-term prognosis. Am J Respir Crit Care Med 2001; 164:1910–1913.
24. Peker Y, Hedner J, Kraiczi H, et al. Respiratory disturbance index; an independent predictor of mortality in coronary artery disease. Am J Respir Crit Care Med 2000; 162:81–86.
25. Miller WP. Cardiac arrhythmias and conduction disturbances in the sleep apnea syndrome. Am J Med 1982; 73:317–321.
26. Becker HF, Koehler U, Stammnitz A, et al. Heart block in patients with sleep apnoea. Thorax 1998; 53(3S):29S–32S.
27. Garrigue S, Bordier P, Jais P, et al. Benefit of atrial pacing in sleep apnea syndrome. N Engl J Med 2002; 346(6):404–412.
28. Javaheri S. Effects of continuous positive airway pressure on sleep apnea and ventricular irritability in patients with heart failure. Circulation 2000; 101:392–397.
29. Fichter J, Bauer D, Arampatzis S, et al. Sleep-related breathing disorders are associated with ventricular arrhythmias in patients with an implantable cardioverter-defibrillator. Chest 2002; 122:558–561.

30. Kanagala R, Narayana SM, Friedman PA, et al. Obstructive sleep apnea and the recurrence of atrial fibrillation. Circulation 2003; 107:2589–2594.
31. Lanfranchi PA, Somers VK, Braghiroli A, et al. Central sleep apnea in left ventricular dysfunction; prevalence and implications for arrhythmic risk. Circulation 2003; 107:727–732.
32. Javaheri S, Parker TJ, Liming JD, et al. Sleep apnea in 81 ambulatory male patients with stable heart failure. Circulation 1998; 97:2154–2159.
33. Sin DD, Fitzgerald F, Parker JD, et al. Risk factors for central and obstructive sleep apnea in 450 men and women with congestive heart failure. Am J Respir Crit Care Med 1999; 160:1101–1106.
34. Laaban JP, Pascal-Sebaoun S, Bloch E, et al. Left ventricular systolic dysfunction in patients with obstructive sleep apnea syndrome. Chest 2002; 122(4):1133–1138.
35. Fung JW, Li JST, Choy DKL, et al. Severe obstructive sleep apnea is associated with left ventricular diastolic dysfunction. Chest 2002; 121:422–429.
36. Chan J, Sanderson J, Chan W, et al. Prevalence of sleep-disordered breathing in diastolic heart failure. Chest 1997; 111:1488–1493.
37. Malone S, Liu PP, Holloway R, et al. Obstructive sleep apnoea in patients with idiopathic dilated cardiomyopathy: effects of continuous positive airway pressure. Lancet 1991; 338:1480–1484.
38. Yan TY, Bradley TD, Liu PP. The role of continuous positive airway pressure in the treatment of congestive heart failure. Chest 2001; 120(5):1675–1685.
39. Kaneko Y, Floras JS, Usui K, et al. Cardiovascular effects of continuous positive airway pressure in patients with heart failure and obstructive sleep apnea. N Engl J Med 2003; 348:1233–1241.
40. Neau JP, Paquereau J, Meurice JC, et al. Stroke and sleep apnoea: cause or consequence. Sleep Med Rev 2002; 6(6):457–469.
41. Redline S, Tishler PV. The genetics of sleep apnea. Sleep Med Rev 2000; 4(6): 583–602.
42. Palmer LJ, Redline S. Genomic approaches to understanding obstructive sleep apnea. Respir Physiol Neurobiol 2003; 135:187–205.
43. Fogel RB, Malhotra A, White DP. Pathophysiology of obstructive sleep apnea/hypopnea syndrome. Thorax 2004; 59:159–163.
44. Fletcher EC. Sympathetic over activity in the etiology of hypertension of obstructive sleep apnea. Sleep 2003; 26(1):15–19.
45. Shamsuzzaman ASM, Winnicki M, Lanfranchi P, et al. Elevated C-reactive protein in patients with obstructive sleep apnea. Circulation 2002; 105: 2462–2464.
46. Geiser T, Buck F, Meyer BJ, et al. In vivo platelet activation is increased during sleep patients with obstructive sleep apnea syndrome. Respiration 2002; 69(3):229–234.
47. Wessendorf TE, Thilmann AF, Wang YM, et al. Fibrinogen levels and obstructive sleep apnea in ischemic stroke. Am J Respir Crit Care Med 2000; 162: 2039–2042.
48. Ip M, Lam B, Lam W, et al. Obstructive sleep apnea is independently associated with insulin resistance. Am J Respir Crit Care Med 2002; 165:670–667.
49. Punjabi NM, Sorkin JD, Katzel, et al. Sleep-disordered breathing and insulin resistance in middle-aged and overweight men. Am J Repir Crit Care Med 2002; 165:677–682.

50. Netzer NC, Stoohs RA, Netzer CM, et al. Using the Berlin questionnaire to identify patients at risk for the sleep apnea syndrome. Ann Int Med 1999; 131:485–491.
51. Flemons WW, Whitelaw WA, Brant R, et al. Likelihood ratios for sleep apnea clinical prediction rule. Am J Respir Crit Care Med 1994; 150:1279–1285.
52. Flemons WW, Buysse D, Redline, S, et al. Report of an American Academy of Sleep Medicine Task Force: sleep–related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. Sleep 1999; 222(5):667–689.
53. Meoli AL, Casey KR, Clark RW, et al. Position paper: hypopnea in sleep-disordered breathing in adults. Sleep 2001; 24(4):469–470.
54. Chesson AL, Ferber RA, Fry JM, et al. An American Sleep Disorders Association review; the indications for polysomnography and related procedures. Sleep 1997; 20(6):423–487.
55. An American Sleep Disorders Association report; practice parameters for the indications for polysomnography and related procedures. Sleep 1997; 20(6): 406–422.
56. Flemons WW, Littner MR, Rowley JA, et al. Home diagnosis of sleep apnea: a systematic review of the literature; an evidence review cosponsored by the American Academy of Sleep Medicine, the American College of Chest Physicians and the American Thoracic Society. Chest 2003; 124(4):1543–1579.
57. Chesson AL, Berry RB, Pack A. Practice parameters for the use of portable monitoring devices in the investigation of suspected obstructive sleep apnea in adults. Sleep 2003; 26(7):907–913.
58. American Academy of Sleep Medicine. International Classification of Sleep Disorders. 2nd ed. Westchester, Illinois: American Academy of Sleep Medicine, 2005.
59. Exar EN, Collop NA. The upper airway resistance syndrome. Chest 1999; 115:11,127–11,139.
60. Ayappa I, Norman RG, Krieger AC, et al. Non-invasive detection of respiratory effort-related arousals (RERAs) by a nasal cannula/pressure transducer system. Sleep 2000; 23(6):763–771.
61. Sin DD, Logan AG, Fitzgerald FS, et al. Effects of continuous positive airway pressure on cardiovascular outcomes in heart failure patients with and without Cheyne–Stokes respiration. Circulation 2000; 102:61–66.
62. Martin TJ, Sander MH. Chronic alveolar hypoventilation: a review for the clinician. Sleep 1995; 18(8):617–634 (57–60).
63. Mehta S, Hill NS. State of the art: noninvasive ventilation. Am J Respir Crit Care Med 2001; 163:540–577.

6

Treating Sleep Apnea: Continuous Positive Airway Pressure, Surgery, and Dental Appliances

William J. DePaso

Sleep Disorders Center at Virginia Mason Medical Center, Seattle, Washington, U.S.A.

Edward M. Weaver

Sleep Disorders Center and Department of Otolaryngology, Head and Neck Surgery, University of Washington and Veterans Affairs Puget Sound Healthcare System, Seattle, Washington, U.S.A.

Behavioral	*Good sleep hygiene*
	Adequate sleep time
	Positional therapy (avoid the supine position)
	Avoid alcohol prior to bedtime (2 oz or less ≥ four hr before bedtime is acceptable)
	Appreciate untoward effects of sedatives and hypnotics
	Benefits of weight loss
	Drowsiness driving precautions
Medical	*Treatment of nasal congestion*
	Pharmaceutical agents
	Noninvasive positive airway pressure therapy (NIPAP)
	• *Continuous positive airway pressure (CPAP)*
	• *Auto-titration positive airway pressure (Auto-PAP)*
	Bi-level positive airway pressure (Bi-level PAP)
Surgical	*Upper airway bypass: tracheosotomy*
	Soft tissue surgery—Phase I: palate, nose, tongue
	Skeletal surgery—Phase II: mandibular and maxillary advancement procedure
Dental	*Mandibular repositioning oral dilators*
	Tongue retaining devices

INTRODUCTION

Sleep-disordered breathing encompasses a wide variety of disorders characterized by abnormal nocturnal respiration, including snoring, obstructive sleep apnea ("sleep apnea"), upper airway resistance syndrome, central sleep apnea, central hypoventilation, and other nonobstructive hypoventilation disorders. For the purposes of this chapter, sleep-disordered breathing and obstructive sleep apnea will be used interchangeably.

Generally speaking, treatment of sleep-disordered breathing is aimed at preventing collapse of the pharyngeal airway during sleep. A variety of treatment options, including behavioral, medical, dental, and surgical, can accomplish this goal. There is great variability in the efficacy and effectiveness of these therapies. The efficacy of treatment is defined by how well it works under ideal conditions (e.g., in the sleep laboratory), while the effectiveness is how well it works under everyday conditions (e.g., depending on patient tolerance and adherence to the therapy). Other factors differentiating these options include reversibility, cost, upper airway anatomy, patient preferences, risks, side effects, and availability of medical/dental expertise. Treatment of sleep-disordered breathing should consider the clinical context, taking into account not only the severity of the sleep apnea but also the presenting complaint and cardiovascular risk profile of the patient.

BEHAVIORAL THERAPY

All patients with sleep-disordered breathing should be encouraged to employ behavioral and lifestyle changes that promote restful sleep and improve upper airway patency, regardless of other treatments. In some cases, these therapies alone resolve the clinical consequences of sleep apnea. If a patient is obese, weight loss to ideal body weight is the most effective and important behavioral therapy for this disorder. Patients already at ideal body weight should avoid weight gain. Good sleep hygiene should be practiced, including a comfortable sleeping environment and adequate sleep time. Avoiding alcohol prior to bedtime is important. In general, no more than two ounces should be ingested within four hour of bedtime. Sedative-hypnotics and analgesics should be avoided prior to sleep if possible. Cessation of tobacco smoking, which can inflame and narrow the upper airway, is also helpful. Finally, all patients must be counseled about the dangers of driving or operating dangerous equipment when drowsy. People involved in an automobile accident or near-miss due to drowsiness are at high risk of further accidents and should receive explicit instructions to avoid driving. The use of a 20-minute power nap prior to commuting home can help those who find afternoon driving difficult.

CPAP THERAPY

Medical Therapy

Patients with sleep-disordered breathing and nasal symptoms benefit from therapy to alleviate nasal congestion. In some mild cases, this can completely eliminate the sleep apnea. In more severe cases, this is useful adjunctive therapy that makes noninvasive positive airway pressure therapy (NIPAP) more tolerable. Allergic rhinitis is treated by avoiding allergen exposure and utilizing nasal steroids or cromolyn and oral antihistamines. Consultation with specialists may be necessary. Evaluation and treatment of sinusitis should be undertaken when necessary, and abnormalities of the turbinates or septum should be corrected surgically.

Currently available pharmaceutical treatment for sleep-disordered breathing is ineffective. Many therapeutic agents have undergone testing, including respiratory stimulants, hormone replacement therapy, protriptyline, selective serotonin reuptake inhibiters, and physostigmine. Some agents have demonstrated utility in maintaining airway patency, but side effects limit their use. In the future, agents that selectively target brainstem centers controlling airway patency may be useful. Until then, pharmacologic therapy is not recommended. A possible exception includes women with mild rapid eye movement (REM) sleep-dependent sleep apnea who seem to respond to selective serotonin reuptake inhibiters and are less prone to side effects.

Noninvasive Positive Airway Pressure Therapy

Upper airway positive pressure delivered via a nasal mask has been the mainstay of treatment for sleep apnea since its initial description in 1981. This therapy is safe and efficacious at treating the clinical consequences of the disorder. Technical innovations in machine and mask design have markedly improved patient tolerance. Continuous positive airway pressure (CPAP), which is positive pressure delivered at a fixed level throughout the respiratory cycle, is considered first-line therapy for most patients. Throughout this chapter, the term CPAP will be used in general reference to therapy with positive airway pressue.

The application of CPAP to the upper airway paradoxically decreases rather than increases upper airway dilator muscle tone. Therefore, CPAP acts primarily as a pneumatic splint, preventing pharyngeal airway collapse. Increased end expiratory lung volumes cause additional reflex-mediated dilation of the upper airway. The resultant increased cross-sectional airway area occurs by virtue of lateral pharyngeal wall movement, as opposed to antero-posterior displacement of the tongue base or soft palate.

An efficacious level of CPAP reliably eliminates snoring, respiratory events, oxygen desaturations, and improves sleep quality. Multiple studies have demonstrated improvement in daytime sleepiness, driving performance, vehicular accidents, mood disorders, memory, concentration, vigilance,

cognitive function, and quality-of-life in patients with sleep-disordered breathing who are regular users of CPAP (1). These beneficial effects are seen even in patients with mild disease. Somatic complaints such as nocturia, impaired libido, night sweats, gastroesophageal reflux, chronic headaches, and global musculoskeletal pain that are due to sleep apnea are improved with the use of CPAP. A patient is generally considered a "regular CPAP user" if he or she wears it for 4 hours on most (5 out of 7) nights.

CPAP therapy reduces cardiovascular stress by eliminating the asphyxia and arousals resulting from upper airway collapse. The beneficial effects of positive intrathoracic pressure on the heart provide an additional rationale for the benefit of CPAP on the adverse cardiovascular consequences of sleep-disordered breathing. In patients with severe disease, the use of CPAP is associated with normalization of mortality as compared to controls. The generalizability of these data to the majority of patients with milder disease is questionable. Several randomized, controlled trials have demonstrated that CPAP reduces diurnal blood pressure in hypertensive patients with sleep-disordered breathing. Patients with sleep apnea and atherosclerotic coronary vascular disease are less likely to have a recurrent cardiovascular event (myocardial infarction, stroke, or cardiovascular death) if they comply with CPAP therapy. Patients with sleep-disordered breathing undergoing hip or knee replacement surgery experience fewer complications when using CPAP pre-, peri-, and postoperatively (2).

Indications for CPAP

CPAP may be used in all cases of sleep apnea in which therapy is indicated. The effectiveness of CPAP, combined with an absence of significant risks and contraindications, makes it an acceptable therapy for the entire spectrum of sleep-disordered breathing, assuming that the obstruction is related to soft tissue collapse and there is no other pressing treatment required (e.g., for neoplasm). Guidelines for the use of CPAP have been published (3). These consensus-based recommendations rely heavily on the apnea–hypopnea index (AHI), and third-party payers often deny payment for CPAP devices when the AHI falls below these somewhat arbitrary thresholds. Regardless of patient preference, a trial of CPAP should always be recommended when the AHI is greater than 15 and/or when patients are poor surgical candidates, obese, excessively sleepy, or experience other significant daytime symptoms.

Positive Airway Pressure Equipment

Positive airway pressure is applied in three ways. CPAP devices vary flow rates to ensure that a fixed pressure is continuously applied to the airway during inspiration and expiration. With optimal management, many patients with sleep apnea do well with CPAP devices due to their reliability, simplicity, and inexpensiveness. Auto-titrating positive airway pressure

(auto-PAP) devices utilize sensors to continuously monitor upper airway patency and automatically adjust the delivered pressure throughout the night to prevent airway obstruction (4,5). The pressure remains constant throughout the respiratory cycle but varies over the course of the night. Patients with obstructive sleep apnea predominantly in supine or REM sleep are delivered lower levels of pressure when they are nonsupine or in non-REM sleep. This allows reduction in the mean airway pressure throughout the night, leading to improved tolerance. These devices can compensate for fluctuations in body weight or alcohol intake over time. Each manufacturer employs a different proprietary computer algorithm integrating analysis of flow with feedback to pressure generating systems. Some of these devices are intended for use with specific mask interfaces. When tested in comparison to in-laboratory CPAP titration, these devices appear to be as effective as fixed CPAP. Anecdotally, they are better tolerated than fixed CPAP in patients with pressure intolerances. All of these devices may be uploaded into a computer to provide nighttime pressure profiles for analysis. These data can be used to estimate an appropriate fixed CPAP pressure in patients who either refused or had an inadequate in-laboratory CPAP titration. Auto-PAP device cost has been dropping but is still too high for routine use in patients with sleep-disordered breathing.

Bi-level positive airway pressure (BiPAP) devices deliver a higher level of pressure during inspiration than expiration. The expiratory positive airway pressure (EPAP) keeps the airway open at end expiration, preventing complete closure of the airway (apnea). The inspiratory positive airway pressure (IPAP) prevents partial airway collapse (hypopnea) and snoring. Unlike CPAP, a pressure gradient exists between IPAP and EPAP. This pressure differential augments flow and ventilation. These devices are used for noninvasive mechanical ventilation and may be operated in a spontaneous mode in which the IPAP is only triggered by patient-initiated inspiratory flow or in a timed mode where IPAP is triggered for a preset time at a specified rate. Simple BiPAP machines have preset inspiratory times and flow rates, while more sophisticated devices allow adjustment of these inspiratory flow parameters. These are important determinants of comfort, particularly in patients with neuromuscular disease or chronic obstructive pulmonary disease (COPD). These devices are more expensive than CPAP or auto-PAP and are rarely first-line therapy for patients with SDB. Patients requiring augmentation of nocturnal ventilation (obesity-hypoventilation syndrome, COPD, neuromuscular disease) are the most appropriate candidates for BiPAP. Patients with periodic central breathing rarely benefit from BiPAP, although those with prolonged central apneas may improve with use of a timed back-up rate. There are little data supporting the use of BiPAP to improve positive pressure compliance. However, patients with significant pressure-related intolerances of CPAP (back pressure, aerophagia, and lacrimal duct reflux) often benefit from BiPAP therapy. Table 1 outlines the

Table 1 Positive Pressure Devices

- Continuous positive airway pressure
- Auto-titrating positive airway pressure
- Bi-level positive airway pressure
- Adjunctive features
  - Humidification
  - C-Flex/Bi-Flex
  - Ramp
  - Compliance monitoring

various positive pressure devices available for treating sleep-disordered breathing.

Mask Interfaces

A plethora of mask interfaces are available for use with PAP devices. Advances in plastics, headgear, and interface design have lead to marked improvements in CPAP mask comfort. Finding a satisfactory match between patient and interface can be challenging but is critical to maximizing compliance. Factors determining the optimal interface are listed in Table 2. The responsibility for mask interface fitting is often delegated by the clinician to a CPAP durable medical equipment company. While many of these companies have considerable expertise in this regard, variation in the quality of these providers necessitates clinician involvement in troubleshooting interface problems.

Most people are nasal breathers; therefore, most CPAP interfaces deliver air through the nose. Masks placed over the nose form a seal against the cheeks and upper lip and are held in place with strapped headgear. Either an air cushion or gel material creates the seal. Air-cushioned masks

Table 2 Factors to Consider when Fitting a Positive Airway Pressure Interface

- Presence of facial hair
- Dentition
- Nasal anatomy, internal and external
- Mandibular length
- Claustrophobia
- Oral breathing
- Head/facial shape
- Desire to wear glasses with continuous positive airway pressure
- Preferred sleep position is on the side
- Noise and direction of airflow from ventilation port
- Ease of application
- Contact skin sensitivities
- Aesthetics

float, while gel masks are tightened against the face. Nasal pillows are small nipple-like rubber pieces placed into the nares, sealed by inflating against each nostril, and held in place with headgear. Nasal cannulas are placed into the nose with tubing draped over the ears, looking and functioning much like large oxygen cannulas. Some patients need a chinstrap to prevent mouth opening, although leakage of air through parted lips often persists.

Oral breathing patients and those with oral air leaks benefit from masks covering both the nose and mouth. Significant design advances have made these masks more tolerable, and concerns regarding mask safety are largely unfounded. In some patients, higher pressures are needed when converting to an oral–nasal mask. This is due to either the tongue being pushed by air pressure into the hypopharynx or by posterior displacement of the mandible from the mask itself.

An oral-only interface that functions like a snorkel mouthpiece is held in place by flaps over and behind the lips. This interface is bulky and often poorly tolerated. Further, velo-pharyngeal reflux of air into the nose limits use of this mask in patients following palatal surgery. The pressure levels required to treat sleep-disordered breathing with this interface are often different than with conventional interfaces and should be titrated in the laboratory. It is essential that heated humidification be employed with oral-only interfaces. Table 3 summarizes the different types of mask interfaces for use with PAP devices.

Choosing a Pressure Level

Once a mask interface is selected, the positive airway pressure must be determined. This pressure should be high enough to normalize upper airway flow throughout the night, regardless of sleep state or body position, resulting in maximum sleep quality. In most cases, obstructive sleep apnea is adequately treated at pressures ranging from 5 to 15 cm H_2O.

The standard approach to determining CPAP levels is to adjust the pressure by remote control while the patient undergoes attended polysomnography. The technologist makes additional mask and headgear adjustments as needed during the night. The patient is encouraged to sleep in the supine

Table 3 Positive Airway Pressure Interfaces

- Nasal interfaces
  - Mask
    - Air cushion
    - Gel cushion
  - Nasal pillows
  - Nasal cannula
- Oral–nasal interfaces
- Oral interfaces

position for at least part of the night. The ideal pressure is that which resolves respiratory events, including snoring, with the patient supine in REM sleep. Highly sensitive nocturnal airflow measures allow pressure adjustments to normalize even subtle degrees of airflow obstruction. Mouth leak is corrected with chinstraps and/or conversion to an oral–nasal mask. When appropriate, conversion to BiPAP or oxygen supplementation is necessary. Coaching and support by the technologist generally leads to greater patient acceptance. The clinician determines pressure thresholds for elimination of apneas, hypopneas, respiratory effort-related arousals, snoring, and oxygen desaturations. Patients experiencing significant pressure intolerances during adaptation to CPAP can be safely started at the minimal pressure keeping their airway open. This pressure can be raised to the optimal level once they adapt to therapy.

In most cases, a full night in-laboratory manual CPAP titration is necessary to identify an appropriate pressure. In some instances, a "split-night" protocol is employed whereby the first portion of the night is used to make a diagnosis of sleep apnea and the second portion is used for a manual CPAP titration. This technique has limitations but remains a pragmatic and efficient approach to certain patients with sleep-disordered breathing. A successful split-night study depends on patient selection and preparation (e.g., education, mask fit) prior to the sleep study as well as the ability of the sleep technologist to make the right decision regarding the sleep apnea diagnosis in the initial portion of the study. Approximately 25% of patients initially diagnosed and treated by a split-night study require dedicated full night in-laboratory manual retitrations. Ideal candidates for a split study are those with a high pretest probability of severe obstructive sleep apnea who are comfortable with the idea of CPAP by virtue of a successful orientation prior to the study. When sleep laboratory access is limited, split-night protocols can obviate delays between diagnosis and treatment. Patients requiring re-evaluation in the sleep laboratory, such as those who have undergone sleep surgery or lost significant weight, are good candidates for split-night studies. Sleep-disordered breathing that persists despite these interventions may require retitration to determine the new optimal CPAP pressure. Lastly, third-party payers often require documentation of sleep apnea before covering services; in this instance, a split-night study can both confirm the diagnosis and update the prescription.

The use of auto-PAP devices theoretically obviates the need for selecting a specific pressure. These devices can be used not only to treat the disorder but also to determine an ideal CPAP pressure. In general, the pressure range is set between 5 and 20 cm H_2O. These devices have been used both in the laboratory and at home to determine CPAP prescriptions. This is done by analyzing the computer-generated pressure profile across the night and picking the pressure at which the patient was at or below for 95% of the night. Although convenient, there are no data supporting this use of auto-PAP

Table 4 Methods for Determining the Optimal Continuous Positive Airway Pressure Setting

- Clinical prediction formulas
- Full night manual titrations in the sleep laboratory
- Split-night manual titrations (diagnostic and titration) in the sleep laboratory
- Home titrations
- Auto titration PAP devices

Abbreviation: PAP, positive airway pressure.

devices, and manual in-laboratory titrations are eventually required in about 25% of patients empirically treated with auto-PAP. Indeed, laboratory-based titration remains the gold standard. Further, although some evidence supports empiric pressures based on either clinical prediction formulas (AHI and anthropomorphic data) or bed partner observations combined with the patient's clinical response, these methods are not considered reliable. Table 4 summarizes the methods for determining optimal CPAP pressures.

All positive airway pressure devices can be fitted with cool or heated humidifiers. Most devices include a "ramp" feature permitting a lower pressure start at bedtime that gradually rises to achieve the prescribed pressure after the patient has fallen asleep. The starting pressure and time period are adjustable. Many modern devices have internal systems to monitor compliance by recording time used and pressure profiles. These data allow clinicians to understand individual CPAP use patterns and identify problems such as mask or oral leak unrecognized by the patient.

The Need for Bi-level Positive Airway Pressure

The need for increased alveolar ventilation is the usual indication for BiPAP, a device that varies pressure throughout the respiratory cycle (6). These patients either struggle to generate adequate tidal volumes (COPD, neuromuscular weakness) or do not generate adequate respiratory rates (central sleep apnea). The pressure gradient created by differences between inspiratory (IPAP) and expiratory (EPAP) pressure augments fresh gas movement into and out of the lungs. A timed back-up rate ensures an adequate number of breaths per minute. Patients experiencing significant pressure-related CPAP side effects including back pressure, aerophagia (air swallowing), and naso-lacrimal duct reflux may benefit from BiPAP. Patients undergoing a CPAP titration should be switched to BiPAP if hypoxemia persists despite elimination of obstructive respiratory events, as this suggests hypoventilation. Similarly, prolonged central apneas occurring throughout the titration indicate that a switch is needed to BiPAP with a low (6–8 breaths per minute) back-up rate. BiPAP provides no advantage in treating the periodic central apneas of Cheyne–Stokes respiration.

In patients undergoing BiPAP titrations, the EPAP is adjusted to eliminate obstructive apneas, while the IPAP is adjusted to eliminate snoring, hypopneas, respiratory effort-related arousals, and oxygen desaturations. In patients with nocturnal hypoventilation and a patent airway, the EPAP should remain low when adjusting IPAP to optimize ventilation. Bi-level positive airway pressure settings can be determined from a well-done CPAP titration by setting the EPAP at the pressure eliminating obstructive apneas and the IPAP at the pressure that eliminated all other respiratory events.

Patients with neuromuscular diseases requiring nocturnal noninvasive ventilation, even in the absence of obstructive sleep apnea, require a special BiPAP adjustment approach. These patients need specialized mask fitting followed by an adaptation period with low-pressure settings (IPAP 6–8, EPAP 4 cm H_2O, respectively), slow inspiratory flow rates, and long maximum inspiratory times. Once tolerance has developed, manual in-laboratory titration is necessary to ensure that the EPAP is high enough to maintain airway patency in the event of obstructive events. Continued pressure adjustments are empiric, based on patient comfort and arterial blood gas analysis.

Adverse Effects of CPAP

Significant positive airway pressure complications such as barotrauma and aspiration are rare and essentially limited to instances in which noninvasive ventilation is used in acute care settings. Side effects, on the other hand, are exceedingly common. The vast majority of complaints are related to air pressure, mask/headgear problems, or nasal symptoms. Patients first experiencing CPAP often note a strange feeling that the device is trying to breathe for them. This unpleasant sensation is exacerbated by the oral airflow that accompanies opening the mouth. Most adapt quickly to these symptoms, but some experience persistent discomfort with the nasal air rush on inhalation and resistance to exhalation. The ramp feature and the C-flex respiratory delivery system (Respironics Corp., Murrysville, Pennsylvania, U.S.A.) are helpful at reducing the sensation of back pressure. C-flex causes a brief slight decrease in pressure at the beginning of exhalation. The decrement in pressure is adjustable and proportional to the absolute CPAP pressure and expiratory flow rate. Reflux of air through the naso-lacrimal duct into the eye is an uncommon problem. Eructation, abdominal bloating, and excessive flatulence are due to aerophagia, occurring in only in a small group of patients. This correlates with end expiratory pressures and improves when patients are treated with BiPAP. Persistent mask leak is rarely a problem in well-fitted patients, but occasionally high-pressure requirements are associated with leak despite a well-fit mask. In general, pressure-related symptoms abate as the patient develops a tolerance to pressure breathing.

Troubles with the mask interface and headgear are common but improving with the advent of newer masks. Specific problems include local pressure points over the bridge of the nose or upper lip and the inability to maintain a seal with body position changes. Sleeping fully prone and wearing CPAP is difficult if not impossible. Some interfaces work better for those preferring to sleep on their side. Some masks, particularly gel-based masks, are made of materials that may cause sensitivity reactions. Patients who enjoy reading or watching TV as they fall asleep require an interface that allows for wearing eyeglasses. Pressure or irritation from headgear straps holding the mask in place can be annoying. Some of these systems are complex and difficult to remove and replace in the middle of the night while other simpler interfaces can be unstable. Mixing masks from one manufacturer with headgear straps from another can solve this problem. Some aesthetically appealing systems are fragile, uncomfortable after regular use, and unstable and prone to leakage. Despite these limitations, a well-fit mask interface addressing the patient's needs and concerns is almost always obtainable.

Nasal symptoms account for a significant number of complaints from patients wearing CPAP and tend to be more prevalent in patients with nasal symptoms prior to treatment. Drying or congestion can result from too much or too little humidity. High pressures applied to a narrow nasal passage can be particularly troublesome. Interestingly, patients with pre-existing allergic rhinitis often experience relief of their symptoms while wearing CPAP because the air they breathe is highly filtered, eliminating nocturnal allergen exposure. Few patients tolerate nasal CPAP while experiencing an upper respiratory infection. Occasionally, patients with nonspecific CPAP-related nasal congestion benefit from increased washing of the mask, tubing, and humidifier beyond the typical weekly schedule. Patients should only use soapy hot water. There is no good evidence that CPAP use increases the rate of sinus infection.

Mouth and throat dryness often signify an oral air leak of which the patient may not be aware. Humidification with or without heat can help, although the dryness rarely abates unless the leak is stopped with a chinstrap or oral–nasal mask. Persistent leak despite these therapeutic maneuvers is problematic. Paper tape placed across the lips or under the lower lip can help. The application of denture paste to the inside of the lips has been tried. Oral air leak is often reduced by lowering the mean pressure via lowering CPAP pressures or changing to auto-PAP or BiPAP. However, mouth leak can occur as a result of inadequate pressures as well. Minimizing nasal resistance medically or surgically can also help reduce oral breathing. The addition of a mandibular repositioning oral appliance with CPAP can help keep the mouth closed. One final rare side effect the clinician should be aware of is chest pressure from CPAP-induced increased end expiratory lung volumes causing chest wall stretching. This rare sensation is typically brief and self-limited.

Table 5 Side Effects of Continuous Positive Airway Pressure

- Pressure related
  - Aerophagia
  - Naso-lacrimal duct reflux
  - Back pressure on exhalation
- Interface related
  - Mask
    - Local pressure (nasal bridge, upper lip)
    - Skin irritation
    - Leakage
  - Headgear
- Nasal symptoms
  - Dryness
  - Congestion/sneezing
- Mouth dryness
- Chest pressure
- Inability to sleep in preferred position
- Bed partner complaints
- Device related
  - Noise
  - Tubing condensation
  - Portability
  - Maintenance

Common machine-related complaints include ease of use, maintenance procedures, noise, portability, and tubing condensation. Most modern machines are quiet but none are silent, and some generate unique sounds that may bother a patient or their bed partner. Machines that vary pressure throughout the respiratory cycle including BiPAP and CPAP C-flex are slightly noisier. Each CPAP mask utilizes a different system for preventing carbon dioxide rebreathing. These so-called ''whisper valves'' are associated with a certain amount of noise. Discomfort from the jet of air that is associated with these valves can also be annoying. Although most bed partners prefer CPAP therapy to noise from snoring and concern from apneas, many are bothered by the noise of the device/mask, the jet of air, or the esthetics of a complex apparatus. Table 5 summarizes CPAP-related side effects.

CPAP Compliance

Compliance is a measure of those who continue to use CPAP for more than a month. Greater than 90% of patients prescribed CPAP are willing to try it at home following a CPAP titration. This CPAP acceptance rate drops slightly in patients who undergo a split-night protocol polysomnogram. Approximately 10% of patients abandon CPAP therapy during the first

month of therapy. Successful CPAP users wear it about five hour per night, most nights per week. Average compliance rates are 65–70%, although rates as high as 90% are seen in sleep clinics providing high levels of support. There are no well-established methods for predicting who will comply with CPAP. Anecdotally, patients with severe diurnal nasal obstruction, claustrophobia, and obligate prone sleepers have severe difficulty wearing CPAP. Patients with symptom relief on CPAP and those with excellent support systems (friends and/or relatives who are successful users of CPAP) do quite well. There is no correlation between severity of sleep-disordered breathing and CPAP compliance.

Improving Compliance

CPAP compliance can improve with aggressive follow-up and intervention in specialized clinics. A team approach including physicians and CPAP technicians is extremely valuable. Successful compliance with positive airway pressure therapy begins with ensuring that the patient has the right CPAP pressure prescription for an appropriate indication within the context of a thoughtful treatment plan. The initial pressure setting can impact CPAP acceptance and compliance. Most sleep clinicians are trained to initiate therapy at the ideal pressure, regardless of level of patient tolerance. A more thoughtful and perhaps more successful approach is to pick an initial pressure based on a variety of factors. Start at the ideal pressure when less than 15 if well tolerated. If pressure is poorly tolerated or more than 15, prescribe the pressure at which obstructive apneas disappeared. Once habituated, the higher ideal pressure can be implemented.

Generally, the purpose of an in-laboratory CPAP titration is to determine the pressure resolving respiratory events. More often than not, the ideal mask is not determined. This process is hampered by limited availability of masks due to sterilization and reuse requirements, lack of time, and inexperienced mask fitting by sleep technologists. Custom mask fitting is best performed by experienced staff with a full array of masks. Additional time spent during the initial mask fitting is helpful and ultimately time saving. Mask fitting success is facilitated by using sizing templates, evaluating for facial hair and dentures, and inquiring about preferred sleep positions. Despite the best efforts at getting things right the first time, repeated refitting is sometimes the only way to find just the right mask. There are successful users of every mask and interface on the market, and no one mask is considered the ''best.'' Some patients prefer using more than one interface to rotate pressure points. During periods of nasal obstruction, such as with upper respiratory infections, a temporary switch to an oral–nasal mask can be helpful. The physician should always query patients about nasal symptoms. The addition of heated humidification as well as the medical and surgical treatment of nasal obstruction can markedly improve CPAP compliance. Nasal surgical procedures improving CPAP tolerance include

Table 6 Improving CPAP Compliance

- Appropriate indication in the appropriate patient
- CPAP use in the context of a complete treatment plan
- Involvement of the sleep clinician in CPAP follow-up
- Correct prescription/pressure
- Custom mask fitting
- Use of newest technologies
- Appropriate use of CPAP, C-flex, BiPAP, auto-PAP
- Maintenance of nasal patency
  - Heated humidification
  - Regular equipment washing
  - Radiofrequency turbinate reduction, deviated nasal septum repair, surgical turbinate reduction, nasal valve repair
  - Sinusitis treatment
  - Allergic or nonallergic rhinitis treatment
- Keep mouth closed
  - Oral–nasal masks
  - Chin straps
  - Oral appliances
  - Tape

Abbreviation: CPAP, continuous positive airway pressure.

radiofrequency or surgical turbinate reduction procedures and deviated nasal septum and nasal valve repair. Table 6 highlights ways to optimize CPAP compliance.

Following Patients on CPAP

Follow-up of patients on CPAP is best optimized by a regular schedule and a team approach. Practitioners, CPAP technologists, and durable medical equipment providers all play a role. The interval between evaluations is short during the adaptation period, gradually extending as CPAP tolerance improves. Patients should be seen within a month of CPAP initiation to rectify problems such as ensuring that the equipment was dispensed as prescribed and adjusting or refitting masks. When available, the internal compliance monitor should be analyzed. CPAP pressure and humidification may require empiric adjustment. Reviewing the patient's nocturnal and diurnal sleep-disordered breathing symptoms helps assess response to therapy. Snoring should be resolved; if not, the pressure may be too low or an oral leak may be present. Nasal symptoms, mouth/throat dryness, and pressure-related complications should be ascertained and corrected. If the patients are doing well, reinstruct them to change filters regularly, wash the hose, humidifier, and mask with soap and hot water weekly, and replace the mask according to the manufacturer's recommendation (3–6 months). Routine follow-up should continue every 6 to 12 months

Table 7 Routine Follow-Up Recommendations for Patients on CPAP

- Adequacy of current therapy
  - Snoring with mask on?
  - Control of nocturnal and diurnal symptoms?
- Review CPAP maintenance
- Check pressure level, interface, filter
- Review nasal symptoms, mouth dryness

Abbreviation: CPAP, continuous positive airway pressure.

thereafter. Patients with significant problems should be followed monthly until their issues are resolved. CPAP follow-up recommendations are outlined in Table 7.

Patients having undergone diagnostic polysomnography and subsequent CPAP titration require repeat sleep testing only in certain circumstances. Patients doing poorly on CPAP who do not respond to empiric pressure changes or auto-PAP trials should be restudied, particularly if the initial study utilized a split-night protocol. Other situations warranting CPAP retitrations include re-emergence of symptoms, passage of greater than five years since initial titration, and change in body weight of more than 10%. Repeat diagnostic polysomnography is indicated following complete recovery from surgical treatments, in order to evaluate for residual sleep apnea. The indications for retesting in the sleep laboratory are outlined in Table 8.

Many patients with sleep-disordered breathing-related hypersomnia experience rapid complete resolution of their symptoms. The persistence of daytime sleepiness despite regular CPAP use is unusual and warrants special attention. The clinician should ensure that the CPAP unit is generating the prescribed pressure and the mask interface is in good repair and functioning properly. If the CPAP unit does not monitor compliance, a month's trial with a compliance tracking unit helps establish usage patterns. Evaluate and correct oral breathing if present. Poor sleep hygiene,

Table 8 Indications for Retesting Polysomnography/CPAP in the Sleep Laboratory

- Poor tolerance of CPAP
- Inadequate initial manual titration, particularly if a split-night protocol was utilized
- Re-emergence of symptoms
- More than five years since initial manual titration
- Greater than 10% change in body weight
- Failure of empiric changes in pressure to resolve a problem
- Following sleep apnea surgery (diagnostic polysomnography)

Abbreviation: CPAP, continuous positive airway pressure.

Table 9 Managing Persistent Hypersomnia Despite CPAP Compliance

- Coexisting sleep disorders?
  - Insomnia
  - Restless legs syndrome
  - Periodic limb movement disorder
  - Narcolepsy
- Adequate use of CPAP? (Obtain objective data)
- Adequate CPAP pressure?
  - Snoring with CPAP on
  - Weight gain
- Condition of equipment?
  - Set at and generating prescribed pressure
  - Mask leak
- Adequate sleep hygiene?
- Oral leak?
- Consider prescribing a wake-promoting agent (modafinil)

Abbreviation: CPAP, continuous positive airway pressure.

insomnia, restless legs syndrome, periodic limb movement disorder, and insufficient sleep syndrome are common potential comorbid sleep disorders that should be sought after and treated. Narcolepsy occurs at a higher frequency in patients with sleep-disordered breathing, and they should be queried for the symptomatic tetrad associated with this disease. The patients should undergo a full night of in-laboratory sleep testing with CPAP at their prescribed pressure with pressure adjustment as necessary. If the CPAP pressure is adequate, the patients should undergo a formal multiple sleep latency test to objectively measure sleepiness and document the presence of sleep-onset rapid-eye movement sleep periods. Sleepy CPAP-compliant patients devoid of other sleep disorders are candidates for wake-promoting agents such as modafinil. Indeed, some patients with well-treated obstructive sleep apnea experience persistent irreversible daytime sleepiness. Guidelines for managing persistent sleepiness in sleep apnea patients are listed in Table 9.

Traveling with CPAP

Traveling with CPAP is necessary and deserves special consideration. Patients deriving benefit from CPAP will go to great lengths to travel with their machine. These delicate medical devices should be carried on an airplane unless packaged carefully. Modern devices are small and fit nicely into carry-on bags. Even smaller ''miniature'' devices are available, although their quality and durability remain untested. Devoid of a humidifier, these tiny machines may fit in a brief case. Modern devices adapt to international currents and altitude changes automatically. A letter from a provider stating

the medical necessity of the device assures easy transport through airport security screening. Patients with less robust symptomatic benefit may not wish to travel with their machine. Brief periods without therapy are safe, provided cardiopulmonary illness, severe oxygen desaturations, and drowsy driving are not issues.

Sleep Apnea in the Perioperative Period

Patients with sleep-disordered breathing are at a higher risk of anesthetic and analgesic complications compared to patients without the disorder. Therefore, it is best if sleep apnea is identified and treated prior to surgical procedures that require general anesthesia. Patients with severe sleep apnea should be monitored postoperatively with continuous oximetry. Further, patients should bring and use their own CPAP units postoperatively.

Sleep Apnea and Impairment

Physicians are encouraged to know and follow local laws restricting the driving of patients with sleep disorders. In most states, this is left to the discretion of the patients and their physicians. In a few states, sleep apnea is a reportable illness. In general, well-treated patients have no difficulty with driving. Federal law governs the restrictions on pilot's and commercial driver's licenses. Commercial drivers merely need to undergo a standard Department of Transportation physical examination. The need to restrict driving privileges is left to the discretion of the examining physician. Recreational and commercial pilots must submit to regular examinations by the Federal Aviation Administration flight surgeon. In most cases, an active license is maintained if the treating physician writes a letter of medical compliance with CPAP, the patient passes a maintenance of wakefulness test, and the patient does not require pharmaceutical agents to maintain alertness.

Role of the Primary Care Physician

Currently, most patients using CPAP obtain routine follow-up in sleep specialty clinics. As the number of patients being treated for sleep apnea grows, responsibility for this regularly scheduled care will fall within the purview of the primary care provider. Working with durable medical equipment companies and sleep clinicians, most primary care practitioners are more than capable of providing high-quality care in this regard.

SURGICAL THERAPY

This section reviews concepts related to the surgical treatment of obstructive sleep apnea. First, the role of surgical treatment in general terms will be outlined. Next, appropriate candidates for surgical intervention will be discussed. Third, several common surgical treatments for sleep apnea and a brief rationale for prescribing each will be reviewed. Then, the

preoperative evaluation will be presented. Finally, expected and adverse outcomes will be reviewed.

The Role of Surgery

There are several roles for surgical treatment of sleep apnea. The main surgical treatments aim to enlarge and stabilize the upper airway (above the vocal cords). While these treatments often do not cure sleep apnea, they usually provide long-term benefit. Adjunctive surgical treatments complement nonsurgical therapy to improve outcomes. Surgical bypass of the obstructing upper airway (i.e., tracheotomy) is the most effective cure for sleep apnea, but is usually reserved for extreme cases. Surgery should be the primary treatment for patients with a fixed upper airway obstruction amenable to surgical correction. When snoring is the sole concern, surgical treatment offers many advantages. Table 10 summarizes the role of surgery in the treatment of sleep apnea.

The main role for sleep surgery is to salvage treatment for patients not using CPAP adequately. There is no consensus on what constitutes adequate CPAP use. We know there is a dose response relationship between CPAP use and CPAP outcome (7–10). CPAP use of more than six hours every night is required to achieve the best outcomes for symptoms, quality-of-life, function, and survival (7,10). Approximately 35% of patients use CPAP consistently in this amount (11,12). It is not clear what is the minimum acceptable CPAP use. Certainly, patients who do not use CPAP at all should be referred for surgical consultation.

Obstructive events occur when a critically vulnerable narrowing in the upper airway collapses during sleep. Various surgical procedures are available to enlarge and stabilize the upper airway to reduce complete collapse. These surgical treatments often do not cure sleep apnea, but do offer significant benefits. There are no issues with compliance, so that once treated the patient benefits nightly from the intervention. There is no equipment maintenance, and the patient does not rely on an electrical source. There are no foreign objects to wear compromising patient comfort or sleep quality. Expected beneficial health outcomes as well as the potential adverse outcomes are discussed in detail below.

Table 10 Roles of Surgery for Sleep Apnea

- Salvage CPAP failures
- Adjunct to CPAP or oral appliance treatment
- Primary therapy for fixed airway obstruction
- Definitive treatment

Abbreviation: CPAP, continuous positive airway pressure.

Surgery has an important role as adjunctive treatment for sleep apnea. Some patients struggle with CPAP due to high-pressure requirements in the setting of severe upper airway compromise. In those patients, surgical enlargement and stabilization of the airway can enable the patient to succeed with CPAP by lowering the pressure requirement or reducing the pressure sensation. In this situation, the surgical goal is not to cure sleep apnea, but rather to improve CPAP outcome. The specific surgical treatment depends on the site(s) of anatomic obstruction.

Nasal surgery is an important adjunctive treatment for sleep apnea. Nasal obstruction can compromise a patient's CPAP compliance (13). While heated humidification and nasal medications improve CPAP tolerance, they are often only partially helpful. Patients with anatomic nasal obstructions or refractory soft tissue obstructions require surgical correction (14). An optimal nasal airway can improve tolerance of nasal CPAP by reducing pressure requirements (15), improving comfort (14), and reducing mouth breathing. Mouth breathing, and hence mouth opening, can displace the tongue base posteriorly in the pharynx, compromising the hypopharyngeal airway. Nasal correction also complements oral appliance therapy by alleviating nasal obstruction not addressed by the appliance and by improving tolerance of limited mouth opening.

Surgical treatment is indicated as primary therapy for sleep apnea when a fixed airway obstruction is responsible for the apnea. For example, patients with markedly enlarged tonsils may experience cure with a simple tonsillectomy. These same patients often require high CPAP pressures to create an adequate airway around noncompliant tonsillar tissue. Oral appliance therapy does not address tonsillar obstruction. A less common example is the patient with large cervical spine osteophytes impinging on the hypopharyngeal airway. Positive pressure or mandible retraction does not correct this obstruction.

The most effective treatment for sleep apnea is a tracheotomy, which bypasses the upper airway obstruction entirely (16). A long-term tracheotomy, however, is not desirable to most patients. This treatment is typically reserved for patients with severe sleep apnea who fail CPAP therapy and who cannot tolerate upper airway reconstruction because of critical comorbidities.

Patient Selection and Surgical Approach

Surgical candidacy depends on several factors. First, the patient must desire surgical therapy after being informed of the expected benefits and risks. Second, there must be a surgically correctible problem. Most sleep apnea patients have some degree of anatomic abnormality that would benefit from surgical correction. Occasionally, the source of obstruction is only evident during an examination while asleep or sedated. Third, comorbidity affects surgical decision-making. Patients with severe illness may be poor candidates for upper airway reconstructive surgery, which can require multiple stages

or complex operations. However, these same patients may be appropriate candidates for tracheotomy. Considering surgical and anesthetic risk, less comorbidity is better. However, sleep apnea patients inherently have some comorbidity (i.e., the sleep apnea) and often have related comorbidities (e.g., hypertension, gastroesophageal reflux disease, depression, etc.). Thus, there are no absolute criteria to judge surgical candidacy with respect to comorbidity, but consideration of this issue plays a major role in surgical decision-making.

Surgery is not recommended for patients who have unrealistic goals or expectations of surgery. The patient should be counseled on realistic surgical outcomes and accept them if he/she wishes to pursue this treatment option. Once surgery is done, it usually cannot be reversed. This issue is important for surgery of any kind, but it may be particularly important for surgical treatment of sleep apnea. Sleep surgery often does not cure the sleep apnea, and this fact must be clearly understood by the patient considering surgical treatment for this condition.

Successful surgical outcomes mandate careful perioperative management and postoperative follow up. The patient must understand and be motivated to follow care instructions carefully to avoid complications. Surgery is a stressful event, and the patient must be able to manage this stress. It puts a temporary strain on family, friends, coworkers, and others, so the patient must be able to accommodate those issues. Table 11 summarizes determinants of surgical candidacy.

A wide variety of surgical procedures can be employed to treat sleep apnea. Procedure selection depends on anatomic abnormalities and patient desire. Table 12 summarizes the upper airway anatomy and structures relevant to sleep apnea. Most sleep surgeons take a site-directed, staged approach to surgical therapy, analogous to the titration process for CPAP pressure selection. The Riley–Powell surgical protocol is a two-stage protocol for upper airway reconstruction (17). However, most sleep surgeons, including Riley and Powell, do not adhere strictly to a two-stage process, but rather take several steps (18).

Primary sites of obstruction are addressed first with site-directed treatments. This approach uses the minimum amount of surgery to achieve the treatment goals and minimize risks. Oropharyngeal compromise by tonsillar enlargement or soft palate prominence are the most common anatomic

Table 11 Determinants of Surgery Candidacy

- Patient's desire for surgery
- Correctible anatomic narrowing/obstruction
- Comorbidity
- Appropriate goals of and expectations from surgery
- Psychological and social stability

Table 12 Upper Airway Anatomy

- Nasal (from nares to posterior choanae)
  - Nares
  - Nasal valves
  - Septum
  - Inferior turbinates
- Nasopharyngeal (from posterior choanae to soft palate)
  - Adenoid
- Velopharyngeal (behind soft palate)
  - Soft palate
  - Tonsils
- Oropharyngeal (from soft palate to tip of epiglottis)
  - Soft palate
  - Tonsils
  - Oral tongue
- Hypopharyngeal (from tip of epiglottis and below)
  - Tongue base
  - Lingual tonsil
  - Epiglottis
- Laryngeal (inside vestibule of the larynx)
  - Epiglottis
  - False vocal folds
  - True vocal folds (glottis)

abnormalities. Therefore, surgery addressing these issues (uvulopalatopharyngoplasty) is the most common sleep apnea surgery (16). A third or more of patients will have a tongue base obstruction, either alone or in addition to a palatal obstruction (16). Thus, tongue base correction is required in a substantial number of sleep surgery patients. Neglecting tongue treatment in these patients is analogous to prescribing a CPAP pressure of 5 cm H_2O to a patient who ideally requires a pressure of 10. Correction of tongue obstruction may require multiple surgical procedures (see below). Nasal obstruction should also be addressed because it sometimes causes higher intrapharyngeal inspiratory pressure and pharyngeal airway collapse. Mouth opening associated with nasal obstruction displaces the tongue posteriorly in some patients, resulting in further compromise of the hypopharyngeal airway. Some evidence suggests that nasal and pharyngeal surgery should not be performed together to avoid postoperative swelling in both areas simultaneously (19). Patients refractory to site-directed treatments may require global airway treatment (16). Maxillo-mandibular advancement provides oropharyngeal and hypopharyngeal stability simultaneously. This major procedure provides best results when following the site-directed treatments described above (20,21).

Nasal Procedures

Turbinate reduction opens the airway by decreasing the obstructing effect of enlarged inferior turbinates. Turbinate mucosa is important for humidifying, warming, and filtering the air we breathe. The goal of turbinate surgery is reduction in size without compromising mucosal function. Several methods are available for turbinate reduction (Table 13), the technical details of which are beyond the scope of this book.

Turbinate reduction is particularly valuable as adjunctive CPAP treatment. Enlarged turbinates cannot be simply pushed aside with extra pressure. CPAP pressure and airflow often causes rebound rhinitis, compounding the problem. In some people, the turbinates become particularly problematic as they engorge with blood when lying supine (22,23). For a patient with difficulty tolerating CPAP therapy, one should examine the patient's nasal caliber with special attention on the turbinates (13).

Septoplasty improves the nasal airway by straightening a deformity of the nasal septum. Septal deformity compromises nasal breathing in many ways, including physically obstructing airflow, creating airflow turbulence patterns that reduce airflow efficiency, or by promoting nasal crusting. Unfortunately, a deviated septum typically does not leave the contralateral nasal airway more patent. The inferior turbinate on the "open" side usually swells to fill the extra space created by the septal deviation. This compensatory turbinate hypertrophy combines with the septal deviation to leave the patient with a compromised nasal airway (24). Surgical correction of the septal deformity improves the nasal airway, and in severe cases concurrent contralateral turbinate reduction results in further improvement (24).

Nasal valve collapse can critically restrict nasal airflow. The nasal valve area has the greatest airflow resistance of the entire upper airway (25). The

Table 13 Nasal Procedures

- Turbinate reduction
  - Radiofrequency
  - Turbinate outfractures
  - Submucous resection
  - Intramural cauterization
  - Cryotherapy
- Septoplasty
- Functional rhinoplasty
- Nasal valve surgery
  - Spreader grafts
  - Flaring suture
  - Suspension suture
  - Batten grafts

Table 14 Uvulopalatopharyngoplasty Variants

- Classic uvulopalatopharyngoplasty (Fujita)
- Uvulopalatal flap (Powell)
- Palatal advancement (Woodson)
- Z-palatoplasty (Friedman)
- Lateral palatopharyngoplasty (Cahali)
- Laser-assisted uvulopalatoplasty (LAUP)
- Radiofrequency palatal stiffening (Somnoplasty®)
- Injection snoreplasty (Mair)
- Palatal implants (Pillar® implants)

nasal valve is the triangular area between the nasal septum, the lateral nasal wall (specifically, the upper lateral cartilage), and the front of the inferior turbinate. Nasal valve collapse is frequently due to a septal deformity or turbinate hypertrophy, and correcting these abnormalities often fixes the collapse. In some patients, however, weak upper lateral cartilage allows persistent valve collapse. In severe cases, the alar rim may also collapse. These problems are corrected in a variety of ways outlined in Table 14. Nasal valve collapse should be less problematic with CPAP due to the positive pressure stabilizing the valve. In cases of severe nasal valve collapse, a nasal pillow CPAP interface may best stabilize the airway.

Other anatomic nasal airway deformities may require surgical correction with a functional rhinoplasty. Bony deviations (e.g., from prior trauma), saddle nose deformity, ptotic nasal tip, wide columella, and other anatomic defects are all correctable causes of reduced nasal airflow.

Oropharyngeal Procedures

Uvulopalatopharyngoplasty (UPPP) is the most common surgical procedure for sleep apnea because a prominent soft palate is the most frequent anatomic airway abnormality (16). This procedure typically removes or reduces the uvula and shortens and/or tightens the soft palate. There are many variations of this procedure (Table 14), with each focused on correcting oropharyngeal and velopharyngeal airway compromise. Some variants (e.g., radiofrequency stiffening, injection snoreplasty, palatal implants) simply stiffen the palate and are indicated only for snoring. The technical details of each procedure are beyond the scope of this book. Usually, a tonsillectomy is performed simultaneously if the tonsils are still present.

Hypopharyngeal Procedures

There are several procedures for improving the hypopharyngeal airway, each aimed at a specific target area or problem (Table 15). Several

Table 15 Hypopharyngeal Procedures

- Tongue advancement/stabilization
  - Genioglossus advancement
  - Hyoid suspension
  - Tongue suspension suture
  - Mandibular advancement
- Tongue reduction
  - Midline glossectomy
  - Lingualplasty
  - Radiofrequency reduction
- Epiglottis correction
  - Epiglottoplasty
  - Hyo-epiglottoplasty
  - Hyoid suspension

procedures advance or stabilize the tongue base. These procedures may be used individually or in combination, depending on the location and severity of tongue base obstruction (26). Genioglossus advancement involves creating an osteotomy around the genial tubercle on the anterior mandible and advancing it 10–15 mm forward without moving the teeth (27). Hyoid suspension advances and stabilizes the hyoid bone to the thyroid cartilage (28). The hyoid bone is attached to the base of the epiglottis via the hyo-epiglottic ligament and to the base of tongue; therefore, stabilization of the hyoid bone helps stabilize the epiglottis and lower tongue base. Another procedure involves attaching a tongue suspension suture to the anterior mandible, creating a tongue base sling. Mandibular advancement moves forward most of the anterior mandible, including the genial tubercle, other sites of tongue attachment, and the lower teeth.

Tongue reduction procedures improve the hypopharyngeal airway by decreasing tongue tissue volume. The midline glossectomy creates a trench (29), and the lingualplasty extends the resection laterally (30). Both procedures produce major perioperative morbidity with bleeding and pain. The radiofrequency reduction creates a submucosal scar that stiffens the tissue and reduces tongue volume by a mean of 17% (31). Although multiple treatments are necessary, this procedure is well tolerated by most patients (32,33).

Posterior retroflexion of the epiglottis impairs the airway. There are procedures to debulk or stabilize the epiglottis. Epiglottoplasty and hyo-epiglottoplasty resect part of the epiglottis with or without resecting adjacent tongue base tissue (34). These procedures are fairly radical, increasing the risk of aspiration by removing an important airway protective mechanism. Hyoid suspension, as noted above, stabilizes the epiglottis indirectly through its attachment to the hyoid bone via the hyo-epiglottic ligament. Patients easily tolerate hyoid suspension. Some of these epiglottis procedures require a neck incision.

Table 16 Global Airway Procedures

- Maxillo-mandibular advancement
- Gastric bypass (bariatric surgery)
- Tracheotomy
  - Cannula
  - Skin-lined

Global Airway Procedures

A few procedures improve or bypass the upper airway and thus are not site directed. Maxillo-mandibular advancement projects the entire lower facial skeleton and attached soft tissues forward. The upper and lower teeth are either moved with the jaw bones in native occlusion or moved differentially to correct an anterior–posterior malocclusion. Occlusion correction usually requires concomitant pre- and postoperative orthodontics. This procedure stabilizes and improves the caliber of the velopharynx, oropharynx, and hypopharynx (20). It also probably tightens the lateral pharyngeal walls by placing soft tissues under tension. This is a major operation typically reserved for patients with persistent significant sleep apnea following other site-directed surgical treatments (17).

Gastric bypass is a bariatric procedure that produces long-term weight loss by a combination of endocrine and mechanical digestive effects (35). This surgery carries a 2% risk of perioperative mortality, and requires life-long dietary supplements. For morbidly obese patients, this treatment can result in long-term loss of excess weight and dramatic improvement in obstructive sleep apnea (36).

As previously mentioned, a tracheotomy bypasses the entire upper airway and eliminates obstructive sleep apnea (16). For sleep apnea patients, a smaller tracheotomy cannula can be used. Patients can eat and speak normally with the cannula capped during waking hours and can breathe easily with the cannula open during sleeping hours (37). The tracheotomy requires vigilant maintenance to minimize complications, such as cannula occlusion, mucus plugging, bronchitis, pneumonia, stomal granulation tissue formation, and peristomal infections. For morbidly obese patients, a skin-lined tracheotomy helps control stomal granulation and peristomal infections (38). Global airway procedures are outlined in Table 16.

Preoperative Evaluation

A full medical history relevant to sleep apnea is indicated for all sleep apnea patients. In particular, the preoperative evaluation includes assessment of both the anatomic corrections to be made and the optimal perioperative management strategies. A thorough upper airway examination provides the

anatomical basis of surgical decision-making. The nasal airway is examined in detail, with special attention to adequacy of airflow. External nasal deformities and nasal valve collapse are examined with respect to nasal airflow. Intranasal deformities are noted. Nasal flow measurements, quantitative anatomical measurements (e.g., acoustic rhinometry), and nasal endoscopic examination may all be indicated to supplement the nasal examination. Specific procedures are available for each type of abnormality of nasal airflow.

A direct examination of the oral cavity and oropharynx provide insight into the role of uvulopalatopharyngoplasty, tonsillectomy, and some tongue procedures. The hypopharyngeal airway is evaluated by indirect (mirror) examination and by inspection of other related structures in the neck and mouth. For example, the position of the hyoid bone relative to thyroid cartilage will determine if hyoid suspension is feasible. The height of the mandible will determine if genioglossus advancement is a viable option. The state and position of the teeth influence surgical decision-making regarding mandible advancement or maxillo-mandibular advancement.

If the indirect examination does not provide an adequate evaluation of the hypopharyngeal airway, or if one suspects tongue base obstruction and wishes to examine the hypopharynx with the tongue in native position, then transnasal flexible fiberoptic laryngoscopy is indicated. Fiberoptic laryngoscopy provides an excellent view of the entire hypopharyngeal and laryngeal airway, without the distortion created by anterior tongue retraction during the indirect examination. The anatomic findings dictate which type of tongue advancement/stabilization procedure is indicated, whether tongue reduction is indicated, and whether epiglottis correction is needed. During this exam, various maneuvers test collapsibility of the airway (Mueller maneuver) and temporarily produce the effects of various surgical maneuvers (e.g., mandible advancement).

X-rays help with surgical planning, especially for procedures involving osteotomies. A panorex (mandible) X-ray reveals the state and position of the tooth roots, the position of the mental nerve foramina, and the presence of bony pathology. A lateral cephalogram provides documentation of relative skeletal positions.

Perioperative Risk Evaluation

There are inherent risks of anesthesia and surgery that are exacerbated in the setting of sleep apnea. A preoperative evaluation assesses these risks to plan for optimal perioperative management. This section reviews some of these perioperative issues.

During anesthesia induction and emergence, when intubating and extubating the patient, sleep apnea patients are vulnerable to airway compromise (39). Preoperative assessment of the airway by fiberoptic laryngoscopy helps anticipate difficulty. The surgeon communicates the

findings with the anesthesiologist in advance, so both can be prepared for a difficult intubation. Sedating preoperative medications are avoided as they may compromise the airway prior to intubation.

Comorbidities are evaluated and optimized prior to surgery. Cardiovascular disease is common in sleep apnea patients. A cardiology consultation is obtained as indicated. Optimization of cardiac status prior to surgery is always a good idea. For patients on anticoagulant therapy, including aspirin, a pretreatment perioperative management plan is developed to balance the risk of bleeding against potential thrombus formation in coronary or cerebral arteries. Hypertension is common postoperatively, so pre-existing hypertension must be optimized. Preparation for perioperative hypertension is always indicated. Diabetes management strategies are implemented as indicated, and gastroesophageal reflux disease treatment is initiated in advance.

Patients with severe sleep apnea and/or those at risk of significant airway swelling should be monitored in intensive care postoperatively. When feasible, postoperative CPAP helps protect the airway, especially when using sedating analgesic medications. Nonsedating analgesics should be substituted (e.g., NSAIDS, ice, topical anesthetics, etc.) whenever possible.

The surgeon should educate the patient preoperatively about all of these issues. Patients who understand the risks and perioperative management plan will have improved outcomes with less anxiety and improved recovery. For example, the patient should anticipate no preoperative anxiolytics, minimization of postoperative narcotics, a possible intensive care unit stay, and possible postoperative CPAP use.

Expected Outcomes

Surgical treatment for sleep apnea provides long-term benefit, even though it often does not entirely cure the disease. Patients and referring physicians considering surgery must have realistic expectations of treatment benefit.

It remains unclear how best to measure treatment outcomes for sleep apnea. Truly, treatment ought to address the clinically important outcomes such as mortality, cardiovascular disease, motor vehicle crashes, daytime function decrements, symptoms, and quality-of-life deficits. Surrogate measures of treatment outcome, like polysomnographic parameters, are important if they translate into clinically important effects. Unfortunately for patients diagnosed with sleep apnea, improvements in polysomnographic parameters do not necessarily translate directly into all the desired outcomes (40). Table 17 highlights the clinically important outcomes of obstructive sleep apnea treatment, while Table 18 addresses the surrogate outcome measures.

As previously mentioned, surgical treatment often does not physiologically cure sleep apnea (i.e., permanently normalize the AHI). This fact has left some people to suggest that surgical treatment often fails. This view

Table 17 Clinically Important Outcomes of Surgical Obstructive Sleep Apnea Treatment

- Reduced mortality
- Reduced cardiovascular events
- Reduced motor vehicle crashes
- Improved daytime function
- Relieved symptoms
- Elevated quality-of-life

neglects the risk to patients who are otherwise inadequately treated. When considering surgical outcomes, one must view them in the context of outcomes from alternative therapies.

Although CPAP at the optimal pressure in the sleep laboratory dramatically improves physiological measures, this is not the case for all patients (41). Physiological normalization with CPAP depends on using 100% of sleep time. The minimum usage needed to consider CPAP physiologically successful is unknown (41). The current standard of four hours per night five nights per week (11) is probably inadequate. This minimum threshold amounts to 20 hour of use per week, covering just 37% of the recommended 56 hours of sleep time per week. Indeed, early research suggests a dose response relationship between CPAP usage and improvement in clinically important outcomes like daily functioning, quality-of-life, symptoms, incident cardiovascular disease, and mortality (7–10).

With this perspective, one can consider the physiological surrogate and clinically important outcomes of surgical treatment. Most data are available for UPPP. Be aware that UPPP alone represents only partial treatment of sleep apnea in many patients. A sampling of published studies will serve as the basis for these comments.

Uvulopalatopharyngoplasty improves but often does not normalize the pathophysiology of sleep apnea. The most widely cited study is a pooled data analysis of published studies on UPPP by Sher et al. (16). This study reports that among all-comers, just 41% of UPPP patients achieve a 50% reduction in respiratory disturbance index (RDI) to less than 20 events/hour or a 50% reduction in apnea index (AI) to less than 10 events/hour. This

Table 18 Examples of Surrogate Outcome Measures

- Polysomnography parameters
  - Apnea–hypopnea index
  - Oxygenation parameters
  - Arousal index
- Critical airway pressure
- Inflammatory markers

same study reports that among patients with known palatal obstruction alone (on which UPPP alone is indicated), 83% of UPPP patients have a 50% reduction in AI, the more severe of sleep-disordered breathing events. In these appropriately selected patients, the average AI improves 75%, respiratory disturbance index (RDI) improves 33%, and lowest oxyhemoglobin saturation (LSAT) improves 25% (Fig. 1). Thus, UPPP appears to improve, if not normalize, the physiology of sleep apnea, especially in anatomically appropriate patients.

What about patients who fail UPPP? These patients commonly have tongue obstructions (Fig. 1), in which case one would not expect UPPP alone to eliminate the sleep apnea (10). Sher also reported on a smaller number of studies involving tongue procedures. He found that 67% of all comers had successful reduction in RDI or AI following tongue procedures. Friedman et al. (42) compared UPPP alone to UPPP with radiofrequency tongue reduction in patients with tongue involvement. UPPP alone achieved 81% success (50% AHI reduction to less than 20 events/hr) in anatomically favorable patients, but just 17% success in anatomically unfavorable patients with tongue involvement. With tongue reduction added to UPPP in anatomically unfavorable patients with tongue involvement, the success rate increased to 41%. It should be noted that the only tongue procedure was radiofrequency reduction, which is a minor tongue treatment. These data support a site-directed approach to surgical therapy.

For patients with significant residual sleep apnea following site-directed therapy, global airway surgery can further improve outcomes. Riley et al. (20) reported 98% success on 84 patients undergoing maxillomandibular advancement after the failure of other procedures. Success was defined as an RDI <20 with normal oxygenation or an RDI equivalent to that on CPAP therapy. Others have confirmed these results (21,43–45).

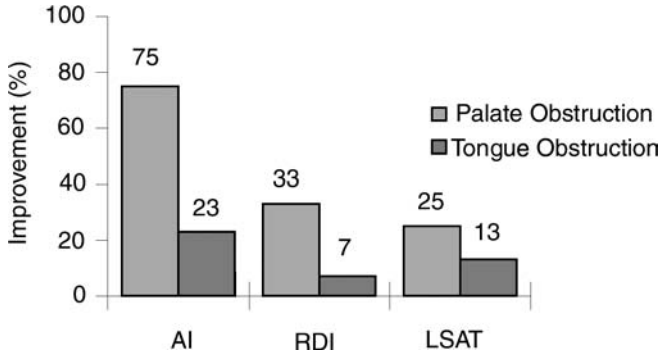


Figure 1 Uvulopalatopharyngoplasty effect on polysomnography parameters: palatal vs. tongue obstruction. *Abbreviations*: AI, apnea index; LSAT, lowest oxyhemoglobin saturation; RDI, respiratory disturbance.

Maxillo-mandibular advancement is most successful in combination with the site-specific procedures discussed above (20,21). In a long-term follow-up of 40 patients, Riley et al. (46) showed 90% success more than four years from surgery.

More important than the physiological outcomes are the clinically important outcomes. Survival improves long-term following UPPP in all-comer sleep apnea patients compared to all-comer CPAP and untreated sleep apnea patients after controlling for age, sex, race, year of treatment, and comorbidity (47,48). The lesser mean survival in CPAP patients is probably due to the significant fraction of patients using CPAP inadequately or not at all (10). Another study comparing UPPP patients to CPAP users showed a comparable 5-year survival rate that was better than untreated sleep apnea patients (49). No large survival studies have been published for other surgical treatments.

Reduced cardiovascular morbidity risk is another clinically important outcome. There are limited data on the effect of surgical therapy on cardiovascular outcomes. These studies are difficult as they require long-term follow-up. One study suggests that UPPP prevents new cardiovascular events at least as well as CPAP, when one includes all patients treated with CPAP (including the inadequate users) (8).

Surgical treatment improves daytime performance and function. Uvulopalatopharyngoplasty appears to reduce motor vehicle crashes (50,51). A randomized placebo-controlled trial demonstrated a statistical trend of a clinically important improvement in reaction time in patients treated with radiofrequency tongue and palate reduction compared to sham placebo treatment (32).

Most importantly to patients, surgery improves symptoms and quality-of-life. Several studies show improved daytime sleepiness with surgical treatment. For example, Friedman et al. (42) found that UPPP with tongue reduction improved daytime sleepiness, with the Epworth sleepiness scale improving from 15 preoperatively to eight postoperatively. Woodson et al. (32) demonstrated a clinically important and statistically significant improvement in sleep-related quality-of-life in his randomized placebo-controlled trial of radiofrequency tongue/palate reduction. In a long-term follow-up study, the benefits measured on validated quality-of-life and sleepiness instruments persisted at least two years (52). Quality-of-life deficits and symptoms most commonly prompt patients to seek care, and surgical treatments offer a means to improve these problems. Table 19 lists the published benefits of UPPP.

Nasal surgical treatment appears to improve CPAP outcomes. Powell studied CPAP patients with turbinate hypertrophy and difficulty tolerating CPAP. In a randomized, placebo-controlled, double-blinded pilot trial, he demonstrated an important improvement in CPAP adherence between those treated with turbinate reduction and those treated with a sham placebo turbinate reduction (14). Friedman et al. (15) demonstrated a measurable

Table 19 Beneficial Outcomes of Uvulopalatopharyngoplasty

- Survival improvement
- Incident cardiovascular disease reduction
- Motor vehicle crash reduction
- Apnea index reduction
- Snoring reduction

decrease in CPAP pressure requirements following septoplasty with or without turbinate reduction in CPAP patients with a nasal obstruction. More study is required to quantify the benefits of nasal surgery, but early data and many anecdotes suggest that even minor nasal interventions may significantly improve CPAP outcomes.

For surgical cure of sleep apnea, tracheotomy offers the most immediate and definitive success. Sher et al. (16) reviewed three series of severe or profound sleep apnea patients who received tracheotomy. Normalization of sleep apnea was achieved in all cases. However, these studies also noted the significant management issues with tracheotomy. For example, in one series, 42% of patients developed granulation tissue at the tracheotomy stoma (53).

Surgical Adverse Outcomes

All surgical treatments have associated risks and potentially adverse outcomes. This section describes adverse outcomes for the major procedures and provides estimates of incidence when available. All surgical treatments of sleep apnea carry the risk of persistent sleep apnea. They all carry risks associated with anesthesia, which are believed to be elevated in sleep apnea patients.

The common adverse outcomes of UPPP include severe transient odynophagia (nearly 100% except for stiffening procedures) (54), and chronic subjective dysphagia (up to 29%) (55). Dysphagia includes patients with coughing at meals (13%), nasal regurgitation/velopharyngeal incompetence (13%), food sticking (6%), globus sensation (3%), and other symptoms (55). These symptoms are usually minor, as only 4% of patients regretted having UPPP (55). These adverse outcomes vary by technique and aggressiveness of the procedure (54). Velopharyngeal incompetence is common temporarily after surgery, but much less common permanently, especially with newer UPPP techniques (54). Serious perioperative complications are rare and include airway/respiratory crisis (1.1%), cardiovascular events (0.3%), hemorrhage (0.3%), or death (0.2%) in a study of U.S. veterans (56), who are known to be sicker than the general population of patients (57). Other potential adverse outcomes include subtle voice change, nasopharyngeal stenosis (rare), wound dehiscence, or other miscellaneous symptoms (54). Acute complications might occur more commonly in patients

Table 20 Uvulopalatopharyngoplasty Adverse Outcomes

- Minor
  - Transient odynophagia (nearly 100%)
  - Chronic minor subjective dysphagia (29%)
  - Wound dehiscence (technique dependent)
  - Nasopharyngeal stenosis (rare)
  - Others
- Life threatening[a]
  - Airway or respiratory complication (1.1%)
  - Cardiovascular event (0.3%)
  - Serious hemorrhage (0.3%)
  - Death (all causes, 0.2%)

[a]Life threatening complication rates based on a study of inpatient U.S. veterans, who are known to be sicker than the general population of patients.
Source: From Ref. (57).

undergoing septoplasty and a turbinate procedure with UPPP (19). Table 20 summarizes the adverse outcomes from UPPP.

The most common adverse outcomes following most intranasal procedures include temporary bleeding, temporary nasal congestion, and residual nasal compromise. Septoplasty adverse outcomes include hematoma, abscess, perforation, and saddle-nose deformity, all of which are rare. Turbinate reduction adverse outcomes include intranasal crusting and tissue sloughing, particularly with aggressive turbinate cautery. Turbinate excision is not recommended because it can cause atrophic rhinitis, or "empty nose syndrome."

Common genioglossus advancement adverse outcomes include transient tongue swelling and permanent mandibular incisor teeth anesthesia or hypesthesia. Rare complications include lip anesthesia, mandibular tooth root injury, missing the genial tubercle resulting in no genioglossus advancement, wound dehiscence, infection, or pathological mandible fracture (Table 21). Hyoid suspension adverse outcomes are rare and include prolonged dysphagia, infection, rupture of hyoid suspension suture (common

Table 21 Genioglossus Advancement Complications

- Transient tongue swelling
- Mandibular incisors anesthesia
- Lip anesthesia
- Tooth root injury
- Missed genial turbercle/genioglossus muscle
- Wound dehiscence
- Infection
- Mandible fracture

when suspended from the mandible, rare when suspended to the thyroid cartilage), or voice change. Maxillo-mandibular advancement adverse outcomes include facial and dental anesthesia/paresthesia, hemorrhage, malocclusion, unfavorable cosmesis, skeletal relapse, or velopharyngeal incompetence. Minor dental or facial anesthesia/hypesthesia and minor occlusal changes are common.

Minor adverse outcomes of radiofrequency tongue reduction include temporary tongue swelling, dysphagia, and pain. These side effects are mild at one week, and completely resolved by three weeks (32). Uncommon complications include tongue hematoma (2.3%, from the anesthetic injection) (32), mucosal ulceration (<1%), tongue abscess (<1%), taste change (<1%), and tongue paresis (<1%) (32,58,59). In their three-year series of cases, Stuck et al. (58) demonstrated a consistent reduction in the overall complication rate each year, from 5.9% to 1.8% to 0.6%. Thus, technical experience is one of the most important factors to prevent complications.

Tongue resection (midline glossectomy or lingualplasty) adverse outcomes include pain, hemorrhage, inadequate excision, tongue infection, prolonged recovery, taste change, and tongue paresis (29,30). The morbidity associated with these procedures has limited their use. Tongue suspension suture adverse outcomes commonly include improper position, pain, swelling, and sialadenitis, and uncommonly include suture rupture, foreign body reaction, tongue paresis, hemorrhage, or infection.

Tracheotomy adverse outcomes commonly include stomal granulation tissue, peristomal cellulitis, and tracheitis/bronchitis. Less common complications include stomal bleeding, thyroid hemorrhage, aspiration, tracheal erosion, or tracheo-innominate fistula. Tracheotomy patients tend to have severe comorbid conditions, which may increase the risk of perioperative complication.

Summary of Surgical Treatment for Sleep Apnea

Surgery plays an important role in the management of sleep apnea, especially as adjunctive treatment and salvage therapy. Proper patient selection and the appropriate application of the multitude of procedures are necessary for optimal results. Surgical treatment can improve the clinically important outcomes of interest to patients, even though it often does not cure the physiological abnormality of sleep-disordered breathing. The benefits of surgery must always be weighed against the risks, while keeping in mind the risks of otherwise inadequately treated sleep apnea.

DENTAL THERAPY

Oral appliances provide an important treatment option for obstructive sleep apnea. Generally speaking, there are two types of appliances: mandibular

advancement devices and tongue retaining devices. The tongue retaining devices are poorly tolerated and less effective than mandibular advancement devices (60), so this section will focus on the latter.

Mandibular advancement devices anchor to the maxillary and mandibular teeth, with the mandibular plate positioned anterior to the maxillary plate. This anterior retraction stabilizes the hypopharyngeal and, to a lesser degree, the oropharyngeal airway (61). The tongue attaches directly to the mandible, and the soft palate attaches indirectly to the mandible, so these soft tissues are retracted anteriorly or tightened. Thus, oral appliances are most appropriate in patients who suffer hypopharyngeal obstruction, although they may also help palatal obstruction when the palate is not severely abnormal and the tonsils are not obstructing. This device is analogous to mandibular advancement surgery.

The clinician should evaluate candidates carefully for this treatment. Candidates must have sufficient teeth to anchor the device. Significant malocclusion can be a contraindication. Periodontal disease inducing tooth mobility is another contraindication. A history of temporomandibular joint disorder is a relative contraindication and active joint disorder is a strong contraindication, because the device can exacerbate this problem. The patient must have adequate mandibular protrusion for the therapy to be useful. In a nonselected sample of 100 sleep apnea patients, 34% had active dental or joint contraindications to this therapy, and another 16% had a history of dental or joint concerns that would require close supervision and follow-up for this therapy (62). Thus, only 50% of sleep apnea patients are good candidates for this therapy before even considering the source of airway obstruction most appropriate for this treatment (i.e., hypopharyngeal obstruction).

Experienced dentists fashion the mandibular advancement devices. Typically, anterior protrusion is limited to 50–75% of maximal protrusion in order to minimize strain on the temporomandibular joint. Dental impressions are taken, and the splint is fashioned from these casts. Newer devices allow adjustment of the advancement, allowing gradual advancement and even titration.

This device can provide significant benefit in the subset of patients who are appropriate candidates. A Cochrane review of published randomized trials of oral appliances concluded that oral appliances improve subjective sleepiness and reduce sleep-disordered breathing relative to controls (63). These devices are less effective than CPAP therapy, and therefore should be reserved for patients who use CPAP inadequately (63). Some studies reveal that patients tolerate the oral appliance better than CPAP, indicating that this treatment should be considered in appropriate CPAP-intolerant patients (64,65). The Cochrane review considered one trial comparing a mandibular advancement device to surgery (UPPP alone for all comers). When comparing the device users to UPPP patients, the device users had a superior rate of control of sleep apnea at four years (66). However, when

one includes the treatment failures (dropouts) in the analysis, the success rates were comparable at approximately 50% (67). In this same trial, UPPP patients had superior contentment than device patients (68).

As with CPAP therapy, patient compliance is a major limiting factor to everyday treatment effectiveness. If patient dropouts are counted, treatment success is limited to approximately 50% of patients (65,67,69). Compliance is limited by patient intolerance and side effects, including tooth movement with occlusal changes, mucosal dryness, tooth discomfort, hypersalivation, temporomandibular joint disorder, pain with chewing, and general discomfort with the device (70–72). Long-term careful dental follow-up is recommended.

FORMULATING A TREATMENT PLAN

The mere presence of sleep-disordered breathing does not necessitate treatment. In fact, the AHI correlates poorly with most clinical outcomes other than cardiovascular disease risk. Thus, the treatment plan should be based on many factors in addition to AHI. The presenting complaint along with the cardiovascular risk profile, severity of disease, presence of anatomic abnormalities, site of obstruction, surgical risk, treatment availability, and patient preference all must be considered when formulating a treatment plan. The clinician should always consider the chief complaint when recommending therapy. Generally, sleep apnea is associated with snoring, daytime sleepiness, insomnia, and cardiovascular risk. Snoring typically disturbs the bed partner and not the patient, except when socially embarrassing or creating arousals. All sleep apnea treatments address snoring but many snoring therapies do not treat sleep apnea. The same goes for many insomnia and sleepiness remedies. Clinicians must resist treating these symptoms instead of the primary disease to avoid the untoward cardiovascular outcomes associated with sleep-disordered breathing. That being said, CPAP compliance improves when patients perceive benefit regarding daytime sleepiness, fatigue, insomnia, and cognitive impairment. Ultimately, asymptomatic patients with severe sleep apnea present our greatest treatment challenge, considering the cardiovascular consequences of the disease.

Positive airway pressure is first-line treatment for most adult patients with sleep apnea and should be strongly recommended for those with disease of moderate or greater severity. This is particularly true if they are at high cardiovascular risk, poor surgical candidates, significantly overweight, or experience significant daytime symptoms. It is critical that these patients are followed up to troubleshoot and to assess the adequacy of use and treatment effect. This treatment is a covered benefit under most health insurance plans.

Mandibular advancement devices work best in nonobese patients with milder disease, hypopharyngeal obstruction, and a chief complaint of snoring. A dentist with expertise in sleep apnea treatment provides these oral

appliances. The more effective adjustable devices are expensive and often uncovered by heath insurance, since many plans exclude all orthognathic therapies.

Soft tissue (Phase I) surgery is usually reserved for adjunctive therapy (with either CPAP or an oral appliance) or for salvage of CPAP failures. Less commonly, it is employed as initial therapy. There is wide availability of the soft tissue procedures, because most general otolaryngologists acquire these skills in their training. The best surgical results occur when experienced otolaryngologists treat optimal candidates employing the most appropriate procedures. These procedures are covered benefits under most insurance plans as long as medical necessity is documented. Surgical treatment for primary snoring (in absence of sleep apnea) is not covered.

Skeletal (Phase II) surgery is reserved for those with severe sleep apnea who fail aggressive attempts at CPAP therapy and soft tissue (Phase I) surgery. Indications for this highly effective therapy may broaden as access to specialized maxillofacial surgeons with expertise in this procedure become more available, and outcome studies demonstrate safety and effectiveness in patients with milder forms of sleep apnea. Insurance reimbursement can be an issue because of the common exclusion of orthognathic surgery; however, many health insurance plans will cover it for sleep apnea when medical necessity is documented.

CLINICAL CHALLENGES IN THE TREATMENT OF OBSTRUCTIVE SLEEP APNEA

We need a better understanding of which patients with sleep apnea will benefit from treatment. Studies are needed demonstrating the relationship between sleep apnea severity, treatment, cardiovascular outcomes, and functional outcomes. The delay between sleep apnea exposure and cardiovascular disease make data collection difficult. Other challenges include predicting the subset of patients likely to benefit most from surgery and identifying the best operation for each patient. Currently, clinical and radiographic airway assessments during wakefulness are marginal predictors of sleep airway mechanics. Successful outcomes from sleep surgery are likely improved in ideal candidates. The maxillo-mandibular advancement procedure is highly effective when performed by a skilled surgeon; however, access to these specialists is limited and many patients are reluctant to undergo this major operation. Finally, it would be exceedingly valuable to find a more tolerable and less expensive therapy as efficacious and safe as positive airway pressure for obstructive sleep apnea. Pharmacologic treatments targeting areas of the brain that maintain wakeful airway patency would be an ideal sleep apnea treatment in the future. In addition, safe and effective drugs, which lead to sustained weight loss, may significantly reduce the need for surgical and medical therapy for sleep-disordered breathing.

REFERENCES

1. Montserrat JM, et al. Effectiveness of CPAP treatment in daytime function in sleep apnea syndrome: a randomized controlled study with an optimized placebo. Am J Respir Crit Care Med 2001; 164(4):608–613.
2. Gupta RM, et al. Postoperative complications in patients with obstructive sleep apnea syndrome undergoing hip or knee replacement: a case-control study. Mayo Clin Proc 2001; 76(9):897–905.
3. Loube DI, et al. Indications for positive airway pressure treatment of adult obstructive sleep apnea patients: a consensus statement. Chest 1999; 115(3): 863–866.
4. Littner M, et al. Practice parameters for the use of auto-titrating continuous positive airway pressure devices for titrating pressures and treating adult patients with obstructive sleep apnea syndrome. An American Academy of Sleep Medicine report. Sleep 2002; 25(2):143–147.
5. Berry RB, Parish JM, Hartse KM. The use of auto-titrating continuous positive airway pressure for treatment of adult obstructive sleep apnea. An American Academy of Sleep Medicine review. Sleep 2002; 25(2):148–173.
6. Mehta S, Hill NS. Noninvasive ventilation. Am J Respir Crit Care Med 2001; 163(2):540–577.
7. Weaver T, et al. CPAP dose duration for effective outcome response. Am J Respir Crit Care Med 2003; 167:A324.
8. Peker Y, et al. Increased incidence of cardiovascular disease in middle-aged men with obstructive sleep apnea: a 7-year follow-up. Am J Respir Crit Care Med 2002; 166(2):159–165.
9. Woodson BT, Weaver EM, Steward DL. CPAP outcomes stratified on CPAP use [abstr]. Sleep Medicine 2003; 4:S53.
10. Campos-Rodriguez F, Pena-Grinan N, Reyes-Nunez N, De la Cruz-Moron I, Perez-Ronchel J, De la Vega-Gallardo F, Fernandez-Palacin A. Mortality in obstructive sleep apnea–hypopnea patients treated with positive airway pressure. Chest 2005; 128:624–633.
11. Kribbs NB, et al. Objective measurement of patterns of nasal CPAP use by patients with obstructive sleep apnea. Am Rev Respir Dis 1993; 147(4):887–895.
12. Pepin JL, Krieger J, Rodenstein D, Cornette A, Sforza E, Delguste P, Deschaux C, Grillier V, Levy P. Effective compliance during the first 3 months of continuous positive airway pressure. A European prospective study of 121 patients. Am J Respir Crit Care Med 1999; 160:1124–1129.
13. Husen AN, et al. Abnormalities on nasal exam associated with decreased CPAP tolerance and use. Sleep 2003; 26:A240.
14. Powell NB, et al. Radiofrequency treatment of turbinate hypertrophy in subjects using continuous positive airway pressure: a randomized, double-blind, placebo-controlled clinical pilot trial. Laryngoscope 2001; 111:1783–1790.
15. Friedman M, et al. Effect of improved nasal breathing on obstructive sleep apnea. Otolaryngol Head Neck Surg 2000; 122(1):71–74.
16. Sher AE, Schechtman KB, Piccirillo JF. The efficacy of surgical modifications of the upper airway in adults with obstructive sleep apnea syndrome. Sleep 1996; 19(2):156–177.

17. Riley RW, Powell NB, Guilleminault C. Obstructive sleep apnea syndrome: a surgical protocol for dynamic upper airway reconstruction. J Oral Maxillofac Surg 1993; 51(7):742–747; discussion 748–749.
18. Riley RW, et al. An adjunctive method of radiofrequency volumetric tissue reduction of the tongue for OSAS. Otolaryngol Head Neck Surg 2003; 129(1):37–42.
19. Mickelson SA, Hakim I. Is postoperative intensive care monitoring necessary after uvulopalatopharyngoplasty? Otolaryngol Head Neck Surg 1998; 119(4):352–356.
20. Riley RW, Powell NB, Guilleminault C. Obstructive sleep apnea syndrome: a review of 306 consecutively treated surgical patients. Otolaryngol Head Neck Surg 1993; 108(2):117–125.
21. Waite PD, et al. Maxillomandibular advancement surgery in 23 patients with obstructive sleep apnea syndrome. J Oral Maxillofac Surg 1989; 47(12): 1256–1261; discussion 1262.
22. Assanasen P, et al. Supine position decreases the ability of the nose to warm and humidify air. J Appl Physiol 2001; 91(6):2459–2465.
23. Kase Y, Hilberg O, Pedersen OF. Posture and nasal patency: evaluation by acoustic rhinometry. Acta Otolaryngol 1994; 114(1):70–74.
24. Grymer LF, Illum P, Hilberg O. Septoplasty and compensatory inferior turbinate hypertrophy: a randomized study evaluated by acoustic rhinometry. J Laryngol Otol 1993; 107(5):413–417.
25. Lenders H, Schaefer J, Pirsig W. Turbinate hypertrophy in habitual snorers and patients with obstructive sleep apnea: findings of acoustic rhinometry. Laryngoscope 1991; 101(6 Pt 1):614–618.
26. Moore KE, Phillips C. A practical method for describing patterns of tongue-base narrowing (modification of Fujita) in awake adult patients with obstructive sleep apnea. J Oral Maxillofac Surg 2002; 60(3):252–260; discussion 260–261.
27. Riley RW, Powell NB, Guilleminault C. Inferior mandibular osteotomy and hyoid myotomy suspension for obstructive sleep apnea: a review of 55 patients. J Oral Maxillofac Surg 1989; 47(2):159–164.
28. Riley RW, Powell NB, Guilleminault C. Obstructive sleep apnea and the hyoid: a revised surgical procedure. Otolaryngol Head Neck Surg 1994; 111(6):717–721.
29. Fujita S, et al. Laser midline glossectomy as a treatment for obstructive sleep apnea. Laryngoscope 1991; 101(8):805–809.
30. Woodson BT, Fujita S. Clinical experience with lingualplasty as part of the treatment of severe obstructive sleep apnea. Otolaryngol Head Neck Surg 1992; 107(1):40–48.
31. Powell NB, Riley RW, Guilleminault C. Radiofrequency tongue base reduction in sleep-disordered breathing: a pilot study. Otolaryngol Head Neck Surg 1999; 120(5):656–664.
32. Woodson BT, et al. A randomized trial of temperature-controlled radiofrequency, continuous positive airway pressure, and placebo for obstructive sleep apnea syndrome. Otolaryngol Head Neck Surg 2003; 128(6):848–861.
33. Steward D, Weaver E, Woodson BT. A comparison of radiofrequency treatment schemes for obstructive sleep apnea syndrome. Otolaryngol Head Neck Surg 2004; 130(5):579–585.
34. Chabolle F, et al. Tongue base reduction with hyoepiglottoplasty: a treatment for severe obstructive sleep apnea. Laryngoscope 1999; 109(8):1273–1280.

35. Cummings DE, et al. Plasma ghrelin levels after diet-induced weight loss or gastric bypass surgery. N Engl J Med 2002; 346(21):1623–1630.
36. Buchwald H, et al. Bariatric surgery: a systematic review and meta-analysis. JAMA 2004; 292(14):1724–1737.
37. Orsini MA, et al. Clinical experience with the silicone tracheal cannula in obstructive sleep apnea. Otolaryngol Head Neck Surg 1984; 92(2):132–135.
38. Campanini A, et al. Role of skin-lined tracheotomy in obstructive sleep apnoea syndrome: personal experience. Acta Otorhinolaryngol Ital 2004; 24(2):68–74.
39. Boushra NN. Anaesthetic management of patients with sleep apnoea syndrome. Can J Anaesth 1996; 43(6):599–616.
40. Weaver EM, Woodson BT, Steward D. Polysomnography indexes are discordant with quality of life symptoms reaction times in sleep apnea patients. Otolaryngol Head Neck Surg; 132(2):255–262.
41. Grote L, et al. Therapy with nCPAP: incomplete elimination of sleep related breathing disorder. Eur Respir J 2000; 16(5):921–927.
42. Friedman M, et al. Combined uvulopalatopharyngoplasty and radiofrequency tongue base reduction for treatment of obstructive sleep apnea/hypopnea syndrome. Otolaryngol Head Neck Surg 2003; 129(6):611–621.
43. Hochban W, Brandenburg U, Peter JH. Surgical treatment of obstructive sleep apnea by maxillomandibular advancement. Sleep 1994; 17(7):624–629.
44. Bettega G, et al. Obstructive sleep apnea syndrome. Fifty-one consecutive patients treated by maxillofacial surgery. Am J Respir Crit Care Med 2000; 40:641–649.
45. Prinsell JR. Maxillomandibular advancement surgery in a site-specific treatment approach for obstructive sleep apnea in 50 consecutive patients. Chest 1999; 116(6):1519–1529.
46. Riley RW, et al. Surgery and obstructive sleep apnea: long-term clinical outcomes. Otolaryngol Head Neck Surg 2000; 122(3):415–421.
47. Weaver EM, Maynard C, Yueh B. Survival of veterans with sleep apnea: continuous positive airway pressure versus surgery. Otolaryngol Head Neck Surg 2004; 130(6):659–665.
48. Weaver EM, Maynard C, Yueh B. Mortality of veterans with sleep apnea: untreated versus treated [abstr]. Sleep 2004; 27:A208.
49. Keenan SP, et al. Long-term survival of patients with obstructive sleep apnea treated by uvulopalatopharyngoplasty or nasal CPAP. Chest 1994; 105(1):155–159.
50. Haraldsson PO, et al. Does uvulopalatopharyngoplasty inhibit automobile accidents? Laryngoscope 1995; 105(6):657–661.
51. Haraldsson PO, et al. Long-term effect of uvulopalatopharyngoplasty on driving performance. Arch Otolaryngol Head Neck Surg 1995; 121(1):90–94.
52. Steward DL, Weaver EM, Woodson BT. Multilevel temperature controlled radiofrequency for obstructive sleep apnea: extended follow-up. Otolaryngol Head Neck Surg 2005; 132:630–635.
53. Guilleminault C, et al. Obstructive sleep apnea syndrome and tracheostomy. Long-term follow-up experience. Arch Intern Med 1981; 141(8):985–988.
54. Rombaux P, et al. Postoperative pain and side effects after uvulopalatopharyngoplasty, laser-assisted uvulopalatoplasty, and radiofrequency tissue volume reduction in primary snoring. Laryngoscope 2003; 113(12):2169–2173.

55. Levring-Jaghagen E, Nilsson ME, Isberg A. Persisting dysphagia after uvulopalatoplasty performed with steel scalpel. Laryngoscope 1999; 109(1):86–90.
56. Kezirian EJ, et al. Incidence of serious complications after uvulopalatopharyngoplasty. Laryngoscope 2004; 114:450–453.
57. Agha Z, Lofgren RP, Van Ruiswyk JV, Layde PM. Are patients at veterans affairs medical centers sicker?: A comparative analysis of health status and medical resource use. Arch Intern Med 2000; 160:3252–3257.
58. Stuck BA, et al. Complications of temperature-controlled radiofrequency volumetric tissue reduction for sleep-disordered breathing. Acta Otolaryngol 2003; 123(4):532–535.
59. Kezirian EJ, Powell NB, Riley RW, Hester JE. Incidence of complications in radiofrequency treatment of the upper airway. Laryngoscope 2005; 115:1298–1304.
60. Schonhofer B, et al. A new tongue advancement technique for sleep-disordered breathing: side effects and efficacy. Am J Respir Crit Care Med 1997; 155(2): 732–738.
61. Ng AT, et al. Effect of oral appliance therapy on upper airway collapsibility in obstructive sleep apnea. Am J Respir Crit Care Med 2003; 168(2):238–241.
62. Petit F-X, et al. Mandibular advancement devices: rate of contraindications in 100 consecutive obstructive sleep apnea patients. Am J Respir Crit Care Med 2002; 166(3):274–278.
63. Lim J, Lasserson TJ, Fleetham J, Wright J. Oral appliances for obstructive sleep apnoea. The Cochrane Database of Systematic Reviews, 2004. Issue 4. Art No.: CD004435.pub 2. DOI:10.1002/14651858. CD004435.pub 2.
64. Randerath WJ, et al. An individually adjustable oral appliance vs continuous positive airway pressure in mild-to-moderate obstructive sleep apnea syndrome. Chest 2002; 122(2):569–575.
65. Ferguson KA, et al. A randomized crossover study of an oral appliance vs nasal-continuous positive airway pressure in the treatment of mild–moderate obstructive sleep apnea. Chest 1996; 109(5):1269–1275.
66. Walker-Engstrom M-L, et al. 4-year follow-up of treatment with dental appliance or uvulopalatopharyngoplasty in patients with obstructive sleep apnea: a randomized study. Chest 2002; 121(3):739–746.
67. Weaver EM, Walker-Engstrom M-L, Ringqvist I. Sleep apnea devices and sleep apnea surgery should be compared on effectiveness, not efficacy [letter]. Chest 2003; 123(3):961–962.
68. Walker-Engstrom ML, et al. Quality of life assessment of treatment with dental appliance or UPPP in patients with mild to moderate obstructive sleep apnoea. A prospective randomized 1-year follow-up study. J Sleep Res 2000; 9(3):303–308.
69. Mehta A, et al. A randomized, controlled study of a mandibular advancement splint for obstructive sleep apnea. Am J Respir Crit Care Med 2001; 163(6): 1457–1461.
70. Rose EC, et al. Occlusal and skeletal effects of an oral appliance in the treatment of obstructive sleep apnea. Chest 2002; 122(3):871–877.
71. Fritsch KM, et al. Side effects of mandibular advancement devices for sleep apnea treatment. Am J Respir Crit Care Med 2001; 164(5):813–818.
72. Tegelberg A, et al. Effects and adverse events of a dental appliance for treatment of obstructive sleep apnoea. Swed Dent J 1999; 23(4):117–126.

7

Narcolepsy and Disorders of Excessive Sleepiness

Nathaniel F. Watson

Department of Neurology, University of Washington School of Medicine, Seattle, Washington, U.S.A.

Symptoms	***Diagnoses***
Sleepiness	*Narcolepsy*
Cataplexy	*Idiopathic hypersomnia*
Sleep paralysis	*Hypersomnia due to medical condition (posttraumatic hypersomnia)*
Hallucinations	*Recurrent hypersomnia*
Fatigue	• *Kleine–Levin syndrome*
Automatic behavior	• *Menstrual-related hypersomnia*
	Behaviorally induced insufficient sleep syndrome

INTRODUCTION

Excessive sleepiness is pervasive in our society affecting up to 13% of the population (1). Sleepiness is experienced as a subjective difficulty maintaining alertness accompanied by a rapid entrance into sleep when the person is sedentary. Often this leads to decrements in quality-of-life, cognitive impairment, and increased accidents (2,3). Each year in the United States greater than 50,000 motor vehicle accidents are attributed to driving while drowsy (4). Sleepiness has many causes including insufficient sleep, sleep disorders, medical and neurological illness, and medication side effects. This chapter focuses on sleep disorders where excessive sleepiness is the primary symptom; this includes narcolepsy (sporadic and secondary), idiopathic hypersomnia, hypersomnia due to medical conditions (posttraumatic hypersomnia), recurrent hypersomnia, and behaviorally induced insufficient sleep syndrome.

Narcolepsy is a nonprogressive sleep disorder of unknown etiology with well-characterized clinical features. Sleepiness is the hallmark of the disease, along with rapid eye movement (REM) sleep phenomena that intrude into wakefulness such as cataplexy, hypnagogic (occurring at sleep onset) hallucinations, and sleep paralysis. These symptoms comprise the "narcoleptic tetrad" and are experienced by patients to different degrees (5). Disturbed nocturnal sleep and automatic behavior are other common symptoms of narcolepsy. Although most cases are sporadic in nature, neurological diseases that damage the hypothalamus or reticular activating system can produce "secondary" or "symptomatic" forms of the disease. Narcolepsy often strikes in adolescence or early adulthood and impacts all aspects of life from family and interpersonal relationships to school and workplace performance. Quality-of-life studies suggest the impact of narcolepsy is equal to that of Parkinson's disease (6). Unfortunately, patients often struggle with symptoms for years before being diagnosed and treated.

Idiopathic hypersomnia shares the debilitating sleepiness of narcolepsy without the associated REM phenomena. As with narcolepsy, the onset is typically during adolescence with devastating consequences. A wide variety of medical conditions, such as traumatic brain injury, encephalitis, cerebrovascular accidents, tumors, neurodegenerative diseases, and inflammatory disorders, are associated with hypersomnia. For the purposes of this chapter, we will focus on sleepiness following traumatic brain injury or posttraumatic hypersomnia when considering hypersomnia due to medical conditions. Recurrent hypersomnia involves intermittent bouts of sleepiness associated with disinhibitory behavior or menstruation. Behaviorally induced insufficient sleep syndrome is distinctive, as it results from a voluntary decision to curtail sleep. Sleep restriction occurs when an individual obtains less sleep than their physiologic sleep need. This is probably the most common cause of sleepiness in our society.

Diagnosing narcolepsy, idiopathic hypersomnia, or other disorders of excessive sleepiness is challenging. Other more common causes of excessive

Table 1 Medical Illness Associated with Excessive Daytime Sleepiness

- Anemia
- Hypothyroidism
- Depression with atypical features
- Parkinson's disease
- Alzheimer's disease
- Arthritis
- Chronic pain syndromes
- Epilepsy
- Asthma
- Chronic obstructive pulmonary disease
- Peptic ulcer disease
- Alcoholism
- Gastroesophageal reflux disease
- Stroke
- Chronic fatigue syndrome
- Fibromyalgia

sleepiness must be ruled out including medical, neurological, and psychiatric diseases as well as primary sleep disorders such as obstructive sleep apnea, restless legs syndrome/periodic limb movement disorder, and circadian rhythm abnormalities. Cataplexy, the quintessential symptom of narcolepsy, can have a variable presentation. The occasional subtle nature of this symptom may cause it to be unappreciated and underreported unless the patient is thoroughly questioned. Lastly, patients are often poor judges of their level of sleepiness, and may underrepresent the severity of their daytime symptoms.

A thorough history and physical examination are necessary to rule out more common causes of sleepiness. The sleep schedule should be ascertained using sleep diaries or wrist actigraphy (see Chap. 2). Special attention should be paid to the presence of medical disorders (Table 1) and medications such as benzodiazepines, anticonvulsants, antihistamines, and beta-blockers that are associated with sleepiness. Sleepiness and fatigue are common complaints in general medical practice, and the clinician should look for clues indicating a primary sleep disorder. Figure 1 outlines the general clinical approach to the sleepy patient.

NARCOLEPSY

Clinical Features

Excessive Daytime Sleepiness

Sleepiness experienced many times a day is often the presenting symptom of narcolepsy (Table 2). The total amount of sleep in a 24-hour period is not increased, but rather inappropriately dispersed around the clock, with frequent naps during the day and fragmented sleep at night. Sleep episodes

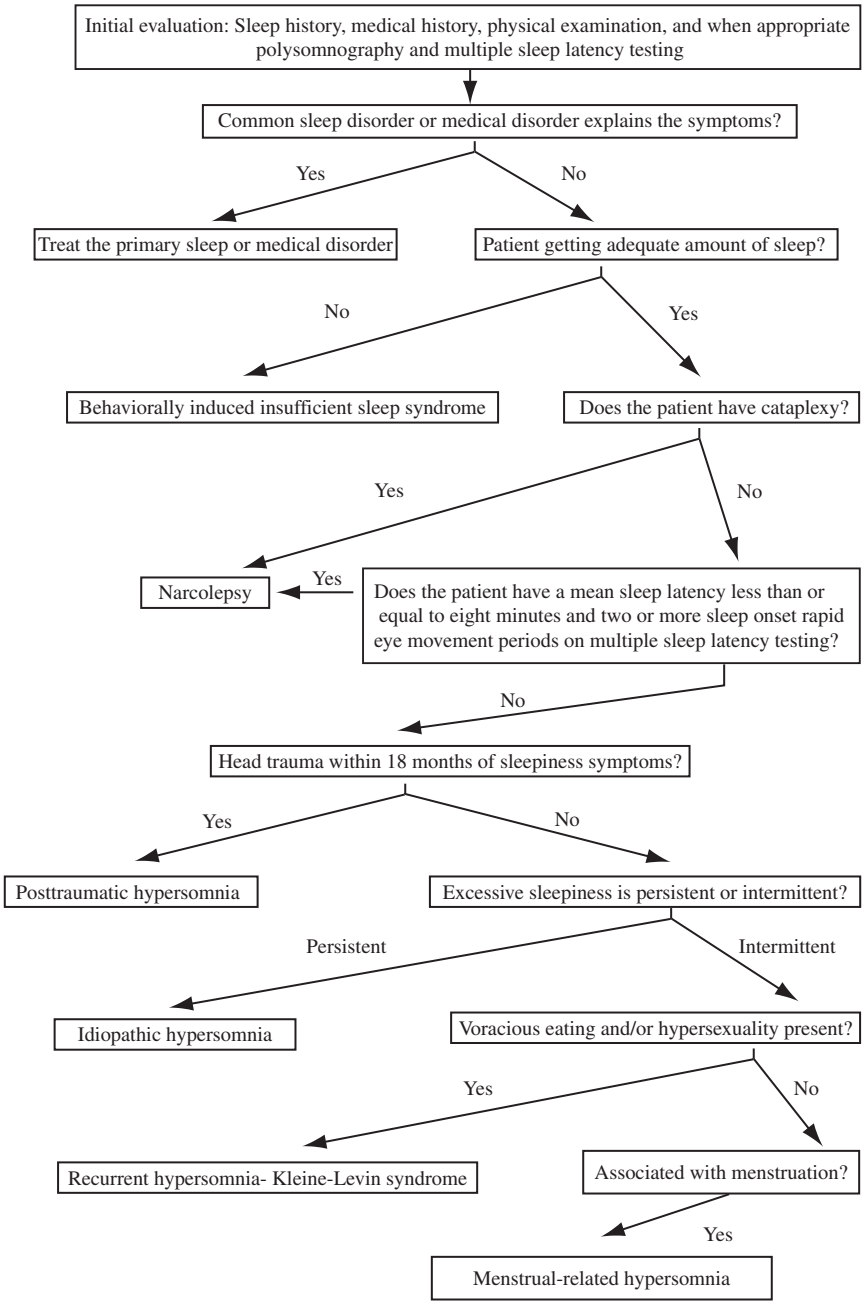


Figure 1 Clinical approach to the sleepy patient.

Table 2 Symptoms of Narcolepsy

- Excessive daytime sleepiness
- Cataplexy
- Hypnagogic hallucinations
- Sleep paralysis
- Automatic behavior
- Disrupted nocturnal sleep

are variable in duration (lasting minutes to over an hour) and can be associated with premature onset of REM sleep. These naps are called "sleep attacks" because of their precipitous nature and often restore normal vigilance for one to several hours after awakening. The restorative aspect of these naps is of significant diagnostic value, as narcolepsy is one of the few sleep disorders where napping will improve the patient's sleepiness. The drowsiness of narcolepsy is often experienced throughout the day and physical inactivity frequently exacerbates the symptom. Common sequelae include memory lapses, poor performance at work, impaired interpersonal relationships, and automatic behaviors.

Cataplexy

Cataplexy is a highly specific feature of narcolepsy and the second to sleepiness as the most common symptom of the disorder (7). It involves a sudden decrement in muscle tone and loss of deep tendon reflexes associated with emotional expression and is virtually pathognomonic of narcolepsy. Consciousness is preserved at the outset, with sleepiness, hallucinations, and sleep onset REM periods (SOREMPs) occasionally occurring at the end of an attack. Cataplectic weakness can be variable in its expression involving anything from slight jaw weakness or knee buckling to complete paralysis and postural collapse. Facial twitching may be observed. Respiration and voluntary eye movements are not compromised. Episodes typically last less than two minutes with some as short as a few seconds and others persisting for hours. *Status cataplecticus* is a term describing lengthy episodes usually occurring in the context of abrupt withdrawal of anti-cataplectic medications.

Genuine cataplectic attacks typically occur in response to laughing and joking. Other triggers include anger, surprise, pride, excitement, stress, or startlement. Facial and nuchal muscle weakness is typical of cataplexy, and the combined presence of cataplexy due to laughter and anger and sagging or dropping of the jaw best differentiate true cataplexy from non-cataplexy (8). These distinctions are important to consider because 6.5% of the general population endorses experiencing a "sudden and abrupt feeling of weakness" in association with laughter or other emotions and up to 15.5% of sleep clinic populations without narcolepsy endorse muscle weakness with various emotions (8,9). True cataplexy is rarely, if ever, seen outside the

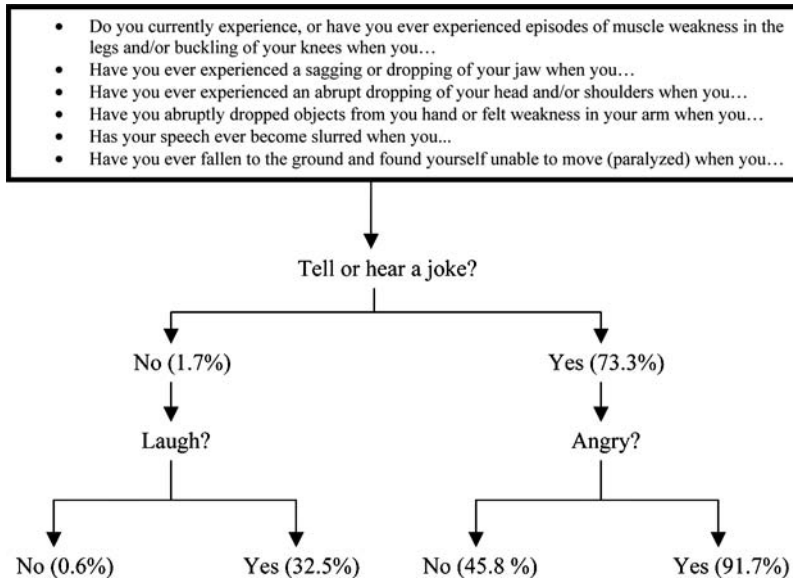


Figure 2 A decision tree for the definition of true cataplexy. (The risk of clear-cut cataplexy is indicated in parentheses.) *Source*: From Ref. 8.

context of narcolepsy. Figure 2 provides an algorithm distinguishing true cataplexy from non-cataplexy (8).

Hypnagogic Hallucinations

Hallucinations occurring at sleep onset (hypnagogic) are commonly reported by patients with narcolepsy. Indeed, 40% to 80% of patients with narcolepsy with cataplexy experience recurrent hypnagogic hallucinations. The phenomena are often dream like and unpleasant, involving visual, auditory, or somesthetic experiences. These hallucinations can be elaborate (animals or people, words or sentences) or simple (colors, sounds). A foreboding feeling that someone is in the bedroom or a sensation of levitation is occasionally reported. These hallucinations represent dream imagery intruding into wakefulness and can be quite distressing at times. Patients may recall events years later.

Sleep Paralysis

Sleep paralysis entails immobility of voluntary muscles and areflexia occurring at sleep onset or after awakening from REM sleep. All voluntary muscles are typically involved except those controlling eye movements and respiration. The paralysis is usually brief and self-limited, lasting seconds to several minutes at a time, with occasional associated hallucinations. Sensorium remains intact and the patient may experience significant anxiety

during the episode. The paralysis resolves spontaneously either gradually or abruptly. External stimulation, such as noise or the touch of another person, may terminate an episode.

Sleep paralysis is experienced by 40% to 80% of narcoleptic patients. Approximately two-thirds of narcoleptics will experience sleep paralysis or hypnagogic hallucinations at one time or another in the course of their illness and these phenomena can occur simultaneously (10). Unlike cataplexy, sleep paralysis is not specific to narcolepsy, as the lifetime prevalence is 20% to 50% in the general population (11). Sleep paralysis occurring at sleep onset is suggestive of narcolepsy.

Miscellaneous Narcolepsy Symptoms

Other common symptoms of narcolepsy include disrupted nocturnal sleep and automatic daytime behavior. Patients may experience trouble falling asleep at night, and frequently report poor sleep continuity due to recurrent arousals. Automatic behavior, such as confused speech, putting objects away in strange locations, and driving to unplanned destinations are thought to result from daytime drowsiness and brief intrusions of sleep ("microsleeps") into daytime wakefulness. Depression, irritability, and social isolation may also be observed.

Narcolepsy and Comorbid Sleep Disorders

A number of sleep disorders occur with increased frequency in patients with narcolepsy. REM sleep behavior disorder involves movement due to loss of muscle atonia during REM sleep and can result in significant injury to the patient or their bed partner (see Chap. 8). This disorder is experienced by up to 10% of narcoleptics, a significantly higher rate than the 0.5% observed in the general population (12). Periodic limb movements in sleep are also common in patients with narcolepsy (see Chap. 4). Whether or not this contributes to the sleepiness of these patients is controversial (13). Sleep-disordered breathing is a common comorbidity, and the clinician should be vigilant for this additional cause of sleepiness (see Chap. 5) (14). Common anti-cataplectic medications such as tricyclic antidepressants or selective serotonin reuptake inhibitors can precipitate both REM sleep behavior disorder and periodic limb movements in sleep.

Epidemiology of Narcolepsy

Establishing accurate prevalence estimates of narcolepsy is challenging. Few physicians are properly trained to diagnose the disorder and testing modalities are often unavailable. The specific population studied and diagnostic criteria employed also contribute to the variability of prevalence estimates. Despite these limitations, a number of prevalence studies have been reported using both validated and invalidated methodologies.

Initial studies based on U.S. population sampling provided prevalence estimates between 3 and 67 cases per 100,000 (15–17). More recently, a U.S. population-based study using validated diagnostic criteria estimated the prevalence of narcolepsy in Olmsted County, Minnesota, at 56 per 100,000 persons, with approximately 36% of cases devoid of cataplexy (18). Studies performed internationally provide variable estimates. A large cohort of Finnish twins were screened with a validated questionnaire, interviewed, and tested revealing a prevalence of narcolepsy with cataplexy of 26 per 100,000 (9). Israel provides the lowest estimate at 0.23 per 100,000, and Japan provides the highest estimates at between 160 and 590 per 100,000 (19,20). Men and women are affected equally.

The only data regarding the incidence of narcolepsy are from the U.S. Olmstead County population-based cohort. The incidence was highest in the second decade of life. Based on an overall average incidence rate of 1.37 cases per 100,000 persons per year, one would expect 14 new narcolepsy diagnoses every year in a city of one million people (18).

Genetics of Narcolepsy

Although most cases of narcolepsy are sporadic, substantial evidence of a genetic predisposition exists. First-degree relatives of narcolepsy patients with cataplexy have a 1% to 2% risk of developing the illness, a value appreciably higher than the 0.02% to 0.18% found in the general population (21). A well-defined association between the human leukocyte antigen (HLA) DQB1*0602 allele and narcolepsy, particularly narcolepsy with cataplexy, has also been established (22). More than 85% of narcolepsy patients with definite cataplexy share this specific allele, compared with 12% to 38% of the general population (21).

Nongenetic factors also play a role highlighted by the observation that most (69–75%) identical twin pairs reported in the literature are discordant for narcolepsy. Also, HLA DQB1*0602 negative cases of narcolepsy with cataplexy have been reported (21). Therefore, narcolepsy is an illness that occurs for unknown reasons in persons with a genetic susceptibility. Genetic factors alone are not necessary or sufficient to develop the illness. Patients with narcolepsy should be reassured that their relatives, although at higher risk than the general population, are very unlikely to contract the illness.

Etiology and Pathophysiology of Narcolepsy

Although the precise etiology of human narcolepsy remains unknown, much has been learned about the pathophysiology of the disorder. In 1998, a novel neuropeptide called hypocretin-1 (also referred to as orexin A) was identified independently by two research groups (23,24). The hypocretin-1 producing cells, found in the dorsolateral and perifornical hypothalamus, project

widely to the cortex, limbic system, and brainstem and contribute to multiple physiologic functions related to alertness and the sleep–wake cycle including thermoregulation, food intake, endocrine function, and cardiovascular regulation (24). The link between hypocretin-1 and narcolepsy was made when a mutation in the hypocretin receptor 2 gene was found in narcoleptic dogs and narcoleptic behavior was discovered in preprohypocretin knockout mice (25,26).

Further research has revealed that hypocretin-1 levels are reduced in the cerebrospinal fluid (CSF) of most humans with narcolepsy with cataplexy, and pathologic studies of brains of narcoleptics revealed the absence of hypocretin-1 producing cells in the hypothalamus (27–30). Yet, the role of the hypocretin system in narcolepsy without cataplexy or with atypical cataplexy is less clear, as the majority of these cases have normal CSF hypocretin-1 levels (28,31).

The cause of hypothalamic hypocretin cell destruction in narcolepsy is unknown. An autoimmune hypothesis is favored due to the previously mentioned association of narcolepsy with the HLA DQB1*0602 allele. This hypothesis is supported by increased HLA expression found diffusely in the white matter of narcoleptic canines (32). Also, monozygotic twins have been reported who are discordant for narcolepsy and CSF hypocretin-1 levels and homozygous for the HLA DQB1*0602 allele. This suggests that narcolepsy with hypocretin deficiency is an acquired rather than congenital disorder, and that, generally speaking, in humans genetics alone is not sufficient to cause hypocretin system abnormalities (33).

There is little other concrete evidence that narcolepsy is an autoimmune disorder. Signs of central nervous system inflammation, such as oligoclonal banding and cellular infiltration in CSF, are not observed in patients with narcolepsy. Furthermore, narcolepsy does not exhibit the immune system abnormalities (e.g., sedimentation rate, complement and serum immunoglobulin levels, lymphocyte subsets ratios, C-reactive protein, autoantibodies) seen in other autoimmune disorders (21). The transient nature of an autoimmune process and the low number and discreet localization of hypocretin cells in the hypothalamus could explain the absence of direct evidence of autoimmunity.

Environmental factors also play a role in the development of narcolepsy. A month of March peak in births is noted for those with the illness, suggesting that season of birth is important to disease development (34). Others have focused on head trauma (35), sudden changes in sleep–wake habits (36), or antecedent infections (37). The infectious hypothesis is particularly intriguing, as infections exhibit seasonal variation and could trigger the illness by inducing an autoimmune process at a particular time in a person's development (38). At present, the precise environmental exposure remains unknown and further research is necessary to discover potential avenues for disease prevention in the future.

A subset of narcolepsy exists where the cause of the illness is known. These cases, termed ''secondary'' or ''symptomatic'' narcolepsy, typically result from diencephalic (hypothalamic) damage from diverse causes (39–41). Focal neurological deficits found while examining these patients are specific to the primary disease process. Many of these cases reveal low CSF hypocretin-1 levels, presumably as a function of less targeted damage to the hypocretinergic cells in the hypothalamus than occurs with sporadic narcolepsy (28,42).

From an etiologic standpoint, narcolepsy may constitute multiple diseases. The best characterized phenotype is represented by the patient with cataplexy, low CSF hypocretin-1 levels, HLA DQB1*0602 positivity, and a mean sleep latency less than or equal to eight minutes and two or more SOREMPs on the multiple sleep latency test (MSLT). Patients with all these findings may be etiologically homogeneous. On the other hand, the presence of patients not fulfilling these criteria, such as HLA-negative and/or cataplexy-negative cases, suggests etiologic heterogeneity for narcolepsy as a whole.

Diagnosis of Narcolepsy

Narcolepsy with cataplexy can be diagnosed clinically based on the dual presence of almost daily excessive daytime sleepiness for three months and definite cataplexy (Table 3) (2). The diagnosis can be confirmed by at least six hours of polysomnography, followed by an MSLT documenting a mean sleep latency less than or equal to eight minutes and two or more SOREMPs. The mean sleep latency on the MSLT in narcolepsy is 3.1 ± 2.9 minutes (2). Most cases of narcolepsy are sporadic, and the physical examination is normal. Clinical scenarios of narcolepsy can be deceptive, particularly when it comes to cataplexy. Because cataplexy is the quintessential narcolepsy symptom, the clinician must become adept at identifying true cataplexy from its imposters. The most compelling history of true cataplexy is weakness of facial or nuchal muscles occurring both in the context of telling/hearing a joke/laughing and anger. Up to one-third of patients with narcolepsy do not have cataplexy and its absence does not rule out the disease. Figure 2 provides an algorithm for the identification of clear-cut cataplexy.

In the absence of cataplexy, the clinician should look for auxiliary symptoms of the disease to make the diagnosis including sleep paralysis, hypnagogic hallucinations, automatic behaviors, or a disrupted major sleep episode. Furthermore, polysomnography must be performed to rule out other causes of sleepiness and establish at least six hours of sleep the night before the MSLT (2). A mean sleep latency on the MSLT less than or equal to eight minutes and two or more SOREMPs must be present to make the diagnosis. No medical, neurological, or mental disorders can account for the symptoms. Table 4 provides the current diagnostic criteria for narcolepsy without cataplexy.

Table 3 Narcolepsy with Cataplexy: International Classification of Sleep Disorders Diagnostic Criteria

A. The patient has a complaint of excessive daytime sleepiness occurring almost daily for at least 3 months
B. A definite history of cataplexy, defined as sudden and transient episodes of loss of muscle tone triggered by emotions, is present[a]
C. The diagnosis of narcolepsy with cataplexy should, whenever possible, be confirmed by nocturnal polysomnography, followed by an MSLT; the mean sleep latency on MSLT is less than or equal to 8 minutes and two or more SOREMPs are observed following sufficient nocturnal sleep (minimum 6 hours) during the night prior to the test. Alternatively, hypocretin-1 levels in the CSF are less than or equal to 110 pg/mL or one-third of mean normal control values[b]
D. The hypersomnia is not better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder

[a]To be labeled as cataplexy, these episodes must be triggered by strong emotions—most reliably laughing or joking—and must be generally bilateral and brief (less than 2 minutes). Consciousness is preserved, at least at the beginning of the episode. Observed cataplexy with transient reversible loss of deep tendon reflexes is a very strong, but rare, diagnostic finding.
[b]The presence of two or more SOREMPs during the MSLT is a very specific finding, whereas a mean sleep latency of less than 8 minutes can be found in up to 30% of the normal population. Low CFS hypocretin-1 levels (less than or equal to 110 pg/mL or one-third of mean normal control values) are found in more than 90% of patients with narcolepsy with cataplexy and almost never in controls or in other patients with other pathologies.
Abbreviations: MSLT, multiple sleep latency test; SOREMPs, sleep onset rapid eye movement periods; CSF, cerbrospinal fluid.
Source: From Ref. 2.

HLA typing and CSF hypocretin-1 measurement are not considered a part of routine testing in the diagnosis of narcolepsy. Although HLA DQB1*0602 is associated with narcolepsy and supportive of the diagnosis, most people with the antigen do not have narcolepsy, and antigen-negative cases of narcolepsy have been reported. Also, only 40% of narcolepsy patients without cataplexy are positive. These limitations impair the usefulness of HLA typing in diagnosing narcolepsy (31). Hypocretin-1 levels are highly specific (99%) and sensitive (87%) in patients with typical cataplexy. However, in patients without cataplexy or with atypical cataplexy the specificity remains high (99%), but the sensitivity drops precipitously (16%) (31). Because the test involves a lumbar puncture and is not widely available or standardized, it should be reserved for specific patients such as those with treatment-resistant disease, secondary narcolepsy, difficulty undergoing the MSLT, or negative MSLT results (31). The diagnosis of secondary narcolepsy (narcolepsy due to medical condition) involves specific criteria as described in Table 5.

Table 4 Narcolepsy Without Cataplexy: International Classification of Sleep Disorders Diagnostic Criteria

A. The patient has a complaint of excessive daytime sleepiness occurring almost daily for at least 3 months
B. Typical cataplexy is not present, although doubtful or atypical cataplexy-like episodes may be reported
C. The diagnosis of narcolepsy without cataplexy must be confirmed by nocturnal polysomnography, followed by an MSLT. In narcolepsy without cataplexy, the mean sleep latency on MSLT is less than or equal to 8 minutes and two or more SOREMPs are observed following sufficient nocturnal sleep (minimum 6 hours) during the night prior to the test[a]
D. The hypersomnia is not better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder

[a]The presence of two or more SOREMPs during the MSLT is a specific finding, whereas a mean sleep latency of less than 8 minutes can be found in up to 30% of the normal population.
Abbreviations: MSLT, multiple sleep latency test; SOREMPs, sleep onset rapid eye movement periods; CSF, cerebrospinal fluid.
Source: From Ref. 2.

Treatment of Narcolepsy

Stimulants

Narcolepsy is a lifelong illness and treatment is necessary. Both pharmacological and nonpharmacological therapies should be employed. Nonpharmacological treatment modalities include scheduled daily naps, proper sleep hygiene, and other behavioral measures (Table 6). Indeed, many patients find a 10 to 15-minute nap is as helpful as medications at improving alertness. Good sleep hygiene entails regular bed and wake times with an adequate total sleep time. In addition, patients should be advised to avoid late-afternoon caffeine and activating behaviors such as exercise or eating prior to sleep onset. Pharmacological treatment should focus on sleepiness and cataplexy since rarely do other symptoms of narcolepsy, such as sleep paralysis or hypnagogic hallucinations, require intervention. Patients are at increased risk for accidental injury, and should be educated about safety issues at work and on the roadways. Impaired interpersonal relationships and social isolation can be alleviated by referral to a narcolepsy support group (Table 7).

Stimulants are used for sleepiness in narcolepsy with variable efficacy. Typical medications include modafinil, methylphenidate, dextroamphetamine, and amphetamines. These medications should be started at low doses and titrated up as needed and tolerated. Dosing should occur in the morning, with repeated doses up until the early afternoon. Sustained release preparations should only be used in the morning hours. Most of these medications exert their effects by presynaptic activation of dopaminergic

Table 5 Narcolepsy Due to Medical Condition: International Classification of Sleep Disorders Diagnostic Criteria

A. The patient has a complaint of excessive daytime sleepiness occurring almost daily for at least 3 months
B. One of the following is observed:
   a. A definite history of cataplexy, defined as sudden and transient episodes of loss of muscle tone (muscle weakness) triggered by emotions, is present[a]
   b. If cataplexy is not present or is very atypical, polysomnographic monitoring performed over the patient's habitual sleep period followed by an MSLT must demonstrate a mean sleep latency on the MSLT of less than 8 minutes with two or more SOREMPs, despite sufficient nocturnal sleep prior to the test (minimum 6 hours)[b]
   c. Hypocretin-1 levels in the CSF are less than 110 pg/mL (or 30% of normal control values), provided the patient is not comatose[c]
C. A significant underlying medical or neurological disorder accounts for the daytime sleepiness
D. The hypersomnia is not better explained by another sleep disorder, mental disorder, medication use, or substance use disorder

[a]To be cataplexy, these episodes must be triggered by strong emotions, most reliably laughing or joking, and must be generally bilateral and brief (less than 2 minutes). Consciousness is preserved at least at the beginning of the episode. In narcolepsy (with cataplexy) due to a medical condition, the diagnosis should, whenever possible, be confirmed by nocturnal polysomnography followed by an MSLT (see MSLT criteria below).
[b]The presence of two or more SOREMPs during the MSLT is a very specific finding, whereas a mean sleep latency of less than 8 minutes can be found in up to 30% of the general population.
[c]In patients with severe medical or neurological illness, nocturnal polysomnography or the MSLT may be impossible to conduct or to interpret. Similarly, the value of measuring hypocretin-1 levels in the CSF in critically ill patients is uncertain. Abnormal polysomnography and low CSF hypocretin-1 levels should be interpreted within the clinical context.
Abbreviations: SOREMPs, sleep onset rapid eye movement periods; CSF, cerebrospinal fluid.
Source: From Ref. 2.

transmission and blockage of dopamine reuptake, although the exact mechanism of action of modafinil remains unclear (43,44).

A few points regarding stimulants should be emphasized. Patients should be aware that despite their efficacy, stimulants do not restore patients to prediagnosis levels of alertness (45). Although these drugs are fairly well

Table 6 Nonpharmacological Treatments for Narcolepsy

- Maintain a regular sleep schedule
- Avoid heavy meals and alcohol intake
- Practice proper sleep hygiene
- Take brief (15–30 minutes), strategically timed, regularly scheduled naps during the day

Table 7 Narcolepsy Support Groups and Resources

Narcolepsy Network, Inc.
10921 Reed Hartman Hwy, #119
Cincinnati, Ohio 45242
narnet@narcolepsynetwork.org
http://www.narcolepsynetwork.org
Tel: 513–891–3522
Fax: 513–891–3836

National Sleep Foundation
1522 K Street NW
Suite 500
Washington, D.C. 20005
nsf@sleepfoundation.org
http://www.sleepfoundation.org
Tel: 202–347–3471 (no public calls please)
Fax: 202–347–3472

National Institute of Neurological Disorders and Stroke Narcolepsy information page:
http://www.ninds.nih.gov/health_and_medical/disorders/narcolep_doc.htm

Stanford Center for Narcolepsy
http://www.med.stanford.edu/school/psychiatry/narcolepsy/

tolerated at lower doses, higher doses often result in side effects such as headache, sweating, nervousness, palpitations, gastrointestinal symptoms, and anorexia. Most symptoms are minor and tolerable, although serious side effects do occur such as arrhythmias, hypertension, seizures, and psychosis. Modafinil can reduce the efficacy of birth control pills and women on this medication should use another and/or additional form of contraception. Tolerance and the addictive nature of many of these medications cause some physicians to advocate occasional drug holidays. Often a brief one to two-week period without the medication will allow resumption of the stimulant at a lower dose with improved efficacy. Stimulants are drugs of abuse and physicians should be cognizant of malingerers attempting to obtain prescriptions for illegal purposes. Please refer to Table 8 for detailed information on stimulant medications including dosage, contraindications, and side effects.

Anti-cataplectic Medications

Cataplexy is a symptom with variable expression. Some patients with narcolepsy will require therapy; others will exhibit only mild symptoms requiring

Table 8 Stimulant Medications Used to Treat Excessive Sleepiness (Adult Dosages Shown)

Name	Dosing (mg/day)	Half-life/ time to peak concentration (hours)	Pregnancy category/ breast feeding	Contraindications/ precautions	Side effects	Comments
Modafinil	100–400 qam or divided qam and qnoon	7.5–15/2–4	C, unknown if excreted in breast milk	Contraindications: hypersensitivity Precautions: cardio-vascular disease, hypertension, severe renal or hepatic impairment, contraceptive use	Common: agitation, anxiety, nervousness, dizziness, headaches, diarrhea, nausea Serious: arrhythmia, hypertension	May impair oral contraceptive efficacy-use alternate form during treatment and one month after stopping treatment
Methylphenidate	10–60 divided bid or tid, preferably 30–45 minutes before meals	IR: 2–7 (SR: 8–10)/ IR: 1–3 (SR: 6–8)	C, unknown if excreted in breast milk	Contraindications: MAOI use, glaucoma, Tourette syndrome, severe anxiety Precautions: hypertension, seizure disorders, history of drug dependence, psychosis	Common: restlessness, slurred speech, loss of appetite Serious: hallucinations, hypertension, tachy-cardia, thrombo-cytopenia	Abuse potential, U.S. schedule II controlled substance

(*Continued*)

Table 8 Stimulant Medications Used to Treat Excessive Sleepiness (Adult Dosages Shown) (*Continued*)

Name	Dosing (mg/day)	Half-life/ time to peak concentration (hours)	Pregnancy category/ breast feeding	Contraindications/ precautions	Side effects	Comments
Dextroamphetamine	5–60 IR: divided bid or tid SR: qam or divided bid	IR: 10–12 (SR: 15+)/ IR: 1–3 (SR: 7–8)	C, unsafe in breast feeding	Contraindications: severe hypertension, symptomatic cardiovascular disease, hyperthyroidism, MAOI use, history of drug abuse Precautions: mild hypertension, Tourette syndrome	Common: anorexia, dry mouth, insomnia, irritability, nervousness, restlessness Serious: irregular heartbeat, tachycardia, psychosis, hyperthermia, severe central nervous system stimulation	Abuse potential, U.S. schedule II controlled substance
Methamphetamine	5–60 divided bid or tid	7–31/1–3	C, unsafe in breast feeding	Contraindications: symptomatic cardiovascular disease, severe hypertension,	Common: nervousness, tremulousness, headache, palpitations	Avoid abrupt discontinuation

				history of drug abuse, glaucoma, hyperthyroidism, MAOI use, advanced atherosclerosis Precautions: mild hypertension, psychosis	Serious: seizures, intracerebral hemorrhage, hyperthyroidism, movement disorders	
Mazindol	3–8 divided bid	30–50/2	C, unknown if excreted in breast milk	Contraindications: symptomatic cardiovascular disease, arrhythmias, glaucoma, history of drug abuse, MAOI use Precautions: hypertension, heart disease, diabetes mellitus	Common: restlessness, dizziness, insomnia, headache, dry mouth Serious: pulmonary hypertension, urinary retention	Increases insulin sensitivity. May alter insulin requirements in diabetics

Note: Hypersensitivity to any medication is a contraindication. Some medications may require doses outside the usual range depending on clinical response. Consult the manufacturer's recommendations for further details regarding these medications. Always consult the manufacturer's recommendations before prescribing medications.
Abbreviations: IR, immediate release; SR, sustained release; MAOI, monoamine oxidase inhibitors; bid, twice a day; tid, three times a day; qam, every morning.

no medications, and still others will have no symptoms at all. Cataplexy often improves as one ages, probably due to improved control of emotions on the part of the patient. Pharmacological options are available for those patients with significant symptoms. Table 9 outlines these medications with special focus on dosing, contraindications, and side effects.

The tricyclic antidepressants protriptyline, clomipramine, and imipramine work mostly through monoamine reuptake inhibition (44). Although effective, at therapeutic doses these medications are often associated with anti-cholinergic side effects such as dry mouth, constipation, urinary retention, impotence, and visual difficulty focusing. The selective serotonin reuptake inhibitors such as fluoxetine and the serotonin/norepinephrine reuptake inhibitor venlafaxine are also effective in treating cataplexy and often have a more favorable side-effect profile. All of these medications have REM suppressing properties and some, particularly the selective serotonin reuptake inhibitors and tricyclic antidepressants, can reduce muscle atonia associated with REM sleep, resulting in REM sleep behavior disorder. Changing or stopping these medications should be done gradually, as abrupt discontinuation can result in rebound cataplexy and status cataplecticus. Although other REM phenomena of narcolepsy, such as hypnagogic hallucinations or sleep paralysis, typically do not require treatment, these medications are effective for these symptoms as well.

Sodium oxybate (gamma hydroxybutyrate) is a novel medication recently introduced for the treatment of cataplexy. This medication may also have effects on daytime sleepiness and has been shown to consolidate sleep and promote both stage REM and non-REM (NREM) stage 3–4 (delta) sleep (46,47). As opposed to the antidepressants, there is no evidence of rebound cataplexy upon abrupt discontinuation (48). Sodium oxybate has abuse potential and is only made available by the manufacturer through a central distribution center. Physicians wishing to prescribe this drug must complete the Xyrem® Success Program℠. Please see the website at: http://xyrem.info/ for more information on this medication.

Narcolepsy Treatment Summary

A treatment strategy employed in some sleep centers is outlined below. Counsel the patient regarding the importance of short (approximately 15 minutes) regular daytime naps, sleep hygiene, and emotion control (49). Inform patients to avoid heavy meals, alcohol, and shifting their sleep schedule. Initiate pharmacological therapy with modafinil 100 mg in the morning, and titrate up the dose as needed to a maximum of 400 mg/day, splitting the medication into a morning and noon dose if the patient experiences late-afternoon drowsiness. If sleepiness persists, one may try methylphenidate or another stimulant as either monotherapy or add-on therapy to the modafinil. A morning and noon dose of 10–20 mg of long-acting methylphenidate SR taken with or without modafinil, with an as-needed

Table 9 Medications for Cataplexy (Adult Dosages Shown)

Name	Dose (mg/day except sodium oxybate)	Half-life/time to peak concentration (hour unless otherwise specified)	Pregnancy category	Contraindications/ precautions	Side effects	Comments
Clomipramine	75–125 qhs or divided bid	19–37/2–6	C	Contraindications: MAOI use, postmyocardial infarction Precautions: seizure disorder, suicidality, pregnancy	Common: anticholinergic (confusion, memory impairment, blurred vision, tachycardia, urinary retention, constipation)	Enhances amphetamine effects, increases half-life of warfarin, other drug/ drug interactions
Protryptiline	5–20 qhs or divided bid	54–198/8–12	C	Contraindications: MAOI and cisapride use, recent myocardial infarction Precautions: seizure disorder, cardiovascular disease, hyperthyroidism, elderly, urinary retention	Common: anticholinergic Serious: agranulocytosis, seizures, myocardial infarction	Enhances amphetamine effects, increases half-life of warfarin, other drug/ drug interactions
Imipramine	25–200 qhs or divided bid	6–18/1	D	Contraindications: MAOI use, cardiovascular disease, pregnancy Precautions: congestive heart failure, elderly, narrow angle glaucoma, hyper-thyroidism, liver disease	Common: anticholinergic Serious: agranulocytosis, arrhythmias, hypertension, syncope	Enhances amphetamine effects, increases half-life of warfarin, other drug/ drug interactions
Venlafaxine	37.5–225 RR: divided bid or tid XR: qam	RR and XR: 5/RR: 1–2 (XR: 5.5)	C	Contraindications: MAOI use Precautions: glaucoma, seizures, SIADH, liver	Common: impotence, anorexia, diarrhea, anxiety Serious: bleeding, mania, hepatitis, seizures,	Drug/drug interactions

(*Continued*)

Table 9 Narcolepsy Without Cataplexy: International Classification of Sleep Disorders Diagnostic Criteria (*Continued*)

Name	Dose (mg/day except sodium oxybate)	Half-life/time to peak concentration (hour unless otherwise specified)	Pregnancy category	Contraindications/ precautions	Side effects	Comments
Venlafaxine (*Cont.*)				disease, unstable heart disease, unstable hypertension, mania	hyponatremia	
Fluoxetine	20–80 qam or divided bid	4–6 days/6–8	C	Contraindications: MAOI or thioridazine use Precautions: hepatic disease, mania, hypoglycemia, seizure disorder	Common: impotence, anorexia, nausea, tremor, insomnia, somnolence Serious: mania, seizure, QTC prolongation, hyponatremia, suicide	Increased risk of bleeding in warfarin-treated patients, other drug/drug interactions
Sodium oxybate, gamma hydroxybutyrate	2.25–9 g/day in divided doses, at bedtime and 2.5–4 hours later	20–53 minutes/ 25–60 minutes	B	Contraindications: concomitant sedative hypnotic treatment, succinic semialdehyde dehydrogenase deficiency Precautions: cardiac failure, hypertension, sleep apnea	Common: nausea, dizziness, headache, enuresis, confusion Serious: seizures, respiratory depression, decreased consciousness	Restricted distribution, available only through the Xyrem Success Program (SM) (1-886-997-3688; http://xyrem.info/) Schedule III controlled substance

Note: Hypersensitivity to any medication is a contraindication. Depending on clinical response, dosages more or less than those listed may be required. Consult manufacturer's recommendations for further details regarding these medications. Always consult the manufacturer's recommendations prior to prescribing medications.

Abbreviations: XR, extended release; RR, regular release; bid, twice a day; tid, three times a day; qhs, every evening before bed; qam, every morning; MAOI, monoamine oxidase inhibitor; SIADH, syndrome of inappropriate antidiuretic hormone.

dose of 5–10 mg of short-acting methylphenidate in the early afternoon is a reasonable strategy. Of course, individual patients exhibit variable responses to stimulant medications, so further adjustment of medications and dosages may be needed to fully control the patient's sleepiness. Treatment-refractory patients may require further testing in the sleep laboratory to ensure that another sleep disorder (obstructive sleep apnea, restless legs syndrome/periodic limb movement disorder) is not contributing to their sleepiness.

Cataplexy should be treated if the patient feels their symptoms interfere with their quality-of-life. Explain to the patient that emotion control can mitigate their symptoms. A reasonable initial pharmacological approach would include a selective serotonin reuptake inhibitor such as fluoxetine or a serotonin/norepinephrine reuptake inhibitor such as venlafaxine. Start at low doses and titrate up as needed and tolerated. Patients with refractory cataplexy or extremely disturbed nocturnal sleep are good candidates for sodium oxybate. The physician should always balance the medication side effects against the cataplexy symptoms when considering whether to continue therapy or try another medication.

IDIOPATHIC HYPERSOMNIA

Clinical Features

Idiopathic hypersomnia is typically defined by prolonged main sleep episodes with persistent excessive sleepiness. Lengthy (1–2 hours) daytime NREM sleep episodes also occur (2). Major sleep episodes may be normal or prolonged with difficulty awakening and more or less permanent sleepiness causing impaired daytime functioning. In contrast to narcolepsy, napping is not refreshing. No amount of sleep resolves the sleepiness. In fact, sleep itself can impair functioning by causing "sleep drunkenness" upon awakening. This phenomenon is characterized by difficulty coming to complete wakefulness often accompanied by confusion, disorientation, poor motor coordination, slowness, and repeated returns to sleep with patients becoming irritable and abusive during efforts to awaken them from sleep (50). Cataplexy and the auxiliary symptoms of narcolepsy are conspicuously absent. Similar to narcolepsy, automatic behavior resulting from "microsleeps" can be observed. The condition develops progressively over several weeks and the symptoms are typically lifelong and consistent, although cases of spontaneous remission have been reported (51). Some patients exhibit evidence of central nervous system dysfunction such as orthostatic hypotension, syncope, vascular headaches, and peripheral vascular complaints.

Epidemiology

The prevalence and incidence of idiopathic hypersomnia is unknown due to the absence of a specific test or physiologic marker of disease, nosologic

uncertainty, and a lack of epidemiologic surveys. Despite our lack of knowledge regarding prevalence, idiopathic hypersomnia is less common than narcolepsy, as evidenced by idiopathic hypersomnia to narcolepsy disease ratios in sleep clinic populations ranging from 7% to 77% (50,52). As with narcolepsy, symptoms typically begin in adolescence or early adulthood (50).

Genetics

A genetic contribution to idiopathic hypersomnia is suggested by familial clustering in some cases (50,52). The search for an HLA association has provided mixed results. Studies of the relationship between idiopathic hypersomnia and HLA markers have noted no association (50,53), positive associations (HLA-Cw2 and DR5) (54), and negative associations (HLA-Cw3) (55). The genetics of this disorder remain to be clarified.

Etiology and Pathophysiology

Idiopathic hypersomnia is a central nervous system disorder of excessive sleepiness of unknown etiology. Destruction of feline locus coeruleus norepinephrine neurons results in a polysomnographic phenotype consistent with idiopathic hypersomnia (56). This and other research on CSF norepinephrine metabolites suggest a malfunction of the norepinephrine system in this disorder (57). CSF hypocretin-1 levels are normal (28). Increased thalamic sleep spindle density has been observed in the second half of the night. The resulting increased thalamic blockade could explain the difficulty awakening and sleep drunkenness exhibited by these patients (58). Phase delay and possible prolongation in melatonin secretion may also contribute to these symptoms (59). Some patients have a history of viral illness including hepatitis, pneumonia, and mononucleosis preceding the onset of sleepiness (60).

Diagnosis

Idiopathic hypersomnia is a diagnosis of exclusion. The clinician should look for typical features of the disorder in the absence of symptoms suggestive of other sleep or medical disorders such as behaviorally induced insufficient sleep syndrome, narcolepsy, sleep-disordered breathing, restless legs syndrome/periodic limb movement disorder, circadian rhythm abnormalities, and depression. Indeed, in the past, many patients initially diagnosed with idiopathic hypersomnia actually had upper airway resistance syndrome or hypersomnia associated with mood disorders (50,61). If the symptoms of idiopathic hypersomnia precede these other sleep disorders then the diagnosis should still be entertained, particularly when treatment of these comorbid disorders does not resolve the sleepiness.

Overnight polysomnography followed by an MSLT and 24-hour continuous polysomnography on an ad lib schedule are necessary to make the diagnosis. Overnight polysomnography excludes other causes of daytime sleepiness and may reveal short sleep latency, increased total sleep times, high sleep efficiency, few arousals, no SOREMPs, and normal sleep architecture. The patient may be difficult to arouse in the morning. The mean sleep latency on the MSLT in idiopathic hypersomnia has been shown to be 6.2 ± 3.0 minutes. From a diagnostic perspective, the MSLT should reveal a mean sleep latency less than eight minutes and fewer than two SOREMPs (2,62). Continuous 24-hour polysomnography often reveals a prolonged main sleep episode and daytime naps with at least one nap of greater than an hour (52). The 24-hour sleep protocol has not yet been standardized. CSF hypocretin-1 levels and HLA typing are not helpful diagnostically (28,52). The current diagnostic criteria acknowledge that not all patients with idiopathic hypersomnia demonstrate prolonged major sleep episodes. Therefore, there are separate diagnostic criteria for idiopathic hypersomnia with (Table 10) and without (Table 11) long sleep time (2).

Table 10 Idiopathic Hypersomnia with Long Sleep Time: International Classification of Sleep Disorders Diagnostic Criteria

A. The patient has a complaint of excessive daytime sleepiness occurring almost daily for at least 3 months
B. The patient has prolonged nocturnal sleep time (more than 10 hours) documented by interview, actigraphy, or sleep logs. Waking up in the morning or at the end of naps is almost always laborious
C. Nocturnal polysomnography has excluded other causes of daytime sleepiness
D. The polysomnogram demonstrates a short sleep latency and a major sleep period that is prolonged to more than 10 hours in duration
E. If an MSLT is performed following overnight polysomnography, a mean sleep latency of less than 8 minutes is found and fewer than two SOREMPs are recorded. Mean sleep latency in idiopathic hypersomnia with long sleep time has been shown to be 6.2 ± 3.0 minutes[a]
F. The hypersomnia is not better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder[b]

[a]A mean sleep latency on the MSLT of less than 8 minutes can be found in up to 30% of the general population. Both the mean sleep latency on the MSLT and the clinician's interpretation of the patient's symptoms, most notably a clinically significant complaint of sleepiness, should be taken into account in reaching the diagnosis of idiopathic hypersomnia with long sleep time.
[b]Of particular importance, head trauma should not be considered to be the cause of the sleepiness.
Abbreviations: MSLT, multiple sleep latency test; SOREMPs, sleep onset rapid eye movement periods.
Source: From Ref. 2.

Table 11 Idiopathic Hypersomnia Without Long Sleep Time: International Classification of Sleep Disorders Diagnostic Criteria

A. The patient has a complaint of excessive daytime sleepiness occurring almost daily for at least 3 months
B. The patient has normal nocturnal sleep (greater than 6 hours but less than 10 hours), documented by interviews, actigraphy, or sleep logs
C. Nocturnal polysomnography has excluded other causes of daytime sleepiness
D. Polysomnography demonstrates a major sleep period that is normal in duration (greater than 6 hours but less than 10 hours)
E. An MSLT following overnight polysomnography demonstrates a mean sleep latency of less than 8 minutes and fewer than two SOREMPs. Mean sleep latency in idiopathic hypersomnia has been shown to be 6.2 ± 3.0 minutes[a]
F. The hypersomnia is not better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder

[a]A mean sleep latency of less than 8 minutes can be found in up to 30% of the general population. Both the mean sleep latency on the MSLT and the clinician's interpretation of the patient's symptoms, most notably a clinically significant complaint of sleepiness, should be taken into account in reaching the diagnosis of idiopathic hypersomnia without long sleep time.
Abbreviations: MSLT, multiple sleep latency test; SOREMPs, sleep onset rapid eye movement periods.
Source: From Ref. 2.

Treatment

Treatment of idiopathic hypersomnia relies on many of the same stimulants used in narcolepsy (Table 8). Approximately three out of four patients have at least a partial response to stimulant treatment, with modafinil being particularly effective (51,63). Clinicians should be aware that the treatment response is often less robust than with narcolepsy, with morning sleep drunkenness being the most refractory symptom. Sleep deprivation and abrupt time shifts can worsen symptoms, so optimizing sleep hygiene and avoiding alcohol, heavy meals, and sleep deprivation are helpful suggestions. Shift work should be avoided. Unlike narcolepsy, napping is often lengthy and unrefreshing. Emerging research suggests that melatonin may shorten nocturnal sleep duration, decrease sleep drunkenness, and decrease daytime sleepiness. Further research is needed before recommending this treatment (59,64). Complete control of daytime sleepiness often cannot be obtained and escalation of stimulant doses above the recommended dose should be avoided.

POSTTRAUMATIC HYPERSOMNIA (HYPERSOMNIA DUE TO MEDICAL CONDITION)

Clinical Features

Excessive sleepiness, fatigue, headaches, and cognitive impairment are the typical symptoms of posttraumatic hypersomnia. They usually occur

immediately following the head injury and can either persist or resolve gradually over weeks and months. Lengthy main sleep episodes and frequent napping may be observed. The amount of hypersomnolence is related to both the severity of the head trauma and the length of time since its occurrence. Symptoms typically improve over time with the hypersomnia resolving in approximately half of patients at one year post injury.

Epidemiology

The prevalence and incidence of posttraumatic hypersomnia in the general population is unknown. Sleepiness is observed in 30% of patients following traumatic brain injury (65).

Etiology and Pathophysiology

Posttraumatic hypersomnia can result from any trauma to the central nervous system, including direct blows and neurosurgical manipulation. Hypersomnia is more likely to occur following trauma to specific areas of the brain such as the third ventricle, posterior hypothalamus, midbrain, or pons (66,67). CSF hypocretin-1 levels are normal in the few patients that have been tested (68).

Diagnosis

Head-injured patients are often sleepy and at risk of developing a number of sleep disorders in addition to posttraumatic hypersomnia including narcolepsy, sleep-disordered breathing, nocturnal seizures, and insomnia (65). Whiplash injuries in particular can lead to sleep-disordered breathing (66). Therefore, posttraumatic hypersomnia is a diagnosis of exclusion. The key to the diagnosis is a history of a traumatic brain injury 6 to 18 months prior to the onset of sleepiness (66). Some patients may describe being in a coma following their injury. Nocturnal polysomnography is typically unremarkable other than occasional prolonged main sleep episodes, while the MSLT reveals a mean sleep latency less than eight minutes with no more than one SOREMP. Twenty-four hour continuous polysomnography can reveal frequent daytime napping. The current diagnostic criteria of posttraumatic hypersomnia (hypersomnia due to medical condition) are shown in Table 12.

Treatment

Treatment of posttraumatic hypersomnia involves resolution of sleep-disordered breathing, epilepsy, or any other sleep or neurological disorder causing sleepiness resulting from the head injury. Proper sleep hygiene should be emphasized. Stimulants such as methylphenidate and somnolytics such as modafinil can be used for sleepiness (Table 8). Headaches are

Table 12 Hypersomnia Due to Medical Condition: International Classification of Sleep Disorders Diagnostic Criteria

A. The patient has a complaint of excessive sleepiness present almost daily for at least 3 months
B. A significant underlying medical or neurological disorder accounts for the daytime sleepiness
C. If an MSLT is performed, the mean sleep latency is less than 8 minutes with no more than one SOREMP following polysomnographic monitoring performed over the patient's habitual sleep period, with a minimum total sleep time of 6 hours
D. The hypersomnia is not better explained by another sleep disorder, mental disorder, medication use, or substance use disorder

Note: In patients with severe medical or neurological illness, conducting and interpreting the results of nocturnal polysomnography or the MSLT may be impossible. Abnormal polysomnographic results should be interpreted within the clinical context. Additionally, mean sleep latency on MSLT of less than 8 minutes can be found in up to 30% of the general population. A clinically significant complaint of excessive daytime sleepiness is far more important than is short sleep latency on MSLT in the diagnosis of hypersomnia due to medical condition.
Abbreviations: SOREMP, sleep onset rapid eye movement period; MSLT, multiple sleep latency test.
Source: From Ref. 2.

frequent side effects of stimulants in these patients. Many patients improve over time and may not require long-term pharmacological treatment.

RECURRENT HYPERSOMNIA

Clinical Features

Recurrent hypersomnia is characterized by intermittent excessive sleepiness occurring weeks or months apart. Kleine–Levin syndrome and menstrual-related hypersomnia encompass this pattern of sleepiness. In Kleine–Levin syndrome the sleepiness is accompanied by hyperphagia and hypersexuality (69). These patients sleep up to 20 hours a day, waking up only to eat and void, and exhibit behavioral and mood changes such as disorientation, depression, confusion, hallucinations, irritability, impulsiveness, and aggression as well as mild autonomic alterations. In some cases, isolated recurrent hypersomnia is the only symptom. Behavior is normal between episodes. Sleepiness typically lasts from a couple of days to several weeks appearing once to 10 times a year. A prodrome such as fatigue or headache is occasionally observed. Facial blushing and perspiration may be present during an episode. Triggering events are occasionally reported including systemic or upper airway infection, gastroenteritis, alcohol consumption, emotional distress, sleep deprivation, and head trauma. Episode termination may be signaled by amnesia, dysphoria, or elation with insomnia (2).

Menstrual-related hypersomnia involves recurrent sleepiness temporally related to menses (70). The onset of this disorder is typically just after

menarche with episodes lasting about a week and terminating abruptly. Sleep and alertness are normal both before and after the menstrual period.

Epidemiology

Kleine–Levin syndrome is more common in males with typical onset in adolescence. Prevalence is unknown and this should be considered a rare disorder. The prevalence of menstrual-related hypersomnia is unknown.

Genetics

Most cases of Kleine–Levin syndrome are sporadic in nature and a family history is rare. However, this syndrome is associated with the HLA-DQB1*0201 allele, and homozygosity for this allele is thought to increase the risk of developing the disorder (71). Despite these findings, distinct genetic markers have not been discovered and Kleine–Levin syndrome is not considered a heritable disease.

Etiology and Pathophysiology

Hypothalamic dysfunction is postulated in Kleine–Levin syndrome due to its role in regulating sleep, food intake, alertness, and sexual behavior. Although symptomatic cases have been reported with abnormalities involving the hypothalamus, other neuropathologic studies point to focal encephalitis of other brain structures (72–75). A mild viral illness or encephalitis precedes up to 50% of cases, suggesting an infectious or inflammatory etiology (76). However, CSF analysis fails to reveal a pleocytosis during attacks and attacks can be precipitated by noninfectious causes.

Patients with Kleine–Levin syndrome exhibit increased prolactin and thyroid stimulating hormone levels and reduced cortisol and growth hormone levels during symptomatic periods (77). Elevated prolactin levels are also seen in menstrual-related hypersomnia (70). These findings suggest reduced hypothalamic dopaminergic tone and possible impairment of other monoaminergic pathways in Kleine–Levin syndrome and menstrual-related hypersomnia. CSF hypocretin-1 levels are normal in Kleine–Levin syndrome, although one patient revealed a twofold decrease during a symptomatic episode (28,68).

The etiology of Kleine–Levin syndrome remains unknown. However, the young age of onset, recurrent nature of the symptoms, infectious precipitants, and association with HLA DQB1*0201 allele all suggest an autoimmune process.

Diagnosis

Diagnosing recurrent hypersomnia involves the appropriate clinical history in the absence of another medical cause for the symptoms. In Kleine–Levin

Table 13 Recurrent Hypersomnia: International Classification of Sleep Disorders Diagnostic Criteria (Including Kleine–Levin Syndrome and Menstrual-Related Hypersomnia)

A. The patient experiences recurrent episodes of excessive sleepiness of 2 days to 4 weeks duration
B. Episodes recur at least once a year
C. The patient has normal alertness, cognitive functioning, and behavior between attacks
D. The hypersomnia is not better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder

Source: From Ref. 2.

syndrome, polysomnography during an episode reveals reduced sleep efficiencies, reduced relative amounts of stage REM and stage 3–4 NREM (delta) sleep, and increased relative NREM stage 1 sleep and wake time after sleep onset (71). Twenty-four-hour polysomnography demonstrates prolonged total sleep times. The MSLT reveals short sleep latencies with SOREMPs possible in one or more naps (78). The absence of cataplexy distinguishes Kleine–Levin syndrome from narcolepsy. Diagnostic neuroimaging is usually unremarkable, although a case report revealed mesial temporal abnormalities on single photon emission computed tomography (79). Table 13 provides the detailed diagnostic criteria for recurrent hypersomnia (Kleine–Levin syndrome and menstrual-related hypersomnia) (2).

In menstrual-related hypersomnia, polysomnography can either be unremarkable or show an alpha–delta sleep pattern with a high REM density and a low percentage of REM sleep. MSLT performed during the hypersomnic period reveals mean sleep latencies less than 10 minutes with no SOREMPs (2,70).

Treatment

In many cases of Kleine–Levin syndrome, the episodes become less frequent over time and eventually subside. Treatment with stimulant medication is partially effective (Table 8), and lithium, valproic acid, carbamazepine, and melatonin have been used as prophylactic measures with variable success (80–83). Menstrual-related hypersomnia responds to suppression of ovulation with oral contraceptive pills or stimulant medications such as methylphenidate (70,84).

BEHAVIORALLY INDUCED INSUFFICIENT SLEEP SYNDROME

Clinical Features

Insufficient sleep syndrome results when an individual consistently fails to obtain sufficient nocturnal sleep to support normal alert wakefulness (2).

The resulting chronic sleep deprivation is therefore voluntary and unintentional. Although sleep need varies from person to person, most agree that between seven and nine hours of sleep per night is needed to avoid excessive sleepiness. These patients develop a persistent sleep debt by chronically obtaining less than an optimal amount of sleep. Chronic sleep restriction results in sleepiness, irritability, concentration and attention deficits, reduced vigilance, distractibility, fatigue, restlessness, and malaise. Furthermore, sleep deprivation has been shown to increase mortality, alter metabolic, endocrine, and immune function, and impair psychomotor vigilance task performance equal to legal intoxication (85–89).

Epidemiology

The exact prevalence and incidence of insufficient sleep syndrome, although more common in men, is not known. It may occur more frequently in adolescence, where social pressures and delayed sleep phase issues combine to curtail sleep. Approximately 25% of the population reports regularly obtaining inadequate amounts of sleep making it the most common cause of sleepiness in society (3,86). The current level of sleep restriction in modern society is dramatic as we now sleep 1.5 hours less per night than we did in 1910 (90).

Etiology and Pathophysiology

Insufficient sleep is a volitional failure to obtain the needed amount of sleep and as such the etiology is self imposed. The deprioritization of sleep in our society has many causes including artificial light, television, the internet, shift work, and a 24-hour economy. These factors as well as personal and social demands have limited the time available for sleep. For many, sleep is erroneously considered a luxury, not a physiologic need.

Diagnosis

The diagnosis of insufficient sleep syndrome requires excluding other medical or primary sleep disorder causes of sleepiness. Testing in the sleep laboratory is necessary when indicated by the medical and sleep history. A short main sleep episode should be observed using sleep diaries and wrist actigraphy. Polysomnography is normal, typically revealing a short sleep latency less than 10 minutes and a sleep efficiency greater than 90%. The MSLT may demonstrate a mean sleep latency less than eight minutes with or without multiple SOREMPs. Patients often report extended sleep times on weekends and during vacations as compared to weekday nights. Sleep extension resolves the sleepiness. Table 14 provides the current diagnostic criteria for behaviorally induced insufficient sleep syndrome (2).

Table 14 Behaviorally Induced Insufficient Sleep Syndrome: International Classification of Sleep Disorders Diagnostic Criteria

A. The patient has a complaint of excessive sleepiness or, in prepubertal children, a complaint of behavioral abnormalities suggesting sleepiness. The abnormal sleep pattern is present almost daily for at least 3 months
B. The patient's habitual sleep episode, established using history, a sleep log, or actigraphy, is usually shorter than expected from age-adjusted normative data[a]
C. When the habitual sleep schedule is not maintained (weekends or vacation time), patients will sleep considerably longer than usual
D. If diagnostic polysomnography is performed (not required for diagnosis), sleep latency is less than 10 minutes and sleep efficiency greater than 90%. During the MSLT, a short mean sleep latency of less than 8 minutes (with or without multiple SOREMPs) may be observed
E. The hypersomnia is not better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder

[a]In the case of individuals with long sleep time, habitual sleep periods may be normal, based on age-adjusted normative data. However, these sleep periods may be insufficient for this population.
Abbreviations: MSLT, multiple sleep latency test; SOREMPs, sleep onset rapid eye movement periods.
Source: From Ref. 2.

Treatment

Treatment involves patient education regarding sleep prioritization. Sleep diaries and daily journals can help the patient understand the impact of sleep deprivation on both their impaired functioning and the improvements associated with sleep extension. Sleep hygiene should be emphasized. Explaining the risks of sleep deprivation in regards to motor vehicle accidents, impaired workplace performance, and disrupted interpersonal relationships can help change behavior (91).

CLINICAL FOLLOW-UP OF PATIENTS WITH NARCOLEPSY AND THE PRIMARY HYPERSOMNIAS

Patients with narcolepsy or the other hypersomnias should be followed regularly by a sleep specialist until they are on a stable medical regimen at which point routine follow-up can occur with their primary care physician. Because many stimulants have significant side effects, annual or biannual visits are recommended to ensure that the medications are well tolerated, and assess if a drug holiday is in order. Patients with narcolepsy are at increased risk of developing other sleep disorders, and should be questioned for symptoms of REM sleep behavior disorder, obstructive sleep apnea, and periodic limb movement disorder at these annual visits. In some patients cataplexy abates over time, allowing the physician to discontinue

Table 15 Diagnostic Tests for Narcolepsy and the Primary Hypersomnias

Disorder	Polysomnography	MSLT	CSF hypocretin-1 levels	HLA-DQB1 *0602 positive
Narcolepsy with cataplexy	Sleep latency <10 min, REM latency <20 min, fragmented sleep	Mean sleep latency ≤8 min, 2 or more SOREMPs	Low in 87%	93%
Narcolepsy without cataplexy	Sleep latency <10 min, REM latency <20 min, fragmented sleep	Mean sleep latency ≤8 min, 2 or more SOREMPs	Low in 14%	56%
Secondary narcolepsy	Variable	Mean sleep latency <8 min, 2 or more SOREMPs	Low in 17%	23%
Idiopathic hypersomnia	Normal or extended sleep time, normal sleep architecture, sleep latency <10 min, normal REM latency	Mean sleep latency <8 min, <2 SOREMPs	Normal (1 of 29 was borderline)	52%
Posttraumatic hypersomnia	Prolonged or normal sleep duration, normal timing and quality of sleep	Mean sleep latency <8 min, no more than 1 SOREMP	Normal	50% (1 of 2)
Recurrent hypersomnia	Reduced sleep efficiency, reduced relative stage REM and NREM stage 3–4, increased relative NREM stage 1 and wake time after sleep onset	Mean sleep latency <10 min, SOREMPs possible	Normal	43% (3 of 7)
Behaviorally induced insufficient sleep syndrome	Sleep latency <10 min, sleep efficiency >90%	Mean sleep latency <8 min, SOREMPs possible	Normal	12–38% of general population

Low CSF hypocretin-1 defined as <110 pg/mL.
Abbreviations: SOREMP, sleep onset rapid eye movement period; CSF, cerebrospinal fluid; MSLT, multiple sleep latency test; min = minutes.
Source: From Refs. 2, 22, 28, 68.

anti-cataplectic medications. Patients with post-traumatic hypersomnia and Kleine–Levin syndrome may resolve their hypersomnolence over time, thus obviating further treatment with stimulants. However, patients with narcolepsy and the primary hypersomnias typically experience lifelong sleepiness and require the continued guidance and support of their physician.

CONCLUSION

Excessive sleepiness is common in our society. The astute physician should have a broad differential diagnosis. Thyroid disease, anemia, and depression should be ruled out. A thorough sleep history, overnight polysomnography and in some cases MSLT, 24-hour polysomnography, wrist actigraphy, and cerebrospinal fluid hypocretin-1 levels are helpful in making a diagnosis. Table 15 summarizes the findings on some of these tests in patients with narcolepsy and the primary hypersomnias.

Common causes of sleepiness such as behaviorally induced insufficient sleep syndrome, obstructive sleep apnea, and restless legs syndrome/periodic limb movement disorder should be ruled out. Narcolepsy must be considered in any patient with the onset of sleepiness in adolescence, particularly if naps are refreshing or they endorse cataplexy. Idiopathic hypersomnia should be considered in the young patient with prolonged nocturnal sleep, daytime naps, and sleep drunkenness in the absence of narcoleptic characteristics. Posttraumatic hypersomnia should be suspected in any person with sleepiness temporally related to a substantial traumatic head injury. Recurrent hypersomnia must be considered in any patient with intermittent sleepiness associated with either hyperphagia/hypersexuality or menstrual periods.

Treatment should involve patient education, stimulants, and in the case of narcolepsy, anti-cataplectics. Emotional support from both physicians and support groups is critical to the overall well being of the patient.

REFERENCES

1. D'Alessandro R, Rinaldi R, Cristina E, Gamberini G, Lugaresi E. Prevalence of excessive daytime sleepiness an open epidemiological problem. Sleep 1995; 18(5):389–391.
2. American Academy of Sleep Medicine. International Classification of Sleep Disorders: Diagnostic and Coding Manual. 2nd ed. Westchester, Illinois: American Academy of Sleep Medicine, 2005.
3. Bonnet MH, Arand DL. We are chronically sleep deprived. Sleep 1995; 18(10): 908–911.
4. Mahowald MW. Eyes wide shut. The dangers of sleepy driving. Minn Med 2000; 83(8):25–30.
5. Yoss RE, Daly DD. Criteria for the diagnosis of the narcoleptic syndrome. Mayo Clin Proc 1957; 32(12):320–328.

6. Beusterien KM, Rogers AE, Walsleben JA, Emsellem HA, Reblando JA, Wang L, et al. Health-related quality of life effects of modafinil for treatment of narcolepsy. Sleep 1999; 22(6):757–765.
7. Bassetti C, Aldrich M. Narcolepsy. Neurologic Clinics 1996; 14:545–571.
8. Anic-Labat S, Guilleminault C, Kraemer HC, Meehan J, Arrigoni J, Mignot E. Validation of a cataplexy questionnaire in 983 sleep-disorders patients. Sleep 1999; 22(1):77–87.
9. Hublin C, Kaprio J, Partinen M, Koskenvuo M, Heikkila K, Koskimies S, et al. The prevalence of narcolepsy: epidemiological study of the Finnish twin cohort. Ann Neurol 1994; 35(6):709–716.
10. Dauvilliers Y, Billiard M, Montplaisir J. Clinical aspects and pathophysiology of narcolepsy. Clin Neurophysiol 2003; 114(11):2000–2017.
11. Kryger M, Roth T, Dement WC. Principles and Practice of Sleep Medicine. 3rd ed. Philadelphia: W. B. Saunders Company, 2000.
12. Schenck CH, Mahowald MW. Motor dyscontrol in narcolepsy: rapid-eye-movement (REM) sleep without atonia and REM sleep behavior disorder. Ann Neurol 1992; 32(1):3–10.
13. Montplaisir J, Michaud M, Denesle R, Gosselin A. Periodic leg movements are not more prevalent in insomnia or hypersomnia but are specifically associated with sleep disorders involving a dopaminergic impairment. Sleep Med 2000; 1(2):163–167.
14. Chokroverty S. Sleep apnea in narcolepsy. Sleep 1986; 9(1 Pt 2):250–253.
15. Dement WC, Zarcone V. The prevalence of narcolepsy [abstr]. Sleep Res 1972; 1:148.
16. Dement WC, Carskadon MA, Ley R. The prevalence of narcolepsy II [abstr]. Sleep Res 1973; 2:147.
17. Solomon P. Narcolepsy in Negros. Dis Nerv Syst 1945; 6:179–183.
18. Silber MH, Krahn LE, Olson EJ, Pankratz VS. The epidemiology of narcolepsy in Olmsted County, Minnesota: a population-based study. Sleep 2002; 25(2): 197–202.
19. Tashiro T, Kanbayashi T, Lijima S, Hishikawa Y. An epidemiological study on prevalence of narcolepsy in Japanese. J Sleep Res 1992; 15:228.
20. Honda Y. Census of narcolepsy, cataplexy and sleep life among teenagers in Fujisawa City. Sleep Res 1979; 8:191.
21. Mignot E. Genetic and familial aspects of narcolepsy. Neurology 1998; 50(2 suppl 1):S16–S22.
22. Mignot E, Lin L, Rogers W, Honda Y, Qiu X, Lin X, et al. Complex HLA-DR and -DQ interactions confer risk of narcolepsy–cataplexy in three ethnic groups. Am J Hum Genet 2001; 68(3):686–699.
23. de Lecea L, Kilduff TS, Peyron C, Gao X, Foye PE, Danielson PE, et al. The hypocretins: hypothalamus-specific peptides with neuroexcitatory activity. Proc Natl Acad Sci USA 1998; 95(1):322–327.
24. Peyron C, Tighe DK, van den Pol AN, de Lecea L, Heller HC, Sutcliffe JG, et al. Neurons containing hypocretin (orexin) project to multiple neuronal systems. J Neurosci 1998; 18(23):9996–10,015.
25. Lin L, Faraco J, Li R, Kadotani H, Rogers W, Lin X, et al. The sleep disorder canine narcolepsy is caused by a mutation in the hypocretin (orexin) receptor 2 gene. Cell 1999; 98(3):365–376.

26. Chemelli RM, Willie JT, Sinton CM, Elmquist JK, Scammell T, Lee C, et al. Narcolepsy in orexin knockout mice: molecular genetics of sleep regulation. Cell 1999; 98(4):437–451.
27. Nishino S, Ripley B, Overeem S, Lammers GJ, Mignot E. Hypocretin (orexin) deficiency in human narcolepsy. Lancet 2000; 355(9197):39–40.
28. Mignot E, Lammers GJ, Ripley B, Okun M, Nevsimalova S, Overeem S, et al. The role of cerebrospinal fluid hypocretin measurement in the diagnosis of narcolepsy and other hypersomnias. Arch Neurol 2002; 59(10):1553–1562.
29. Peyron C, Faraco J, Rogers W, Ripley B, Overeem S, Charnay Y, et al. A mutation in a case of early onset narcolepsy and a generalized absence of hypocretin peptides in human narcoleptic brains. Nat Med 2000; 6(9):991–997.
30. Thannickal TC, Moore RY, Nienhuis R, Ramanathan L, Gulyani S, Aldrich M, et al. Reduced number of hypocretin neurons in human narcolepsy. Neuron 2000; 27(3):469–474.
31. Mignot E, Chen W, Black J. On the value of measuring CSF hypocretin-1 in diagnosing narcolepsy. Sleep 2003; 26(6):646–649.
32. Tafti M, Nishino S, Aldrich MS, Liao W, Dement WC, Mignot E. Major histocompatibility class II molecules in the CNS: increased microglial expression at the onset of narcolepsy in canine model. J Neurosci 1996; 16(15):4588–4595.
33. Dauvilliers Y, Maret S, Bassetti C, Carlander B, Billiard M, Touchon J, et al. A monozygotic twin pair discordant for narcolepsy and CSF hypocretin-1. Neurology 2004; 62(11):2137–2138.
34. Dauvilliers Y, Carlander B, Molinari N, Desautels A, Okun M, Tafti M, et al. Month of birth as a risk factor for narcolepsy. Sleep 2003; 26(6):663–665.
35. Lankford DA, Wellman JJ, O'Hara C. Posttraumatic narcolepsy in mild to moderate closed head injury. Sleep 1994; 17(8 suppl):S25–S28.
36. Orellana C, Villemin E, Tafti M, Carlander B, Besset A, Billiard M. Life events in the year preceding the onset of narcolepsy. Sleep 1994; 17(8 suppl):S50–S53.
37. Mueller-Eckhardt G, Meier-Ewart K, Schiefer HG. Is there an infectious origin of narcolepsy? Lancet 1990; 335(8686):424.
38. Carlander B, Eliaou JF, Billiard M. Autoimmune hypothesis in narcolepsy. Neurophysiol Clin 1993; 23(1):15–22.
39. Malik S, Boeve BF, Krahn LE, Silber MH. Narcolepsy associated with other central nervous system disorders. Neurology 2001; 57(3):539–541.
40. Marcus CL, Trescher WH, Halbower AC, Lutz J. Secondary narcolepsy in children with brain tumors. Sleep 2002; 25(4):435–439.
41. Scammell TE, Nishino S, Mignot E, Saper CB. Narcolepsy and low CSF orexin (hypocretin) concentration after a diencephalic stroke. Neurology 2001; 56(12):1751–1753.
42. Dempsey OJ, McGeoch P, de Silva RN, Douglas NJ. Acquired narcolepsy in an acromegalic patient who underwent pituitary irradiation. Neurology 2003; 61(4):537–540.
43. Nishino S, Mao J, Sampathkumaran R, Shelton J. Increased dopaminergic transmission mediates the wake-promoting effects of CNS stimulants. Sleep Res Online 1998; 1(1):49–61.
44. Nishino S, Mignot E. Pharmacological aspects of human and canine narcolepsy. Prog Neurobiol 1997; 52(1):27–78.

45. Mitler MM, Aldrich MS, Koob GF, Zarcone VP. Narcolepsy and its treatment with stimulants. ASDA standards of practice. Sleep 1994; 17(4):352–371.
46. Lammers GJ, Arends J, Declerck AC, Ferrari MD, Schouwink G, Troost J. Gammahydroxybutyrate and narcolepsy: a double-blind placebo-controlled study. Sleep 1993; 16(3):216–220.
47. U.S. Xyrem® Multicenter Study Group. A 12-month, open-label, multicenter extension trial of orally administered sodium oxybate for the treatment of narcolepsy. Sleep 2003; 26(1):31–35.
48. U.S. Xyrem® Multicenter Study Group. Sodium oxybate demonstrates long-term efficacy for the treatment of cataplexy in patients with narcolepsy. Sleep Med 2004; 5(2):119–123.
49. Black JE, Brooks SN, Nishino S. Narcolepsy and syndromes of primary excessive daytime somnolence. Semin Neurol 2004; 24(3):271–282.
50. Billiard M, Merle C, Carlander B, Ondze B, Alvarez D, Besset A. Idiopathic hypersomnia. Psychiatry Clin Neurosci 1998; 52(2):125–129.
51. Bassetti C, Aldrich MS. Idiopathic hypersomnia. A series of 42 patients. Brain 1997; 120(Pt 8):1423–1435.
52. Billiard M, Dauvilliers Y. Idiopathic hypersomnia. Sleep Med Rev 2001; 5(5):349–358.
53. Harada S, Matsuki K, Honda Y, Someya T. Disorders of Excessive Daytime Sleepiness Without Cataplexy, and Their Relationship with HLA in Japan. Berlin: Springer-Verlag, 1988.
54. Montplaisir J, Poirier G. HLA in Disorders of Excessive Daytime Sleepiness Without Cataplexy in Canada. Berlin: Springer-Verlag, 1988.
55. Honda Y, Honda M. Idiopathic hypersomnia—review of literatures and clinical experiences on 16 Japanese cases. Nippon Rinsho 1998; 56(2):371–375.
56. Petitjean F, Jouvet M. Hypersomnia and increase of cerebral 5-hydroxyindoleacetic acid due to isthmic lesions in the cat. C R Seances Soc Biol Fil 1970; 164(11):2288–2293.
57. Faull KF, Thiemann S, King RJ, Guilleminault C. Monoamine interactions in narcolepsy and hypersomnia: a preliminary report. Sleep 1986; 9(1 Pt 2): 246–249.
58. Bove A, Culebras A, Moore JT, Westlake RE. Relationship between sleep spindles and hypersomnia. Sleep 1994; 17(5):449–455.
59. Nevsimalova S, Blazejova K, Illnerova H, Hajek I, Vankova J, Pretl M, et al. A contribution to pathophysiology of idiopathic hypersomnia. Suppl Clin Neurophysiol 2000; 53:366–370.
60. Brooks S, Mignot E. Narcolepsy and idiopathic hypersomnia. In: Lee-Choing T, Sateia MJ, Carskadon M, eds. Sleep Medicine. Philadelphia: Hanley and Belfus, 2002:193–201.
61. Guilleminault C, Stoohs R, Clerk A, Cetel M, Maistros P. A cause of excessive daytime sleepiness. The upper airway resistance syndrome. Chest 1993; 104(3):781–787.
62. Guilleminault C, Faull KF. Sleepiness in nonnarcoleptic, non-sleep apneic EDS patients: the idiopathic CNS hypersomnolence. Sleep 1982; 5(suppl 2): S175–S181.

63. Bastuji H, Jouvet M. Successful treatment of idiopathic hypersomnia and narcolepsy with modafinil. Prog Neuropsychopharmacol Biol Psychiatry 1988; 12(5):695–700.
64. Montplaisir J, Fantini L. Idiopathic hypersomnia: a diagnostic dilemma. A commentary of "idiopathic hypersomnia" (M. Billiard and Y. Dauvilliers). Sleep Med Rev 2001; 5(5):361–362.
65. Masel BE, Scheibel RS, Kimbark T, Kuna ST. Excessive daytime sleepiness in adults with brain injuries. Arch Phys Med Rehabil 2001; 82(11):1526–1532.
66. Guilleminault C, Faull KF, Miles L, van den Hoed J. Posttraumatic excessive daytime sleepiness: a review of 20 patients. Neurology 1983; 33(12):1584–1589.
67. Guilleminault C, Yuen KM, Gulevich MG, Karadeniz D, Leger D, Philip P. Hypersomnia after head–neck trauma: a medicolegal dilemma. Neurology 2000; 54(3):653–659.
68. Dauvilliers Y, Baumann C, Carlander B, Bischof M, Blatter T, Lecendreux M, et al. CSF hypocretin-1 levels in narcolepsy, Kleine–Levin syndrome, and other hypersomnias and neurological conditions. J Neurol Neurosurg Psychiatry 2003; 74(12):1667–1673.
69. Chung KF. Recurrent hypersomina: a case report with polysomnographic findings. Hong Kong Med J 1997; 3(1):107–110.
70. Bamford CR. Menstrual-associated sleep disorder: an unusual hypersomniac variant associated with both menstruation and amenorrhea with a possible link to prolactin and metoclopramide. Sleep 1993; 16(5):484–486.
71. Dauvilliers Y, Mayer G, Lecendreux M, Neidhart E, Peraita-Adrados R, Sonka K, et al. Kleine–Levin syndrome: an autoimmune hypothesis based on clinical and genetic analyses. Neurology 2002; 59(11):1739–1745.
72. Fenzi F, Simonati A, Crosato F, Ghersini L, Rizzuto N. Clinical features of Kleine–Levin syndrome with localized encephalitis. Neuropediatrics 1993; 24(5):292–295.
73. Carpenter S, Yassa R, Ochs R. A pathologic basis for Kleine–Levin syndrome. Arch Neurol 1982; 39(1):25–28.
74. Takrani LB, Cronin D. Kleine–Levin syndrome in a female patient. Can Psychiatr Assoc J 1976; 21(5):315–318.
75. Koerber RK, Torkelson R, Haven G, Donaldson J, Cohen SM, Case M. Increased cerebrospinal fluid 5-hydroxytryptamine and 5-hydroxyindoleacetic acid in Kleine–Levin syndrome. Neurology 1984; 34(12):1597–1600.
76. Katz JD, Ropper AH. Familial Kleine–Levin syndrome: two siblings with unusually long hypersomnic spells. Arch Neurol 2002; 59(12):1959–1961.
77. Chesson AL Jr, Levine SN, Kong LS, Lee SC. Neuroendocrine evaluation in Kleine–Levin syndrome: evidence of reduced dopaminergic tone during periods of hypersomnolence. Sleep 1991; 14(3):226–232.
78. Rosenow F, Kotagal P, Cohen BH, Green C, Wyllie E. Multiple sleep latency test and polysomnography in diagnosing Kleine–Levin syndrome and periodic hypersomnia. J Clin Neurophysiol 2000; 17(5):519–522.
79. Portilla P, Durand E, Chalvon A, Habert M, Navelet Y, Prigent A, et al. SPECT-identified hypoperfusion of the left temporomesial structures in a Kleine–Levin syndrome. Rev Neurol (Paris) 2002; 158(5 Pt 1):593–595.

80. Poppe M, Friebel D, Reuner U, Todt H, Koch R, Heubner G. The Kleine–Levin syndrome—effects of treatment with lithium. Neuropediatrics 2003; 34(3):113–119.
81. Mukaddes NM, Kora ME, Bilge S. Carbamazepine for Kleine–Levin syndrome. J Am Acad Child Adolesc Psychiatry 1999; 38(7):791–792.
82. Crumley FE. Valproic acid for Kleine–Levin syndrome. J Am Acad Child Adolesc Psychiatry 1997; 36(7):868–869.
83. Kornreich C, Fossion P, Hoffmann G, Baleriaux M, Pelc I. Treatment of Kleine–Levin syndrome: melatonin on the starting block. J Clin Psychiatry 2000; 61(3):215.
84. Sachs C, Persson HE, Hagenfeldt K. Menstruation-related periodic hypersomnia: a case study with successful treatment. Neurology 1982; 32(12): 1376–1379.
85. Irwin M. Effects of sleep and sleep loss on immunity and cytokines. Brain Behav Immun 2002; 16(5):503–512.
86. Wingard DL, Berkman LF. Mortality risk associated with sleeping patterns among adults. Sleep 1983; 6(2):102–107.
87. Kripke DF, Garfinkel L, Wingard DL, Klauber MR, Marler MR. Mortality associated with sleep duration and insomnia. Arch Gen Psychiatry 2002; 59(2):131–136.
88. Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. Lancet 1999; 354(9188):1435–1439.
89. Dawson D, Reid K. Fatigue, alcohol and performance impairment. Nature 1997; 388(6639):235.
90. Webb W, Agnew H. Are we chronically sleep deprived? Bull Psychon Soc 1975; 6:47–48.
91. Dement WC, Mitler MM. It's time to wake up to the importance of sleep disorders. JAMA 1993; 269(12):1548–1550.

8

Parasomnias and Other Nocturnal Events

Bradley V. Vaughn

Department of Neurology,
The University of North Carolina School of Medicine,
Chapel Hill, North Carolina, U.S.A.

Symptoms	***Diagnoses***
Unusual nocturnal behavior	*Disorders of arousal*
Sleepwalking	*Sleepwalking*
Hallucinations	*Sleep-related eating disorder*
Sleep talking	*Sleep-related intercourse*
Dream enactment	*Sleep terrors*
Nightmares	*Confusional arousals*
Fearful awakenings	*Sleep transition disorders*
	Sleep talking
	Sleep-related groaning (catathrenia)
	Automatic behavior
	Sleep enuresis
	Sleep starts (hypnic jerks)
	Exploding head syndrome
	Sleep-related bruxism
	Periodic limb movements of sleep/restless legs syndrome
	Sleep-related rhythmic movement disorder
	REM sleep-related events
	REM sleep behavior disorder
	Cataplexy
	Nightmare disorder
	Recurrent isolated sleep paralysis
	Sleep-related hallucinations
	REM sleep sinus arrest
	Psychogenic states
	Panic disorder
	Sleep-related dissociative disorders
	Conversion disorder
	Nocturnal seizures
	Nocturnal paroxysmal dystonia
	Autosomal dominant nocturnal frontal lobe epilepsy
	Benign focal epilepsy with centrotemporal spikes (benign rolandic epilepsy)
	Epileptic myoclonus

INTRODUCTION

Parasomnias are undesirable physical or sensory experiences that occur with sleep. These events often involve bizarre and unusual behaviors, and can challenge even the most ardent sleep specialist or epileptologist. Although some events are uncommon, 3% of adults and 20% of children may have recurring nocturnal behaviors. Many of these events are passed off as little more than frivolous episodes. Yet, nocturnal events may provide important clues to sleep and neurological function. The diagnosis of paroxysmal nocturnal events can be difficult because of the frequent overlap of clinical descriptions and lack of diurnal findings. Patients may not follow the "classical" patterns of parasomnia or epilepsy, and some patients may have parasomnias provoked by other sleep disturbances or seizures. Thus, the diagnosis of these patients often requires intensive investigation and extensive neurophysiological monitoring.

Nocturnal events can be generally categorized into three major groups: sleep disorders, psychiatric events, or seizures. For sleep disorders, neuronal processes project the distinguishing features of the states of wakefulness, nonrapid eye movement (NREM) sleep, and rapid eye movement (REM) sleep. These state changes are neither concise nor instantaneous. Some sleep disorders are a mixture of the sleep and wake states. Disorders of arousal, such as sleepwalking or sleep terrors, represent a classic example of the mixture of wakefulness with NREM sleep. Sleep transition disorders, such as sleep talking, rhythmic movement disorder, or sleep starts, are events that occur at the transition between wakefulness and sleep. In other sleep disorders, patients may exhibit loss of isolated components of stages of sleep. REM sleep behavior disorder is an example of the loss of the normal paralysis occurring in REM sleep. Psychiatric events, such as panic attacks and fugue states, may present as nighttime events. These psychogenic episodes, although occurring in the traditional sleep–wake states, cause a clear aberration in the patient's usual behavior. Other processes not directly involved in the regulation of the sleep–wake state can cause sleep-related behavior through induction of a pathological state apart from sleep. Epileptic seizures frequently cause impairment of consciousness and abnormal behaviors. In approximately 20% of patients with epilepsy, these seizures only occur during sleep. Other events, such as metabolic derangement or effects from toxins, can alter consciousness and impair neuronal function and sleep–wake differentiation.

The history and physical exam are the cornerstones of the evaluation of paroxysmal nocturnal events. Key features can help differentiate nocturnal events (Table 1). Although there are no absolutes, evaluations hinge on the ability to ascertain the age of onset, event characteristics and timing, provoking factors, patient's memory of the event, family history, and associated symptoms. The physical exam can suggest focal neurological lesions, increasing the likelihood of certain disorders. Focal lesions in the cerebrum increase

Table 1 Distinguishing Features of Nocturnal Events

Feature	Disorder of arousal	Sleep transition disorders	REM sleep behavior disorder	Psychogenic events	Nocturnal seizures
Age of onset	Childhood/ adolescence	Variable	Older adult	Adolescence/adult	Variable
Time of occurrence	First third of night	Near sleep onset	During REM	Anytime	Anytime
Memory of event	Usually none	Variable	Dream recall	None	Usually none
Stereotypical movements	No	Potentially	No	No	Yes
Polysomnography findings	Arousals from slow-wave sleep	Variable depending upon event	Excessive EMG tone during REM	Occur from awake state	Potentially epileptiform activity

Abbreviations: REM, rapid eye movement; EMG, electromyography.

the risk of epileptic seizures, whereas findings indicative of Parkinson's disease suggest REM sleep behavior disorder. By the end of the initial consultation, the physician should answer three important questions: (1) Is there potential for harm or harm to someone else? (2) Are the symptoms suggestive of an associated sleep disorder? and (3) Do the features suggest epileptic seizures? Determining the etiology of nocturnal events is difficult, requiring a high index of suspicion. In this chapter, we review the distinguishing features and treatment of these unusual paroxysmal nocturnal events.

NREM SLEEP-RELATED EVENTS

We currently recognize three normal states of being: wakefulness, NREM, and REM sleep. These states are defined by physiological measurements, including the electroencephalogram (EEG), eye movements, and muscle tone (see Chap. 2). A wide array of physiological parameters, including respiration, thermoregulation, blood pressure, and variability in heart rate, are altered by sleep stage (1,2). Monitoring these parameters demonstrates that change of state is not "a flick of a switch" phenomenon. Disruption of the neuronal processes determining a state of being can cause "mixing" of these states. Thus, behaviors normally accompanying one state intrude into another (3). This process of state change can be disrupted by disorders causing arousals, such as sleep apnea or a poor sleeping environment. Most of these disorders reveal features that provide clues to their basis.

In general, key features of arousal disorders distinguish these events from other disorders (Table 1). Most of these events occur in the first third of the sleep period, with patients often amnestic for the events. The episodes typically last seconds to minutes, involving a variety of nonstereotyped behaviors. Some patients experience spells at atypical times and/or report a memory of visual imagery and auditory hallucinations. Sleep transition disorders are heterogeneous behaviors occurring at sleep–wake transitions. These events have similar features and represent a continuum.

Arousal Disorders

Disorders of arousal from NREM sleep are defined by the incomplete arousal from NREM stage 2 or NREM stages 3 and 4 (slow-wave) sleep, resulting in wakeful behaviors while asleep. Disorders of arousal are more common in the first half of the night and variable in the behavior. Patients have total or near total amnesia for the event (Table 1). The events can range from simple behaviors as seen in sleepwalking to the florid, frightful events of sleep terrors. The NREM parasomnias sleepwalking, sleep terrors, and confusional arousals are common in children and to a lesser extent in adults. Approximately 30% of children and 1% to 3% of adults have sleepwalking or sleep terror events, and events generally improve with age.

Patients often report a positive family history of disease (4). First-degree relatives of patients with sleepwalking have a 10-fold greater incidence of sleepwalking, and identical twins have a six times greater incidence of events than fraternal twins (5,6). Although many of these behaviors represent a continuous spectrum, classification of the behaviors has lead to the following categorization of these nocturnal behaviors.

Sleepwalking

Sleepwalking occurs out of slow-wave sleep during the first third of the sleep period. The behavior with these events can be subdued or elaborate, including dressing, unlocking locks, cleaning, cooking, and even driving. Some patients describe events involving firearms and other dangerous items (7). Patients observed while sleepwalking do not fully react to their environment, and speech is often slow and less animated. Patients usually have no memory for the event but may describe vague feelings, impressions, or event-related imagery. These patients are normal neurologically but should be questioned for symptoms of other sleep disorders.

Sleep-Related Eating Disorder

This disorder involves involuntary eating episodes occurring as a partial arousal from sleep. Patients have little to no memory of the events. Patients may eat peculiar foods such as raw meats, wrapped candies, boxes of cookies, cake mix, or coffee grounds, usually in a messy manner. Patients may have morning anorexia and unexplained weight gain. These events can occur multiple times per night from all stages of sleep. Patients with eating disorders exhibit a higher prevalence of sleep-related eating disorder than the general population, and a history of childhood sleepwalking is common. Those with sleep-related eating disorder should be evaluated for obstructive sleep apnea, periodic limb movements of sleep, or other potential sleep disorders. Some patients respond to individualized therapies such as dopaminergic medications or topiramate (8).

Sleep-Related Intercourse

Sleep-related intercourse may occur as an extension of sleepwalking. Bed partners may describe the patient grabbing or fondling in a clumsy manner. Individuals often have little or no memory of the event. Sleep deprivation may act as a trigger. Many patients have a history of sleepwalking, but individuals should be questioned about the possible coexistence of other sleep disorders.

Sleep Terrors

Sleep terrors (night terrors, pavor nocturnes) are frightening disorders of arousal involving autonomic hyperactivity. These striking events typically begin with a piercing scream and look of intense fear differentiating it from

sleepwalking. Event onset is abrupt, with patients exhibiting tachycardia, tachypnea, flushing, diaphoresis, and mydriasis. Patients are confused and disoriented and attempts to intercede can be dangerous. Witnesses rarely forget these occurrences. Violence can occur during an event, resulting in injury to the patient or their bed partner. Episodes typically occur in the first third of the night and patients have no memory of the event. Some witnesses describe events occurring throughout the night and patients may recall portions of the episodes. Sleep deprivation, shift work, alcohol, and psychological stress may precipitate events. Patients typically have a normal diurnal neurological exam. As with sleepwalking, patients should be questioned for the presence of other sleep disorders.

Confusional Arousals

Confusional arousals occur following arousal from NREM sleep and are characterized by disorientation, slow speech and mentation, or inappropriate behavior (9). Patients have difficulty remembering the event, and events can be induced with forced arousal. Common presentations include military recruits who punch their superior officer following sudden arousal and children who stare unknowingly at their parent when awoken. These events may be brief or last as long as 40 minutes in some children. Episodes are usually shorter in adults. The natural history of this disorder dictates improvement with age, although it may persist into adulthood. Genetic factors play a role, with many patients endorsing a positive family history. Sleep deprivation, shift work, alcohol and psychological stressors, and affective disorders may precipitate events.

A milder form of confusional arousals known as "sleep drunkenness" represents an inability to attain full alertness upon awakening from sleep. Patients are drowsy, disoriented, poorly coordinated, and may exhibit automatic behavior. Sleep drunkenness represents dysfunction of the arousal system and is associated with idiopathic hypersomnolence. Medications such as hypnotics, antidepressants, and tranquillizers can precipitate events. If symptoms persist, patients should have a complete neurological examination to look for a central nervous system dysfunction.

Evaluation of Arousal Disorders

NREM sleep parasomnias such as sleep terrors, sleepwalking, and confusional arousals involve multiple regions of the brain. Events are provoked in susceptible adults following arousal from sleep. The clinician should view these disorders as partial arousals of the waking of portions of the brain with retention of sleep in the remaining parts of the cerebrum. The partial waking state of the hypothalamus and limbic structures explains the flurry of autonomic responses observed in some events, particularly sleep terrors. Disturbed sleep or frequent arousals precipitate all of these NREM sleep

parasomnias. Therefore, physicians should search for cause of the arousal, such as other sleep disorders or environmental disturbances (Table 2).

A detailed sleep history and physical examination are critical for diagnosis. The physician should search for factors that precipitate parasomnias, such as improper sleep hygiene, sleep deprivation, circadian rhythm abnormalities, fever or other illnesses, emotional stress, medication use, and ingestion of alcohol or sedatives before sleep onset. Sleep disorders, such as obstructive sleep apnea, narcolepsy, or periodic limb movement disorder, may also exacerbate the arousal process (10). Medical disorders such as gastroesophageal reflux, congestive heart failure, pulmonary disorders, and renal failure can increase arousals. Neurological insults and seizures need to be considered as possible factors perpetuating the arousal disorder. Stereotypical features at event onset, such as tonic posturing of an arm or a specific movement or vocalization, strongly suggest a seizure disorder. Neuroimaging is necessary in these patients as well as those with focal neurological findings on exam.

Overnight polysomnography is necessary if the history is atypical, sleepiness is significant, other sleep disorders are suspected, or the patient is at risk for harming themselves or others (Table 3).

Patients with classical features of disease do not require polysomnography (Table 4). Some patients demonstrate the classical slow-wave sleep arousals on polysomnography (11). This pattern of hypersynchronous delta waves begins prior to the arousal and is not observed in all patients (12). Continuation of slowing into the arousal is a more consistent and potentially diagnostically helpful finding (5). It is rare to observe a parasomnia event in the sleep laboratory. In those cases that are captured, accurate assessment requires time-synchronized video monitoring, additional cephalic electrodes, and faster recording speeds to delineate epileptic etiologies.

Table 2 Factors Exacerbating Disorders of Arousal

- Environmental disturbances (noise, light, bed partners, children, pets)
- Sleeping in unfamiliar surroundings
- Sleep deprivation
- Obstructive sleep apnea
- Periodic limb movement disorder
- Headaches
- Gastroesophageal reflux disease
- Neurological deficits (head injury, stroke, seizures)
- Hyperthyroidism
- Alcohol
- Central nervous system depressant medication
- Stress
- Evening exercise

Table 3 Indications for Polysomnography in Patients with Paroxysmal Nocturnal Behaviors

- Atypical presentation for a parasomnia (time of night, behavioral description)
- Events are injurious or have significant potential for injury
- Significant disturbance to patient's home life
- Unusual age of onset
- Events are stereotyped or repetitive
- Unusual frequency of the events
- Patient has excessive daytime sleepiness or complaints of insomnia
- Complaints suggestive of sleep apnea, periodic limb movements, or other sleep disorders

Treatment/Management of Arousal Disorders

Treatment of arousal disorders should consider the degree of functional impairment and risk of the events (9). Mild events occurring without threat of injury may not require medical therapy. However, all patients should be advised of the underlying disorder, features making it more likely to occur, and risks of the disease (Table 5).

Family and bed partners should be instructed that during events patients should be kept safe and softly guided back to bed. The patient should not be awakened or abruptly handled. Confrontation during events may escalate the interaction into violence. Limitation of arousal phenomena is the mainstay of treatment. Sources of arousal, such as extraneous sound or light, should also be minimized. Sleep deprivation, alcohol, and exercise in the evening should be avoided. Patients should improve their sleep environment by removing dangerous objects, placing mattresses on the floor, covering windows and glass doors with thick drapes, and locking doors. Other sleep disorders should be diagnosed and treated as they may provoke events (10).

Medical treatment is necessary when parasomnias occur frequently, disrupt family life, or put the patient or others at risk of physical harm. Low doses of benzodiazepines such as temazepam, clonazepam, or diazepam may limit arousals, and may be used to cover at risk periods or times when episodes need to be avoided. Some patients respond to imipramine, desipramine, or paroxetine. In older patients and those with mental handicaps, medications may provoke morning confusion. Decreased doses or alternative therapies are

Table 4 Features Suggesting Polysomnography Is Not Necessary

- No potential for injury
- Family history of similar events
- Time of occurrence is atypical
- Events are rare

Table 5 Treatment of Arousal Disorders

- Improve sleep environment
- Reduce arousals
- Treatment of other sleep disorders
- Diazepam/clonazepam/temazepam
- Imipramine
- Paroxetine
- Hypnosis

helpful in these instances. Behavioral therapy, stress management, and hypnosis are helpful in patients with underlying psychological issues.

Anticipatory arousal therapy is effective in children who have a consistent time of occurrence for their events. For this therapy, the parent awakens the patient approximately 15 minutes before the time of the typical event. Thus, if the patient typically has an event 45 minutes after being placed in bed, the parent may wake the child after 30 minutes and then allow the child to return to sleep. This technique is repeated nightly for four weeks and then discontinued. The therapy can be reinstituted if the events return.

Clinical follow-up depends on event frequency. Patients should keep diaries or event calendars to assess therapy efficacy and identify potential aggravating factors. Patients with frequent events should be followed by a sleep specialist.

SLEEP TRANSITION EVENTS

Sleep Transition Disorders

Most sleep transition behaviors are self-limiting minor problems that do not reflect underlying pathology. If the patient or bed partner is at risk for harm, evaluation and therapy should be pursued. Below we describe some of the well-recognized sleep transition disorders. Key features and polysomnography findings of sleep transition disorders are summarized in Table 6.

Sleep Talking

Sleep talking is the phenomenon of brief utterances or longer soliloquies during stage 2, slow-wave, or REM sleep. Sleep talking is more likely in the first half of the night, although it may occur at any time during the sleep period. Patients are more likely to have episodes during acute medical illness, stress, or upon starting new medications. Some patients have sleep talking provoked by an underlying sleep disorder. Simple sleep talking does not require evaluation or treatment unless another sleep disorder is suspected. In the rare case for which treatment is necessary, reduction of exacerbating factors, avoidance of alcohol and sedatives, and arousal avoidance are helpful strategies. The physician should question the patient

Table 6 Sleep Transition Disorders

Disorder	Key features	Polysomnography findings
Sleep talking	Talking, mumbling	Talking during any stage of sleep
Sleep-related groaning (catathrenia)	Groaning or chanting occurring in light sleep	Expiratory groan with irregular respirations
Automatic behavior	Confused behavior after awakening	Mixture of normal waking EEG with background slowing
Sleep enuresis	Bedwetting	—
Sleep starts/hypnic jerks	Brief movement, sound, or sensation at sleep onset	Quick muscle jerk without epileptiform activity
Sleep-related bruxism	Quick jaw clenching or grinding	Repetitive temporalis or masseter muscle activity
Periodic limb movements	Repetitive nonmyoclonic limb movements	Periodic limb movements
Restless legs syndrome	Crawling or discomfort that resolves with movement	Periodic limb movements
Sleep-related rhythmic movement disorder	Head banging or body rocking that occurs prior to or in light sleep	Rhythmic movement artifact in light sleep

Abbreviation: EEG, electroencephalography.

and bed partner about more elaborate events to differentiate the possibility of sleepwalking and REM sleep behavior disorder.

Sleep-Related Groaning (Catathrenia)

This disorder is characterized by a light to loud distressing expiratory groan in the second half of the night about 2 to 6 hours after sleep onset. The groan, occurring during REM and lighter stages of NREM sleep, is prolonged and monotonous. Patients may display an anguished expression despite their lack of awareness of the vocalization. Polysomnography reveals events occurring in clusters associated with respiratory dysrhythmia and slowing. The groan occurs during the expiratory phase and ends with a sigh or snort. Evaluation should include polysomnography to exclude obstructive sleep apnea or sleep-related laryngospasm. Reassurance is the mainstay of therapy, as pharmacotherapy is usually not required or helpful.

Automatic Behaviors

Automatic behaviors are purposeful but inappropriate activities lasting minutes to hours that occur with the patient partially awake or asleep. Patients relay stories of putting milk containers in the microwave oven, cereal bowls

in the dryer, or missing an exit on the highway. Sleep-deprived soldiers have continued marching in the wrong direction. Patients appear drowsy or groggy during the episode and are usually partially or totally amnestic for the event. This phenomena is more common in individuals with idiopathic hypersomnia or narcolepsy, but is also observed in patients with delayed sleep phase disorder. Most events are associated with NREM sleep, although REM activity is witnessed in patients with narcolepsy.

These events are distinguished from automatisms associated with seizures by the lack of stereotypic behavior, such as picking, rubbing, or lip smacking. Patients with sleep-related automatic behavior appear sleepy, but can be alerted and answer questions appropriately, which also differentiates the behavior from postictal confusion or metabolic or toxic encephalopathy. The quick return of orientation with a lack of bewilderment and anxiety differentiates automatic behavior from transient global amnesia. Patients with recurring episodes should be evaluated for sleep disorders such as sleep apnea, idiopathic hypersomnia, or narcolepsy.

Sleep Enuresis

Bedwetting is considered normal at certain ages. As maturation allows for greater control over voiding, sleep enuresis is only considered significant after the age of five years with a minimum of two events per week. The disorder is considered primary in those patients without a six-month enuresis-free period and secondary in patients with a six-month free period. Primary enuresis results when children do not arouse from sleep in response to bladder sensations. Some of these children have low vasopressin release during sleep or neurourological impairment. Secondary sleep enuresis is related to psychological stressors, as well as the inability to concentrate urine, increased urine production, neurological pathology, seizures, and obstructive sleep apnea. Evaluation focusing on urological function and assessing neurological function, especially of the lower extremities, may provide etiologic clues (13). Reassurance and trust are the foundation of treatment, and children should be given positive reinforcement for attaining even small goals. Treatments should be directed toward the underlying cause. Patients should limit nighttime liquid intake and urinate before going to bed. Behavioral therapy, including micturitional training or bed alarms (to detect early wetness), may improve urinary control. For bladder-detrusor hyperactivity oxybutynin may be beneficial, and in rare patients desmopressin is needed to reduce the amount of urine made.

Sleep Starts (Hypnic Jerks)

Sleep starts or hypnic jerks are quick, brief, sudden movements occurring at sleep onset. The movements may involve all or part of the body. These events are very common, occurring in virtually everyone, and should be differentiated from myoclonus, which occurs during wakefulness. Some patients

experience brief sensory phenomena such as a bang, roaring buzz, flash of light, brief visual scene, sense of floating, or pain during the event. Events are more common following sleep deprivation or when sleeping in an unfamiliar environment. Stress can also be a trigger. Most of these events do not require further evaluation or treatment (14). If the patient snores or displays symptoms of other sleep disorders, further evaluation should be undertaken.

Exploding Head Syndrome

A variation of the sensory start is the "exploding head syndrome" in which the patient typically experiences a loud, painless, explosion-like sound near sleep onset. This syndrome encompasses a variety of sensory events that occur just at the onset of sleep (15). Subjects may describe a painless loud bang to more subtle sounds just as they are falling asleep. These auditory events are more common in individuals who are sleep deprived or under personal stress. Occasionally, the subject may note a jerk or stab of pain with the sound. These events do not require treatment.

Sleep-Related Bruxism

Sleep-related bruxism is a rhythmic repetitive sleep movement (16). Grinding or clenching of the teeth during sleep produces bizarre sounds. Patients may vocalize during the episode. Abnormal wear of the teeth, jaw pain, headache, facial pain, or tooth pain are often observed. Patients can experience hundreds of events per night, which tend to increase with emotional stress. Studies suggest that as many as 85% of the population grinds their teeth to some degree. These events typically begin in adolescence, and a family history is common. The polysomnogram demonstrates repetitive bouts of increased temporalis muscle activity prior to sleep onset continuing through NREM stage 2 sleep.

Patients with bruxism should see a dentist to quantify dental wear and intervene when necessary. Children rarely require treatment as they usually "outgrow" the sleep bruxism by their teens. Patients with severe bruxism may benefit from a protective occlusal bite splint protecting against tooth damage. Although most patients continue to brux with the splint, tooth wear and other symptoms are often reduced. Excessively worn teeth may be crowned.

Some patients require further therapy to reduce the bruxism. In stress-related bruxism, psychological or psychiatric counseling is helpful. Medications may also be necessary for symptom reduction. Intermittent use of diazepam (5 mg, 30 minutes before bedtime) may relieve anxiety, improve sleep, and reduce symptoms during acute exacerbations. Long-term benzodiazepine therapy is rarely, if ever, indicated (17). Beneficial effects have been reported with other medications such as propranolol, L-dopa, bromocriptine, and gabapentin (18,19). Yet in a recent study, bromocriptine produced no significant improvement in bruxism (20) and amitriptyline showed no statistical improvement in a double-blind study (21). In severe intractable

patients, botulinum toxin injections have shown some benefit (22). For patients with selective serotonin reuptake inhibitor-induced bruxism, buspirone appears to have relieved the symptoms of bruxism in a small series (23). A variety of other treatments, such as nocturnal electromyographic (EMG) biofeedback therapy and masseter relaxation techniques, have shown limited value in the treatment of bruxism (24).

Periodic Limb Movements of Sleep/Restless Legs Syndrome

Periodic limb movements of sleep are repetitive stereotyped movements of the lower extremities that occur during sleep, consisting of extension of the great toe with dorsiflexion of the ankle and flexion of the knee and hip.

Movements can also occur in the arms and axial muscles. The individual movements are brief, lasting 0.5 to 4.0 seconds, and occur at 20 to 120-second intervals. Only a minority of patients with periodic movements of sleep will have periodic limb movement disorder, which includes sequela such as excessive daytime sleepiness or insomnia. Patients, as opposed to bed partners, may be unaware of the movements.

Restless legs syndrome involves deep aching sensations in the legs or arms, improved by movement of the extremities. Some note uncontrollable leg movements or dancing. These movements and uncomfortable sensations are often worse in the evening. Diagnostic criteria focusing on the main symptoms have been established (25). Patients with restless leg syndrome may experience debilitating discomfort, driving some to pursue extreme measures to decrease the symptoms. Most patients experience symptoms while sitting or lying down and may complain of needing to walk or continuously move their legs. These symptoms can lead to continuous nocturnal walking or attempts to sleep with continuous leg movements. Some utilize a combination of medication and alcohol to reduce the symptoms.

Restless legs syndrome and periodic limb movements of sleep are often comorbid conditions. The majority of individuals with restless legs syndrome have periodic limb movements of sleep. These movements may seem either periodic or random. Factors that provoke periodic limb movements also increase the likelihood of restless leg syndrome. Periodic limb movements of sleep have been associated with uremia, peripheral vascular disease, anemia, arthritis, peripheral neuropathy, spinal cord lesions, rheumatoid arthritis, fibromyalgia, antidepressants, and caffeine use. Patients may respond to dopamine agonists or gabapentin. More severe patients may require benzodiazepines or narcotics. Both periodic limb movements and restless legs syndrome are discussed in more detail in Chapter 4.

Sleep-Related Rhythmic Movement Disorder

Patients with sleep-related rhythmic movement disorder present with complaints of rocking movements occurring prior to sleep onset (26,27). The

movements are stereotyped, involving large muscles, usually of the head and neck, and are sustained into light sleep. Movements may include head banging (jactatio capitis nocturna), body rocking, leg rolling, humming, and chanting. Some events can be violent, leading to skull fractures and subdural hematomas. Some patients are unaware of the movements, while others describe the movement as a calming compulsion prior to sleep. This behavior is observed in nearly half of infants. The prevalence at age four is less than 10% and continues to decline with age. Rhythmic movement disorder is more prevalent in males and more commonly seen in individuals with mental handicaps or autism. Emotional stress may provoke the movements. Typical episodes on polysomnography involve rhythmical movements preceding sleep onset and during NREM stage 1 sleep. Bruxism can coexist and evidence for other comorbid sleep disorders should be sought when suspected.

Treatment should focus on education of the family and patient. Medication is not needed for patients with minor movements or for infants and young children. Reassurance and psychological support for the patient and family are helpful. Determination of underlying stressors may help reduce the behavior. Treatment with short-acting hypnotics or tricyclic antidepressants is necessary in patients with violent movements. Unfortunately, medication therapy is not universally effective.

REM SLEEP-RELATED EVENTS

REM sleep is characterized by low amplitude fast EEG activity, rapid movements of the eyes, and paralysis of the somatic muscles (28). Components of REM sleep can occur in concert or as separate fragments. Fragmentation of REM sleep can present as symptoms of visual imagery (hypnogogic hallucinations), loss of muscle tone (cataplexy or sleep paralysis), or dream enactment (REM sleep behavior disorder). The most well known disorder with REM sleep fragmentation is narcolepsy. Another fragmentary disorder of REM sleep involves patients who retain wakeful muscle tone in REM sleep. This dangerous and potentially violent situation is the basis of REM sleep behavior disorder. A list of REM sleep-related events are provided in Table 7.

REM Sleep Behavior Disorder

REM sleep behavior disorder is characterized by intermittent loss of REM sleep, EMG atonia, and elaborate motor activity associated with dream mentation (Table 1). Loss of REM sleep-induced atonia and dream enactment was originally demonstrated by Jouvet and Delorme (29) in 1965 by lesioning specific pontine tegmental regions in cats. The human correlate was not described until 1986 by Schenck and Mahowald (30). Behaviors include punching, kicking, leaping, running, talking, yelling or anything that could occur during a dream. Bed partners and patients are frequently injured. The

Table 7 REM Sleep-Related Events

- REM sleep behavior disorder
- Nightmare disorder
- Recurrent isolated sleep paralysis
- Cataplexy
- Sleep-related hallucinations (hypnogogic and hypnopompic hallucinations)
- REM sleep sinus arrest

Abbreviation: REM, rapid eye movement.

events vary in content and activity, differentiating them from seizures. Patients vividly recall dreams correlating with the witnessed behavior. Dream recall is not uniformly noted and many patients may be unwilling to discuss the dream, leading them to seek medical attention. Events occur more commonly in the latter half of the night, but can occur any time that the patient enters REM sleep. Most cases begin in late adulthood, but children as young as age two may present with the disorder. Males are more likely to exhibit the disorder.

Acute REM sleep behavior disorder can be induced by medications such as tricyclic antidepressants, monoamine oxidase inhibitors, and serotonin reuptake inhibitors. The disorder can also occur during alcohol and benzodiazepine withdrawal. Patients with chronic forms of the disorder may experience behaviors for years prior to presenting for medical evaluation. Approximately 60% of these patients have no clear identifiable cause. The rest have an identifiable neurological disorder, such as strokes, posterior fossa tumors, demyelination, or degenerative disorders blocking induction of REM sleep atonia. Thirty percent of patients with idiopathic REM sleep behavior disorder eventually develop Parkinson's disease, multiple system atrophy, or Lewy body dementia within five years of symptom onset (31). Thus, REM sleep behavior disorder may be a marker for subsequent degenerative disorders, lending an opportunity for earlier intervention.

The diagnosis of the disorder is made by a combination of history and polysomnography (3). Patients or witnesses should describe annoying, disruptive, or harmful sleep behaviors. The polysomnogram demonstrates excessive EMG tone in the chin or excessive twitching of the chin or limb leads during REM sleep. Additionally, there should be videotape documentation of excessive limb or body jerks, complex movements, or vigorous movements during REM sleep. The report of dream memory can be supportive evidence. Patients may exhibit increased REM density.

Patients should undergo a complete physical exam. The clinician should look for features of obstructive sleep apnea or breathing disorders that might disrupt REM sleep. Patients should also undergo a thorough neurological exam to look for features of Parkinsonism, dementia, autonomic instability, or findings suggestive of brainstem lesions. Any neurological abnormalities should prompt magnetic resonance imaging of the brain.

Table 8 Treatment of REM Sleep Behavior Disorder

- Protect bed partner (sleep in separate room)
- Make the sleep environment safe
- Clonazepam/temazepam
- Melatonin
- Donepezil
- Dopamine agonists

Abbreviation: REM, rapid eye movement.

Most patients respond to treatment. Patients and their families should understand that some events could be violent. Thus, the bed partner should sleep in a separate room until the events are controlled. Only then should they move back into the same room, sleeping in separate beds. Families should lock away firearms and other items potentially used as dangerous weapons. Patients generally respond well to clonazepam (0.5–3.0 mg) or temazepam (15–45 mg). Alternative therapies include melatonin, donepezil, and dopamine agonists. Anticonvulsants, clonidine, and even tricyclic antidepressants have been reported anecdotally helpful in intractable cases. The treatment of REM sleep behavior disorder is summarized in Table 8.

Cataplexy

Cataplexy is the abrupt loss of muscle tone triggered by strong emotional stimuli or physical exercise. Patients are aware of their surroundings and have clear memory for the complete events. Events can be triggered by a joke, surprise, anger, fear, or athletic endeavors. Individual experiences vary from a mild feeling of weakness to severe falls. Cataplectic attacks are generally brief, lasting less than five minutes. Patients then regain their muscle control without postictal confusion or deficits. Longer events may terminate with the patient entering sleep and then awakening. The combination of excessive daytime sleepiness and cataplexy is nearly always related to narcolepsy. Cataplexy can rarely be seen as an isolated symptom, suggesting an underlying neurological disorder.

Examination of the patient during a cataplectic attack will demonstrate paralysis with diffuse hypotonia, absence of deep tendon reflexes, diminished corneal reflexes, preserved pupillary responses, and phasic muscle twitching. Phasic twitching can occur as single jerks or repetitive muscle twitching, most commonly seen in the face. Maintenance of consciousness and memory help differentiate these events from most seizures and syncope. The history of a clear emotional trigger differentiates cataplexy from vertebral basilar insufficiency or neuromuscular disorders producing periodic paralysis. The abrupt onset and absence of muscle fatigue with repetitive stimulation differentiate cataplexy from myasthenia gravis. Selective serotonin reuptake inhibitors, desipramine, protriptyline, and venlafaxine are mainstays of treatment.

Intractable cases may respond to gamma hydroxybutyrate. Further information on cataplexy can be found in Chapter 7.

Nightmare Disorder

Nightmares are distressing or frightening dreams involving clear visual imagery and auditory perception that suddenly awaken patients with a sense of fear or anxiety. Subjects may recount the dream with plot-like clarity. Significant autonomic outlay may follow the event, but memory remains intact and consciousness is preserved upon awakening. These events usually occur out of REM sleep. More common in younger subjects, nightmares diminish in frequency with age. Personal stress and antihypertensive or antidepressant medications that alter norepinephrine, serotonin, or dopamine are common causes (14).

Recurring nightmares may result from personal trauma or underlying psychological issues. These patients suffer frequent recurring dreams or dreams of the same theme. Common diagnoses include posttraumatic stress disorder, affective disorders, or other psychological pathology. Imagery rehearsal is helpful for many patients (32). In this therapy, the patient is instructed to recall the dream in detail. At a critical point of conflict, the patient constructs a new ending to the dream, resulting in a feeling of empowerment. Patients rehearse this ending for 20 to 30 minutes each day at times away from the sleep period. Most patients note improvement in dream content within one month. Patients who continue to have recurring nightmares should undergo more intense therapy. Medical therapy with the alpha-1 adrenergic antagonist prazosin has been shown to be helpful in these patients as well (33).

Recurrent Isolated Sleep Paralysis

Sleep paralysis is an inability to move during the transition into or out of sleep. The association with intentional sleep distinguishes these events from cataplexy. Patients describe complete awareness of their surroundings or feeling half asleep while remaining aware with an inability to move even their fingers or speak. Attempts to scream only produce a whisper. Some describe a feeling of suffocation with resumption of "normal" breathing only when the event has passed. Patients frequently describe a strong feeling of impending doom, being chased, or having to escape imminent danger. Occasionally, patients note a feeling that someone else is in the bedroom. Auditory and tactile hallucinations may accompany the episode, with some patients recounting dramatic stories. These events can be emotionally profound, leaving a lasting memory patients vividly recall years later. Most sleep paralysis episodes last a few minutes, ending after the patient is touched or alerted by a sound. If the event is allowed to persist, the patient usually re-enters sleep and awakens later. These events are experienced by many individuals after severe sleep deprivation, schedule disruption, or ingestion of alcohol and in patients with narcolepsy or depression.

Infrequent isolated sleep paralysis does not require therapy. However, patients should be advised to avoid sleep deprivation and alcohol. For patients with recurring sleep paralysis, evaluation of potential sleep disturbance and depression should be considered.

Sleep-Related Hallucinations (Hypnagogic and Hypnopompic Hallucinations)

Hallucinations can occur with sleep onset (hypnagogic) or at the end of sleep (hypnopompic). They may include visual, auditory, or tactile components and last seconds to minutes. These events occur at the transition between wake and sleep, incorporating some dream-like features. They can be pleasant or terrifying and difficult to distinguish from reality. Patients may note weightlessness, falling, flying, or out-of-body-like experiences that sometimes terminate with a sudden jerk (hypnic jerk). Visual hallucinations may involve poorly formed colors or shapes, or well-formed images of people or animals that vary in expression. The events are aborted once the patient awakens. In the face of excessive daytime sleepiness, patients should be evaluated for narcolepsy. These events may be repetitive but are not usually stereotypic (same event occurring each time). This lack of stereotypia distinguishes these hallucinations from seizures.

Sleep deprivation, alcohol ingestion, withdrawal of REM suppressing medications, or change in sleep schedule may trigger these events. The relationship of sleep to these hallucinations distinguishes them from hallucinations of psychosis and dementia. The length of time is shorter than that seen with peduncular hallucinations.

Treatment includes reassurance and explanation of the underlying process. For patients with recurring hypnogogic hallucinations, selective serotonin reuptake inhibitors may provide benefit.

REM Sleep Sinus Arrest

A rare disorder, REM sleep sinus arrest can present as events of sudden arousal with a sense of impending doom. In these patients, the sense of panic and fear is a symptom, and some may experience isolated nocturnal panic attacks. Polysomnography will show sinus pauses of 2.5 seconds or greater during REM sleep. These patients should be identified and referred for cardiac evaluation and pacemaker placement.

NREM–REM Overlap Syndromes

Some patients have events in both NREM and REM sleep. This makes differentiation of their events as solely NREM- or REM-related phenomena difficult. Patients may or may not have a memory of the event. The behaviors can be subtle or violent and may occur multiple times per night. Some

of these patients have suffered significant central nervous system injury or degeneration, or they are experiencing toxic or metabolic derangement and require tailored pharmacological regimens.

PSYCHOGENIC STATES

Nonepileptic seizures can present as nocturnal events. This broad class of behavioral phenomena lacks findings suggestive of epilepsy and is subdivided by underlying psychological classification, including sleep-related dissociative disorders, conversion disorders, panic disorders, depression, or anxiety. These patients typically wake up prior to the onset of the events. Unfortunately, some patients labeled as having psychogenic events can still have unrecognized epilepsy, and therefore the diagnosis of nonepileptic seizures should always be considered with skepticism.

Panic Disorder

Panic disorders range in prevalence between 1% and 3% of the general population. Approximately 6% to 14% of young adults report at least one panic attack (34). The majority of attacks occur during the day, but as many as 2.5% occur exclusively at night. Two-thirds of patients with panic attacks have experienced one or more events at night, yet nocturnal panic has been significantly underrecognized (35). Typically, the attack occurs after awakening, but polysomnographic data demonstrate that attacks can occur at sleep onset, in NREM stage 2, or slow-wave sleep. Polysomnography reveals an abrupt arousal from sleep with tachycardia, tachypnea, diaphoresis, tremulousness, and feelings of impending doom. Patients have a clear memory of the event, differentiating them from disorders of arousals. Other parasomnias, nightmares, sleep-related gastroesophageal reflux disease, REM sleep sinus arrest, sleep-related laryngospasm, paroxysmal nocturnal dyspnea, nocturnal asthma, or seizures require further monitoring to distinguish these etiologies from panic attacks. Nocturnal panic attacks are treated similarly to diurnal attacks. Selective serotonin reuptake inhibitors such as paroxetine and anxiolytics (alprazolam or clonazepam) can reduce the frequency of the attacks.

Sleep-Related Dissociative Disorders

These disorders involve dissociative events during the transition from wakefulness to sleep or within minutes of awakening from sleep. Patients have disruption of consciousness, memory identity, or environmental perception. These disorders are divided into: dissociative identity disorder (multiple personality disorder), dissociative fugue, and dissociative disorder not otherwise specified. These disorders are rare and may initially present as nocturnal events. These fugue states last minutes to hours with loss of identity and memory (36). Patients usually have some diurnal symptoms and

may have a history of physical, sexual, or emotional abuse. Common clinical features include a history of multiple suicide attempts, major mood disorders, self-mutilating behaviors, and posttraumatic stress disorder (37). During monitoring, patients frequently demonstrate polysomnographic findings of wakefulness at least 15 to 60 seconds prior to spell onset. Events can involve elaborate behaviors such as driving or flying on an airplane. Simultaneous time-synchronized video monitoring is required to correlate the behavior with the electrographic data. Events are more predominant in females, and age of onset ranges from childhood to adult. Patients with these events require full psychological evaluation.

Conversion Disorder

Conversion disorders can also present as nocturnal events. These patients have significant underlying stressors or conflicts, which initiate or exacerbate the episodes. These events usually start in young adults but may begin in later years (38). They may be exposed to someone with epilepsy who provides a model for spell emulation. Although unintentional, these events impair the patient's ability to function. Most patients with nocturnal conversion disorders have arousals prior to their events and may or may not have memory for the events (Table 1).

NOCTURNAL SEIZURES

Seizures are one of the most common symptoms of disturbed brain function. Over 300,000 people per year in the United States require medical evaluation for their first seizure, and approximately 10% of the population will have a seizure at some point in their life. Although the broad definition of seizure includes any sudden onset attack involving the body, an epileptic seizure is a discrete pathological event composed of paroxysmal firing of neurons producing an abnormal behavior. Some epileptic seizures are self-limited, provoked as part of an acute medical condition or exposure to toxins. Other patients have seizures from unclear etiologies. By either account, seizures are a cardinal sign of dysfunction of the brain's gray matter.

Seizures are of two types: focal onset (partial) or generalized onset (primary generalized). Focal onset seizures are further divided into simple partial, complex partial, and secondarily generalized. Simple partial seizures are defined by retention of consciousness or memory during the spell. Complex partial seizures are defined by impairment of consciousness or loss of memory during the seizure. A partial seizure may evolve into a secondarily generalized seizure. A secondarily generalized seizure begins in one location and spreads to the whole brain. Most generalized seizures in adults are secondarily generalized. Primary generalized seizures begin diffusely across the brain and comprise various types of behavior. Absence seizures

are characterized by brief staring episodes. Atonic seizures cause a sudden loss of tone, resulting in falling. Tonic seizures produce a diffuse increase in tone. Clonic seizures are associated with repetitive jerking. Tonic–clonic seizures start with tonic activity and progress to clonic activity. Myoclonic seizures are single rapid jerks.

In contrast to seizures, epilepsy is a chronic disorder whose hallmark is recurrent unprovoked seizures. For the diagnosis of epilepsy, a patient must have two or more unprovoked seizures. Patients having a single seizure do not have epilepsy. Patients may have multiple seizure types but only one form of epilepsy. Thus, epileptic seizures are the events and epilepsy is the chronic condition.

In 1881, Gowers described a strong connection of sleep to epilepsy. He found that 21% of institutionalized epilepsy patients had seizures strictly when asleep, while 42% had seizures strictly when awake. These results were confirmed by Janz's and Billiard's studies of epileptic patients 100 years later (39).

Nocturnal seizures can present in a variety of ways. Witnesses often provide cardinal clues to the etiology. The key feature of seizures is the stereotypic behavior. Epileptic seizures generally display some portion of behavior that is common for each seizure occurring in the patient. This key feature separates seizures from most other parasomnias. Patients having seizures in their sleep usually lack memory for the seizures, unless the patient awakens from a simple partial seizure. Seizures can occur at any time in the sleep period (day or night). Most nocturnal seizures occur in NREM sleep whether they are temporal or frontal in onset (40). Rare REM-related seizures have been described involving recurrent dreams or dream enactment (41).

A clear description of the seizure-related behaviors is paramount to the proper diagnosis. Patients can display a variety of nocturnal behaviors such as ambulation, confused wandering, or screaming, which can appear similar to NREM parasomnias such as sleepwalking or sleep terrors. Some seizures have a repetitive nature easily confused with sleep-related rhythmic movement disorder. The overlap of symptomatology makes classification of nocturnal seizures difficult.

Nocturnal seizures can manifest as a wide range of behaviors. Seizure semiology depends on the location of the epileptic focus (Table 9). The frontal and temporal lobes are the most common seizure foci and these areas are typically involved in sleep-related epilepsies (39). Seizures involving the frontal lobes may evoke vocalization, screaming, tonic posturing, jerking, and complex bizarre motor activity such as ambulation, running, turning, pelvic thrusting, bicycling, yawning, spitting, eye deviation, sitting up, bouncing on all four extremities, jumping, masturbating, and even violent behavior. Temporal lobe seizures can produce episodes of staring, psychic phenomena, auditory and olfactory hallucinations, and some complex behaviors. Patients with frontal or temporal lobe seizures frequently display seizure-related

Table 9 Location of the Epileptic Focus and Seizure Semiology

Epileptic focus	Seizure semiology (possible behaviors)
Frontal	Posturing of extremities, vocalization, rocking, turning, ambulation, sitting up, pelvic thrusting, gestural automatisms, jerking of face or extremities
Temporal	Staring, an absence of other activity, autonomic events, olfactory and auditory hallucinations, out of body and psychic experiences, oralimentary automatisms, expressions of fear, rising epigastric sensation, belching
Parietal	Somatosensory events (tingling, electrical, wave like, temperature change, or numbness), feeling of movement in a portion of the body or vertigo, metamorphsia
Occipital	Visual hallucinations (sparks, flashes, or more formed images), hemianopsia, scatoma, visual distortion

automatisms. These purposeless, undirected repetitive motor activities may include lip smacking, sucking, swallowing, chewing, hand movements, picking at clothes, or fidgeting. Accompanying gestures may include smiling, laughing, or expressions of fright or anger. Temporal and frontal lobe seizures can also evoke a wide range of autonomic symptoms such as bradycardia, asystole, tachycardia, emesis, and respiratory disturbances. Parietal and occipital lobe seizure foci are less likely to present as sleep-related epilepsies. Parietal onset seizures are more likely to evoke disturbances or distortion of sensory perception. Patients may feel tingling sensations or note abdominal sensations, vertigo, or language disturbances. Occipital lobe onset seizures are usually associated with visual phenomena, visual distortion, or eye movement. The complexity and overlap of seizure behaviors with parasomnias demonstrates the difficulty differentiating these two phenomena.

Patients are frequently confused and disoriented following a seizure. Wandering behavior, pronounced violence, masturbation, rhythmic movement, snoring, and even psychosis have been demonstrated postictally. The confusion can either resolve in minutes or until the patient awakens from sleep. Postictal somnolence is common, making seizures and parasomnias difficult to differentiate.

Memory loss for the event is a hallmark symptom for complex partial or generalized seizures. Amnesia indicates that both hippocampal structures were prevented from incorporating recent memories during the seizure. Some memory loss may occur if the patient remains asleep throughout the seizure. Patients can retain seizure memories despite complex motor behaviors if they are awakened and one hippocampus has preserved functioning during the event. This is also true of patients without temporal lobe involvement in general. These patients are occasionally mislabeled as having psychogenic disorders.

Nocturnal Paroxysmal Dystonia

Previously known as hypnogenic paroxysmal dystonia, this disorder is characterized by repeated dystonic or dyskinetic episodes occurring at night (42–44).

The movements can involve a single extremity or all four extremities and the neck. Patients may vocalize during the spell and frequently recall the event. They come in two forms, usually out of NREM sleep: short duration (15–60 seconds) and long duration (up to 60 minutes). Patients may have multiple spells per night or clusters of spells with quiescent periods. Nocturnal paroxysmal dystonia is considered a form of frontal lobe epilepsy. This complex disorder involves episodes of nocturnal dystonia, paroxysmal arousals, and nocturnal wandering. Patients can demonstrate any combination of these behaviors with few EEG changes. Most patients respond to anticonvulsant medication.

Autosomal Dominant Nocturnal Frontal Lobe Epilepsy

Described by Philips et al. (45) and Oldani et al. (46), this disorder is rare. It shares clinical characteristics with paroxysmal nocturnal dystonia and has an autosomal dominant inheritance pattern. Lugaresi and Cirigonotta (42) have described an Italian form, and other forms from Norway have also been described. Patients have recurrent nocturnal events characterized by brief tonic movements, hypertonic activity, or brief arousals. The EEG fails to demonstrate epileptic changes during the spells, and daytime EEGs are normal. The family history can be difficult to obtain since the spells are often unrecognized or not acknowledged to family members. About one in four patients has daytime seizures that often respond to anticonvulsant therapy. These forms of autosomal dominant nocturnal frontal lobe epilepsy are linked to dysfunction of the neuronal nicotinic acetylcholine receptor subunits. Some patients appear to benefit from manipulation of acetylcholine (47).

Benign Focal Epilepsy with Centrotemporal Spikes (Benign Rolandic Epilepsy)

Another form of inherited nocturnal seizures, benign focal epilepsy with centrotemporal spikes (benign rolandic epilepsy), occurs in children between the age of 5 and 12 years. Patients present with episodes of hemifacial and body tonic activity, drooling, and speech impairment. These events occur approximately 20 minutes to 2 hours after going to bed. Electroencephalography demonstrates a high-amplitude centrotemporal spike and wave discharge associated with bifrontal positivity. Patients are easily treated with anticonvulsant medication as the seizures diminish with age.

Epileptic Myoclonus

Epileptic-based myoclonus occurs soon after awakening. The rapid jerk of myoclonus involves any portion of the body. The jerks can occur in rapid succession or as single events. Sleep deprivation exacerbates the events. They should be differentiated from hypnic jerks, which occur at sleep onset, and periodic limb movements of sleep by the rapidity of the jerk and its occurrence during wakefulness.

Evaluation of Nocturnal Epilepsy

Diagnosing nocturnal seizures can be difficult. In the setting of nocturnal events, the clinician should always maintain a high index of suspicion for seizures. Historical features such as stereotyped events, the occurrence of a clear epileptic seizure while awake, or family history of seizures are helpful. Zacconi and Ferini-Strambi (48) proposed that multiple events per night and continuity between minimal and major events were more typical of nocturnal frontal lobe epilepsy than NREM parasomnias. The physical exam in these patients is often normal, but findings indicative of a cerebral insult suggest an increased risk for seizures.

Diurnal EEG is frequently normal in those with sleep-related epilepsies, although recording sleep may improve the likelihood of observing interictal activity. The absence of epileptiform discharges does not rule out epilepsy. Incorporation of a full 10 to 20 electrode array and a polysomnographic paper speed of 30 mm/sec are helpful when evaluating for seizures. Foldvary et al. (49) found that a seven-channel EEG montage and paper speed increased to 30 mm/sec improved the accuracy of distinguishing epileptic events over the traditional four channel, 10 mm/sec recording. These settings allow for better delineation of epileptiform discharges from normal variants or artifacts. The expanded electrode facilitates this delineation by identifying a discharge's polarity, field potential, and location.

An accurate diagnosis of epilepsy is assisted by capturing multiple events on video-EEG recording and comparing the behaviors. Obtaining prolactin levels can also be useful. Epileptic seizures may occur without clear EEG changes. The ictal discharge may be obscured at the surface EEG for multiple reasons. The electrical potential can be located away from recording electrodes, be too small to be acquired, or represent desynchronized activity. Furthermore, the surface EEG is prone to be obscured by muscle activity, movement, and 60 Hz artifacts. The dura, bone, and configuration of the skull may distort the EEG. Depth electrode studies show that surface EEG may not reveal an ictal discharge in the face of a well-documented discharge near the depth electrodes (50). Even depth electrodes may not demonstrate the electrographic discharge if they are not located near the seizure focus. Despite these limitations, video and EEG recording of multiple events still provides the best method for seizure identification (Table 10).

Table 10 Indications for Video-EEG Monitoring

- Stereotypical or repetitive events
- Multiple spells per night with a minimum of one event per week
- Lack of response to medication trials
- Other history suggestive of epileptic or nonepileptic events

Abbreviation: EEG, electroencephalography.

When the events are stereotypic and reproducible, the clinician should still consider a diagnosis of epilepsy, even if electrographic changes are lacking.

Other Sleep Disorders with Epilepsy

Seizures can be aggravated by other sleep disorders. Patients with epilepsy and obstructive sleep apnea show significant improvement in their frequency of recurrent seizures with treatment of the sleep apnea (51). Similar improvements in seizure frequency are seen with treatment of periodic limb movement disorder, sleep hygiene improvement, and sleep deprivation reduction. Patients with nocturnal epilepsy and other symptoms of sleep disturbance (excessive daytime sleepiness or insomnia) should undergo a detailed sleep evaluation.

Epilepsy can provoke sleepwalking. Nocturnal wandering is more common in patients with nocturnal epilepsy if they have a history of sleepwalking. The epileptic foci may cause arousals, provoking the sleepwalking events.

Treatment and Management of Nocturnal Seizures

Patients with nocturnal seizures are challenging to treat. Some respond to their first medication, although over half fail this treatment. Medication should be chosen on the basis of its effectiveness in the seizure type, potential side effects, and willingness of the patient to accept the risk of those side effects. Medication should be started at a low dose and gradually increased until the patient becomes seizure free or develops side effects. Blood levels can provide information regarding compliance, but only give a rough estimate of the amount of drug in the brain. Patients with focal onset seizures often respond to carbamazepine, lamotrigine, or topiramate. Those with primary generalized seizures respond better to valproate or lamotrigine. For some patients not responding to medication, the addition of clonazepam or clorazepate at bedtime may provide benefit. These patients should be followed by a neurologist or specialists at an epilepsy center.

CONCLUSION

The vast array of paroxysmal nocturnal events provides a diagnostic challenge for physicians. An accurate history and physical exam guides the

clinician in determining if further investigation is required. Polysomnographic investigation of patients with nocturnal events is useful in identifying possible provoking factors such as sleep apnea or periodic limb movements that increase the likelihood of arousals or sleep deprivation. The American Academy of Sleep Medicine guidelines suggest that polysomnography should be performed in patients who start having events at an unusual age, present with atypical symptoms for benign parasomnias, or have multiple spells per night. The presence of excessive daytime sleepiness or dangerous behaviors also warrants polysomnography (Tables 3 and 4) (52). Approximately 35% of patients will have spells during polysomnography, and polysomnography helps identify the etiology in 35% to 80% of patients (53,54). Two-night polysomnographic evaluation increases the likelihood of capturing a nocturnal event and may lead to identification of exacerbating factors.

Treatment goals should focus on patient and family safety, reduction of risk of harm, and improvement in lifestyle. Many of these disorders have diverse treatment options. Patients should be vested in the treatment plan and understand the risks and benefits of the various therapies. As a team, the clinician and patient can engage these challenging events.

ACKNOWLEDGMENT

The author wishes to express his profound gratitude to Michelle Wrightsell for her contributions to this manuscript.

REFERENCES

1. Orem J, Barnes CC. Physiology in Sleep. New York: Academic Press, 1980.
2. Vaughn BV, Quint SR, Messenheimer JA, Robertson KR. Heart period variability in sleep. Electroencephalogr Clin Neurophysiol 1995; 94:155–162.
3. Mahowald Mark W, Schenk, Carlos H. REM Sleep Parasomnias: Principles and Practice of Sleep Medicine. 4th ed. Chapter 75. Philadelphia: Elsevier Saunders, 2005:897–916.
4. Kales A, Soldatos CR, Bixler EO, et al. Hereditary factors in sleepwalking and night terrors. Br J Psychiatry 1980; 137:111–118.
5. Klackenberg G. Incidence of parasomnias in children in a general population. In: Guilleminault C, ed. Sleep and Its Disorders in Children. New York: Raven Press, 1987:99–113.
6. Hublin C, Kaprio J, Partinen M, Heikkila K, Koskenvuo M. Prevalence and genetics of sleep walking: a population-based twin study. Neurology 1997; 48: 177–181.
7. Mahowald MW, Bundlie SR, Hurwitz TD, Schenck CS. Sleep violence—forensic science implications: polygraphic and video documentation. J Forensic Sci 1990; 35:413–432.
8. Winkelman JW. Treatment of nocturnal eating syndrome and sleep-related eating disorder with topiramate. Sleep Med 2003; 4:243–246.

9. Broughton R. NREM Arousals Parasomnias: Principles and Practice of Sleep Medicine. 3rd ed. Chapter 62. Philadelphia: W. B. Saunders Company, 2000: 693–706.
10. Espa F, Duavilliers Y, Ondze B, Billiard M, Besset A. Arousal reactions in sleepwalking and night terrors in adults: the role of respiratory events. Sleep 2002; 25:871–875.
11. Halasz P, Ujszaszi J, Gadoros J. Are microarousals preceded by electroencephalographic slow wave synchronization precursors of confusional awakenings? Sleep 1985; 8:231–238
12. Schenck CH, Pareja JA, Patterson AL, Mahowald MW. Analysis of polysomnographic events surrounding 252 slow-wave sleep arousals in thirty-eight adults with injurious sleepwalking and sleep terrors. J Clin Neurophysiol 1998; 15:159–166.
13. Fritz G, Rockney R, Work Group on Quality Issues. Summary of the practice parameter for the assessment and treatment of children and adolescents with enuresis. J Am Acad Child Adolesc Psychiatry 2004; 43:123–125.
14. Nielson TA. Dreaming Disorders: Principles and Practice of Sleep Medicine. 4th ed. Chapter 78. Philadelphia: Elsevier Saunders, 2005:936–945.
15. Sachs C, Svanborg E. The exploding head syndrome: polysomnographic recordings and therapeutic suggestions. Sleep 1991; 14:263–266.
16. Lavigne GJ, Manzini C. Bruxism: Principles and Practice of Sleep Medicine. 3rd ed. Chapter 67. W. B. Saunders Company, 2000:773–785.
17. Montgomery MT, Nishioka GJ, Rugh JD, Thrash WJ. Effect of diazepam on nocturnal masticatory muscle activity. J Dent Res 1986; 65:1980.
18. Amir I, Hermesh H, Gavish A. Bruxism secondary to antipsychotic drug exposure: a positive response to propranolol. Clin Neuropharmacol 1997; 20: 86–89.
19. Brown ES, Hong SC. Antidepressant-induced bruxism successfully treated with gabapentin. J Am Dent Assoc 1999; 130:1467–1469.
20. Lavigne GL, Soucy JP, Lobbezoo F, Manzini C, Blanchet PJ, Montplaisir JY. Double-blind, crossover, placebo-controlled trial of bromocriptine in patients with sleep bruxism. Clin Neuropharmacol 2001; 24:145–149.
21. Raigroski AJ, Christensen LV, Mohamed SE, Gardiner DM. The effect of four week administration of amitriptyline on sleep bruxism. A double-blind crossover clinical study. Cranio 2001; 19:21–25.
22. Tan EK, Jankovic J. Treating severe bruxism with botulinum toxin. J Am Dent Assoc 2000; 131:211–216.
23. Bostwick JM, Jaffee MS. Buspirone as an antidote to SSRI-induced bruxism in 4 cases. J Clin Psychiatry 1999; 60:857–860.
24. Pierce CJ, Gale EN. A comparison of different treatments for nocturnal bruxism. J Dent Res 1988; 67:597–601.
25. Garcia-Borreguero D, Odin P, Schwarz C. Restless legs syndrome: an overview of the current understanding and management. Acta Neurol Scand 2004; 109: 303–317.
26. Culebras A. A Clinical Handbook of Sleep Disorders. Boston: Butterworth-Heinemann, 1996.

27. Hoban TF. Rhythmic movement disorder in children. CNS Spectr 2003; 8(2): 135–138.
28. Siegel JM. Brainstem mechanisms generating REM sleep. In: Kryger MH, Roth T, Dement WC, eds. Principles Practice of Sleep Medicine. 3rd ed. Philadelphia: Saunders, 2000:125–144.
29. Jouvet M, Delorme F. Locus coeruleus et sommeil paradoxal. Comptes Rendus des Seances de la Societe de Biologie 1965; 159:895–899.
30. Schenck CH, Mahowald MW. Polysomnographic, neurologic, psychiatric, and clinical outcome report on 70 consecutive cases with the REM sleep behavior disorder (RBD): sustained clonazepam efficacy in 89.5% of 57 treated patients. Clev Clin J Med 1990; 57:S10–S24.
31. Boeve BF, Silber MH, Parisi JE, Dickson DW, Ferman TJ, Benarroch EE, Schmeichel AM, Smith GE, Petersen RC, Ahlskog JE, Matsumoto JY, Knopman DS, Schenck CH, Mahowald MW. Synucleinopathy pathology and REM sleep behavior disorder plus dementia or Parkinsonism. Neurology 2003; 61:40–45.
32. Krakow B, Hollifield M, Johnston L, Koss M, Schrader R, Warner TD, Tandberg D, Lauriello J, McBride L, Cutchen L, Cheng D, Emmons S, Germain A, Melendrez D, Sandoval D, Prince H. Imagery rehearsal therapy for chronic nightmares in sexual assault survivors with posttraumatic stress disorder: a randomized controlled trial. JAMA 2001; 286:537–545.
33. Raskind MA, Peskind ER, Kanter ED, Petrie EC, Radant A, Thompson CE, Dobie DJ, Hoff D, Rein RJ, Straits-Troster K, Thomas RG, McFall MM. Reduction of nightmares and other PTSD symptoms in combat veterans by prazosin: a placebo-controlled study. Am J Psychiatry 2003; 160:371–373.
34. Craske MG, Krueger MT. Prevalence of nocturnal panic in a college population. J Anxiety Disord 1990; 4:125–139.
35. Shapiro CM. Nocturnal panic—an underrecognized entity. J Psychosom Res 1998; 44:181–182.
36. Rice E, Fisher C. Fugue states in sleep and wakefulness: a psychophysiological study. J Nerv Mental Dis 1976; 163:79–87.
37. Mellman TA, Kulick-Bell R, Ashlock LE, Nolan B. Sleep events among veterans with combat-related posttraumatic stress disorder. Am J Psychiatry 1995; 152(1):110–115.
38. Fakhoury T, Abou-Kahalil B, Newman K. Psychogenic seizures in old age: a case report. Epilepsia 1993; 34:1049–1051.
39. Vaughn BV, D'Cruz. In: Avidon A, ed. Sleep and Epilepsy Seminars in Neurology. 2004.
40. Malow BA, Bowes RJ, Ross D. Relationship of temporal lobe seizures to sleep and arousal: a combined scalp-intracranial electrode study. Sleep 2000; 23: 231–234.
41. D'Cruz OF, Vaughn BV. Nocturnal seizures mimic REM behavior disorder. Am J Electro-Neurodiagn Technol 1997; 37:258–264.
42. Lugaresi E, Cirigonotta F. Hypnagogic paroxysmal dystonia: epileptic seizures or a new syndrome? Sleep 1981; 4:129–138.
43. Montplaisir J, Godbout R, Rouleau, I. Hypnogenic paroxysmal dystonia: nocturnal epilepsy or sleep disorder? Sleep Res 1985; 14:193

44. Silvestri R, De Domenico P, Raffaele M, et al. Hypnogenic paroxysmal dystonia: a new type of parasomnia? Funct Neurol 1988; 3:95–103.
45. Phillips HA, Scheffer IE, Berkovic SF, Hollway GE, Sutherland GR, Mulley JC. Localization of a gene for autosomal dominant nocturnal frontal lobe epilepsy to chromosome 20q 13.2. Nat Genet 1995; 10(1):117–118.
46. Oldani A, Zucconi M, Asselta R, Modugno M, Bonati MT, Dalpra L, Malcovati M, Tenchini ML, Smirne S, Ferini-Strambi L. Autosomal dominant nocturnal frontal lobe epilepsy. A video-polysomnographic and genetic appraisal of 40 patients and delineation of the epileptic syndrome. Brain 1998; 121 (Pt 2):205–223.
47. Willoughby JO, Pope KJ, Eaton V. Nicotine as an antiepileptic agent in ADNFLE: an N-of-one study. Epilepsia 2003; 44:1238–1240.
48. Zacconi M, Ferini-Strambi L. NREM parasomnias: arousals and differentiation from nocturnal frontal lobe epilepsy. Clin Neurophysiol 2000; 111 (suppl 2):S129–S135.
49. Foldvary N, Caruso AC, Mascha E, Perry M, Klem GR, McCarthy V, Qureshi F, Dinner D. Identifying montages that best detect electrographic seizure activity during polysomnography. Sleep 2000; 23:221–229.
50. So NK, Gloor P, Quesney F, Jones-Gotman M, Olivier A, Andermann F. Depth electrode investigations in patients with bitemporal epileptiform abnormalities. Ann Neurology 1989, 25:423–431.
51. Vaughn BV, D'Cruz OF, Messenheimer JA. Improvement of seizure frequency with treatment of obstructive sleep apnea in patients with epilepsy. Seizure 1996; 5:73–76.
52. Chesson, Andrew L, Ferber, Richard, Fry, June, Grigg-Damberger, Madeleine, Hartse, Kristyna, Hurwitz, Thomas D, Johnson, Stephen, Kader A, Littner, Michael, Rosen, Gerald, Singal, Bart, Schmidt-Nowara, Wolfgang, Sher, Aaron. An American Sleep Disorders Association review: the indications for polysomnography and related procedures. Sleep 1997; 20:(6):423–487.
53. Aldrich MS, Jahnke B. Diagnostic value of video-EEG polysomnography. Neurology 1991; 41:1060–1066.
54. Schenck CH, Milner DM, Hurwitz TD, Bundlie SR, Mahowald MW. A polysomnographic and clinical report on sleep-related injury in 100 adult patients. Am J Psychiatry 1989; 146:1166–1173.

9

Circadian Rhythms: Problems with the Body Clock

Mark Quigg

Department of Neurology,
University of Virginia,
Charlottesville, Virginia, U.S.A.

Symptoms of Circadian Rhythm Sleep Disorders	***Diagnoses***
Difficulty initiating sleep	*Delayed sleep phase disorder*
Early morning awakening	*Advanced sleep phase disorder*
Difficulty awakening	*Irregular sleep–wake rhythm disorder*
Excessive daytime sleepiness	*Nonentrained disorder*
Fatigue	*Jet lag disorder*
Impaired cognition	*Shift work disorder*

INTRODUCTION

The intrinsic circadian clock organizes many aspects of life, including sleep and wakefulness. These cycles attempt to synchronize specific physiological functions with the time of day to improve efficiency. When the circadian clock runs contrary to the local environment or is absent altogether, morbidities in terms of social dysfunction or medical problems may emerge. To understand the range of circadian disorders, a brief review of chronobiology follows.

BASIC PRINCIPLES OF CIRCADIAN RHYTHMS

Definitions

A circadian rhythm (*circa*—about, *dian*—day) is any behavioral or physiological activity that, in a self-sustained fashion, regularly oscillates or recurs every 24 hours. The principle property of a circadian rhythm is that it continues unabated if isolated from time cues. Common examples of circadian rhythms are core body temperature, the hormonal secretion of cortisol, vasopressin, melatonin, and the daily patterns of rest–activity and sleep–wake cycles. In fact, most human functions ranging from cellular processes to complex behaviors demonstrate circadian rhythmicity.

Circadian Dynamics

The unifying pathophysiology in most circadian disorders is desynchronization between circadian rhythms and the local day–night cycle. Two basic properties of circadian modulation necessary to explain the morbidity of desynchronization and the maintenance of synchronization are (1) circadian entrainment, and (2) the interactions between the circadian cycle of vigilance and sleep debt.

Circadian Entrainment to Local Time Cues

Organisms maintain synchronization to the local solar cycle through the process of entrainment. Organisms with an activity period entrained to the dark portion of the solar cycle are considered nocturnal, while those whose activity is entrained to the light portion are diurnal. A free-running environment lacks time cues, allowing circadian rhythms to oscillate at their inherent period, which may slightly exceed or fall short of 24 hours. For humans, the circadian period has been calculated at 24.18 hours (1,2).

Most organisms do not have a perfect 24-hour circadian rhythm. Therefore, they must adjust their rhythm to remain synchronized with the solar cycle. This adjustment of phase requires the use of time cues or zeitgebers (German: *zeit*—time, *geben*—to give). The most important daily zeitgeber is the solar light–dark cycle (1). Other weaker zeitgebers include exercise, feeding, exogenous melatonin, and social cues.

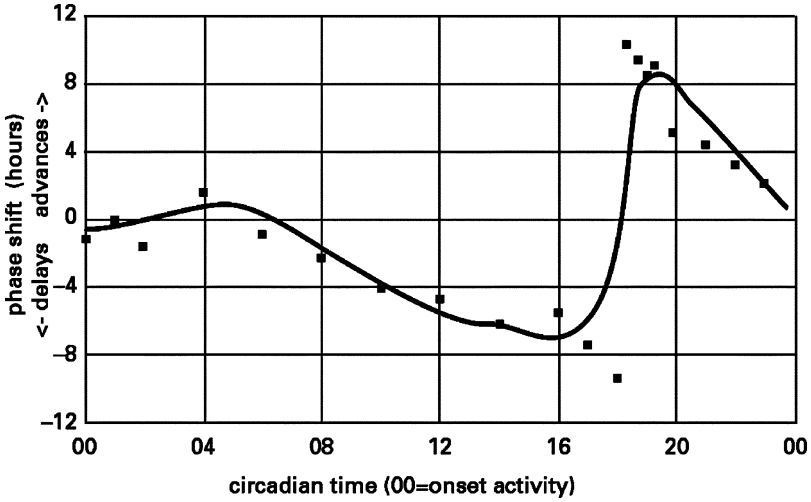


Figure 1 Human phase response curve to bright light exposure. CT "00" in the *x*-axis is referenced to the onset of locomotor activity. The *y*-axis indicates, in the positive direction, phase advances, and in the negative direction, phase delays. Each data point represents the phase advance or delay in subsequent timing of the onset of locomotor activity following exposure to bright light in individuals who are in conditions that lack other timing cues. Light exposure during day time hours (CT 00–08) has little effect in shifting the subsequent circadian phase. Light exposure from about CT 12 to 18 causes gradually increasing amounts of phase delay. Light exposure from about CT 18 to 00 induces phase advances. *Abbreviation*: CT, circadian time. *Source*: From Ref. 3.

The process of entrainment requires resetting the phase of the main clock to match that of the local environment. The strength and direction of phase shifts induced by light exposure varies with the time of day (more specifically, the phase of the circadian cycle). Light stimuli have little effect on the circadian phase during the circadian day. Light exposure during the circadian evening delays the subsequent phase of a circadian rhythm that is running a little ahead. In contrast, light exposure in the early circadian morning/late night advances the phase of a rhythm that is running a little behind. A graph of the response is represented in the phase response curve (Fig. 1). These responses are remarkably conserved across species. This graph allows clinicians to predict the circadian response to specific time cues.

Circadian Modulation of Vigilance

One of the main functions of the circadian timing system is to consolidate and organize sleep and wakefulness. Although the sleep–wake propensity is endogenously mediated, the actual human behavioral patterns of sleep–wake

states are often susceptible to volitional interruption, or in many cases, mismanagement. Thus, the true circadian component of sleep–wake states is the waxing and waning rhythm of the propensity to sleep, or its opposite, the maintenance of vigilance.

The circadian rhythm of vigilance can be modeled as the sum of two opposing forces termed Process S and Process C (Fig. 2) (4). Process S is analogous to a "sleep battery," which is drawn upon to maintain vigilance and is "recharged" by sleep. The degree of "recharging" depends on the depth and duration of sleep. Process S decreases as the duration from the last episode of sleep increases. Thus, Process S is at a maximum in the morning just after arising from sleep and at a minimum right before falling asleep. To counteract

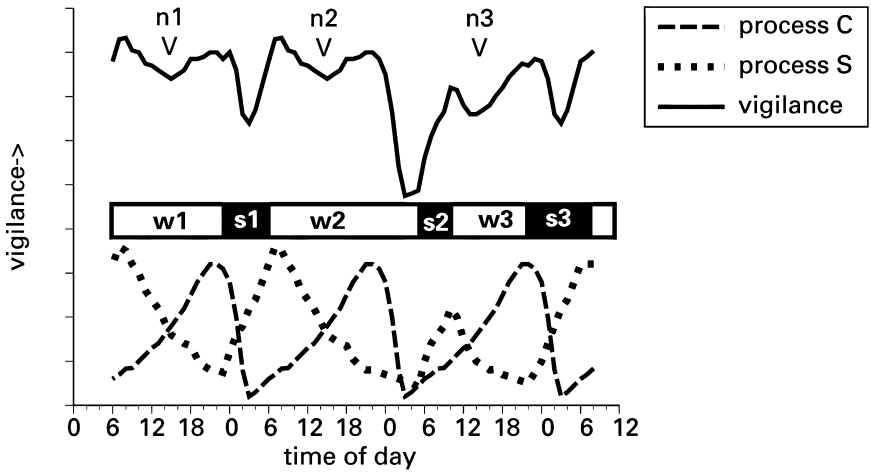


Figure 2 Cumulative interactions between sleep (Process S) and the circadian maintenance of vigilance (Process C) consolidate the level of vigilance into a biphasic distribution. In this theoretical example, during a normal 24-hr day, wakefulness occurs between 06:00 and 23:00 (w1) and sleep between 23:00 and the following 06:00 (s1). The day starts just after awakening with a high level of vigilance, which gradually declines as sleep debt begins to accumulate following the last episode of sleep. In the late afternoon, a nadir in vigilance (n1) occurs with worsening sleep debt and an insufficient circadian drive. Nadirs n1 and n2 correspond to times during which a siesta or an afternoon nap might occur. The circadian drive to vigilance increases through the remaining day, maintaining high vigilance levels. Circadian drive abruptly drops in the late night, allowing sleep to occur (s1). Day 2 shows the effects of an "all-nighter" spent finishing a textbook article on deadline. This results in a prolonged epoch of wakefulness (w2) ending with extremely poor vigilance. Although an attempt at "catch-up" sleep occurs at s2, it is limited in duration and intensity by the rising circadian influence, whose timing remains entrained to the local solar cycle. Limited sleep at s2 allows only partial recharging of sleep debt, causing the remaining waking hours (w3) to be affected by an extended nadir (n3) of vigilance.

this loss of the Process S drive, Process C is a rhythmic drive to maintain wakefulness that peaks every 24 hours in the late evening. This offsets the decline in vigilance that occurs as sleep debt accumulates and the Process S "battery" is reduced. Process C drops precipitously late at night, achieving a nadir in the early morning hours. Unlike Process S, the continuous cycles of Process C are not under volitional control.

The two-process model depicted in Figure 2 accurately predicts several observations regarding the circadian modulation of sleep. First, many people experience a late afternoon dip in vigilance, a feature culturalized in many societies as the siesta or its modern antidote, the coffee break (5). The late afternoon siesta occurs at the point when Process C has not raised high enough to counter the decline in Process S. Second, it accounts for observations that sleep is attenuated in depth and duration if it occurs during an inappropriate circadian phase (6). Data show that the circadian clock, determined by core body temperature, facilitates or limits the distribution of sleep electroencephalographic (EEG) activities in a phase-dependent fashion (6), thus consolidating sleep and wakefulness. Such observations also explain why "catch-up" sleep is so hard to achieve. Although sleep debt may have accumulated, the ability to sleep enough to make up the debt is limited by Process C. Therefore, the two processes are intertwined, and resolution of disruption of one process requires consideration of the other.

ORGANIZATION OF THE CIRCADIAN TIMING SYSTEM

The circadian timing system consists of three parts: the primary circadian clock, its afferents, and efferents (Fig. 3).

The Primary Circadian Clock

The main mammalian clock is located in the paired suprachiasmatic nuclei in the ventral hypothalamus. These nuclei maintain an endogenous rhythm of cellular activity that oscillates every 24 hours (7,8), which in turn organizes sleep and wakefulness into daily cycles. Ablation of the suprachiasmatic nuclei produces a loss of this circadian rhythm. Yet, transplantation of wild-type suprachiasmatic nuclei neurons into animals with a circadian mutation restores normal circadian rhythmicity (9).

Over the past five years, the basic genetic mechanisms of the clock have been elucidated. Several genes encode proteins essential to clock function, forming an oscillatory autoregulatory feedback loop involving both transcription and translation (10,11). In mammals, the transcription factors CLOCK and BMAL1 bind together and activate the expression of three Period (*Per*) and two cryptochrome (*Cry*) genes. Protein products of these genes leave the nucleus and combine into functional multimers. These multimers then return

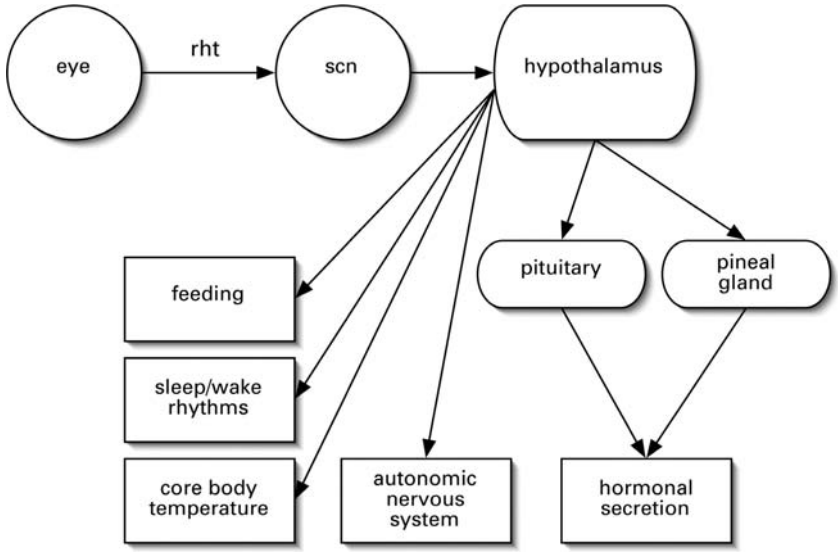


Figure 3 Schematic of the circadian timing system with arrows indicating the direction of influence. *Abbreviations*: rht, retinohypothalamic tract; scn, suprachiasmatic nucleus.

to the nucleus and repress transcriptional activity of the CLOCK–BMAL1 complex. The period of oscillation is determined by the rate of *Per* and *Cry* protein accumulation, which are susceptible to degradation and phosphorylation in their uncombined forms.

A surprising finding is that expression of clock genes is not confined to the suprachiasmatic nuclei. Indeed, diverse peripheral organs such as liver, kidney, and other non-neural tissues also express these genes. These tissues utilize the clock genes to maintain their own circadian oscillations (12). A key difference between the central oscillator of the suprachiasmatic nuclei and peripheral oscillators is that peripheral oscillators quickly attenuate when isolated from the central oscillator, such as in cell cultures. In contrast, cell cultures of suprachiasmatic neurons remain robustly oscillatory (12). Recent data suggest that peripheral clocks have higher degrees of autonomy than previously thought, as some preparations (counter to earlier studies) demonstrate sustained circadian activities (13) and can even be phase-shifted by stimuli different from that effective with the suprachiasmatic nuclei (14). Certainly, the relationships between the central clock and the variety of peripheral clocks are a matter of current investigation. Therefore, the suprachiasmatic nuclei can be thought of as the central "master clock," which in turn drives a series of secondary, peripheral clocks. Alternatively, this "master clock" may be considered a reference clock by which peripheral clocks fine-tune their individual oscillations.

Afferents to the Suprachiasmatic Nucleus

Information regarding the duration, timing, and intensity of light exposure is carried to the suprachiasmatic nuclei from specialized photoreceptors in the retina (15,16) via the retinohypothalamic tract (17). Circadian photoreceptors are distinct from those that mediate vision (18). The identification of the involved photopigments are controversial, but the list currently includes melanopsin and cryptochromes (CRY1 and CRY2) (15,19). The presence of clock genes in peripheral organs raise the possibility that photoreception may occur separately from the visual system. However, controversy remains regarding experiments showing alterations in circadian timing following cutaneous light exposure (20,21).

Afferents to the suprachiasmatic nuclei from areas responsible for nonphotic entrainment (such as exercise or feeding) are unknown. The findings of peripheral clock genes lead to speculation that local organs (liver, in the case of carbohydrate metabolism) might regulate their own 24-hour rhythms, but feedback mechanisms to the central clock are unclear.

Efferents from the Suprachiasmatic Nucleus

The suprachiasmatic nuclei carry out their influence via projections throughout different regions of the hypothalamus, which in turn modulates specific physiology or behaviors (Fig. 3). These nuclei influence time of feeding, activity, and autonomic and endocrine functions to synchronize them with the anticipated task. Toward this end, the suprachiasmatic nuclei utilize a dynamic array of outputs and three main neurotransmitters including GABA, vasopressin, and vasoactive intestinal peptide to influence primarily hypothalamic neurons. This influence probably occurs via a diffusible molecule, as demonstrated by experiments in which suprachiasmatic neurons trapped within a permeable capsule restored circadian rest–activity cycles in lesioned animals (22). Some output function may require direct innervation, since these sites are relatively distant from the nuclei.

The pineal body is the other major component of the mammalian circadian timing system. The pineal body is driven by the suprachiasmatic nuclei to synthesize nocturnal melatonin via the sympathetic limb of the autonomic nervous system. Melatonin, beyond temperature-lowering and sedative effects (23,24), may act directly on suprachiasmatic neurons in a feedback loop to influence phase shifts and entrainment (25). Light suppresses melatonin synthesis so that the daily oscillation of melatonin peaks during the night in both diurnal and nocturnal animals (26). The hypothesized primary function of melatonin is to transmit information concerning light–dark cycles and day length to organize behavior dependent on season.

CIRCADIAN RHYTHM SLEEP DISORDERS

Disorders of the circadian system can be organized neurologically by localization or phenotypically based on clinical patterns. These two approaches are not mutually exclusive, as patterns of circadian dysfunction are often reflected in localization within a portion of the circadian timing system. The phenotypic approach is endorsed by the International Classification of Sleep Disorders–2 (ICSD–2) and therefore will be the basis for the following discussion (Table 1) (27). Table 2 summarizes the clinical features and treatment of the circadian rhythm sleep disorders.

In circadian rhythm sleep disorders, it can be difficult to determine where preference ends and pathology begins. For example, many people identify themselves as "morning larks" or "evening owls" based upon their preferred phase of activity. Circadian "pathology" may only become apparent when social or work schedules fit poorly with individual patterns. The ICSD–2 divides circadian rhythm sleep disorders into predominately behavioral or physiological categories. In the future, distinguishing between these categories may be more difficult as data become available demonstrating that "morning lark" or "evening owl" behavior patterns are associated with specific genetic and physiological backgrounds. A frequently used tool in the clinical and research classification of circadian disorders is the Horne–Östberg morningness–eveningness questionnaire. This self-survey quantifies the direction and magnitude of morning or evening preferences (28).

DELAYED SLEEP PHASE DISORDER

Definitions and Clinical Features

Delayed sleep phase disorder is a phenotype characterized by normal sleep duration and architecture with an unconventional and intractable pattern of delayed sleep onset and awakening. In this syndrome, habitual bedtimes occur late at night with awakenings late in the morning (Fig. 4). As with advanced sleep phase disorder (described below), problems arise when social conventions clash with endogenous cycles. When patients with delayed sleep phase disorder try to adhere to a conventional schedule, they complain of difficulty falling asleep at night and difficulty awakening in the morning. Sluggishness and falling asleep during early morning activities may be noticed by teachers or employers, and tardiness or absenteeism may cause social problems. Patients with this disorder often force themselves to adhere to a conventional schedule during work or school days. On weekends, they compensate for the resulting chronic sleep deprivation by "catching up" on their sleep while adhering to their preferred delayed phase.

The incidence of delayed sleep phase disorder in the general population is unknown. Adolescents often prefer delayed phases of activity and are the most prevalent group of subjects with the disorder. In fact, adolescence is

Table 1 Proposed Classification of Circadian Rhythm Sleep Disorders in the ICSD–2

- Circadian rhythm sleep disorder, delayed sleep phase type (delayed sleep phase disorder)
- Circadian rhythm sleep disorder, advanced sleep phase type (advanced sleep phase disorder)
- Circadian rhythm sleep disorder, irregular sleep–wake type (irregular sleep–wake rhythm)
- Circadian rhythm sleep disorder, free-running type (nonentrained type or non-24-hr sleep–wake rhythm)
- Circadian rhythm sleep disorder, jet lag type (jet lag disorder)
- Circadian rhythm sleep disorder, shift work type (shift work disorder)
- Circadian rhythm sleep disorder due to medical condition
- Other circadian rhythm sleep disorder (circadian rhythm disorder, NOS)
- Other circadian rhythm sleep disorder due to drug or substance

Source: From Ref. 27.

Table 2 Summary of the Clinical Features and Treatment of the Circadian Rhythm Sleep Disorders

Diagnosis	Symptoms	Associated features	Predisposition	Treatment
Delayed sleep phase disorder	Difficulty initiating sleep in the P.M., trouble waking in morning	Higher risk of depression, schizophreniform personality disorder	Adolescence, family history	Bright light in the A.M., melatonin in the P.M., progressive advancement of bedtime
Advanced sleep phase disorder	Trouble maintaining wakefulness in the P.M., difficulty maintaining sleep in A.M.	Advanced age	Family history	Bright light in the P.M., light evening exercise, progressive advancement of bedtime
Irregular sleep–wake rhythm disorder	Polyphasic sleep–wake patterns, insomnia, frequent awakenings and daytime naps	Dementia, other degenerative or multifocal neurologic disease	N/A	Regular externally monitored schedules

Abbreviations: A.M., morning; P.M., evening; N/A, not applicable.

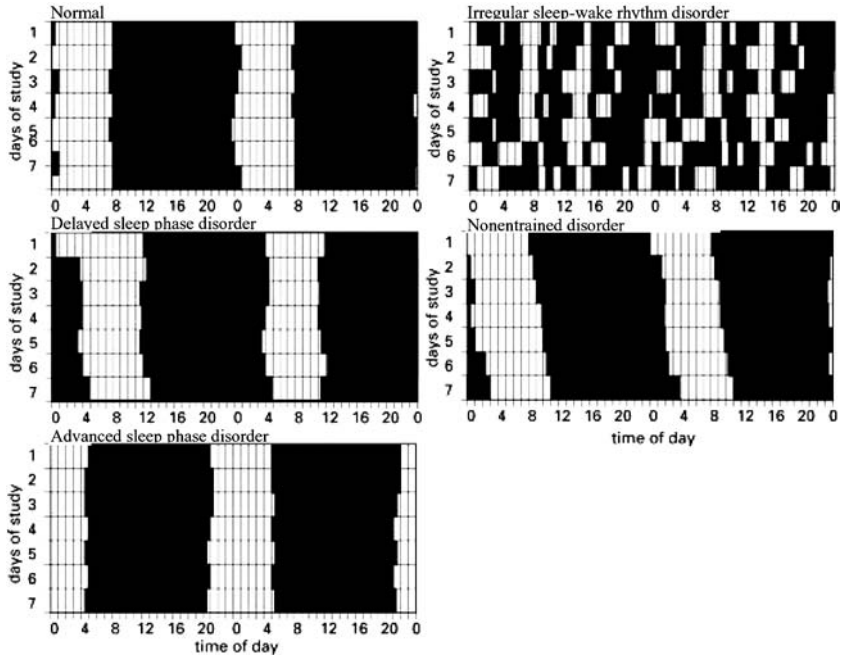


Figure 4 Double-plotted actigraphs of idealized circadian disorder patterns with black indicating activity and white rest. "Double–plotted" refers to the technique of plotting 2 days of data along the *x*-axis, and then replotting the last 24-hrs of data along each day indicated on the *y*-axis. Through this method, circadian period can be calculated by noting the drift in the activity onset time, and the circadian phase of activity can be observed in relation to time of day. A normal pattern of ~7 hr nocturnal episodes of rest and 17 hrs of diurnal activity is shown in the "normal" plot. In delayed sleep phase disorder, the onset of activity is delayed ~3–4 hrs from conventional schedules. In advanced sleep phase disorder, onset of activity occurs ~4–5 hrs before conventional schedules. In irregular sleep–wake rhythm disorder, short episodes of rest are randomly interspersed throughout the day, although there might be persistent daily patterns imposed by external schedules (mealtimes, group activities, etc). In nonentrained disorder, a slightly prolonged circadian period of ~24.5 hrs that is unentrained to the time of day allows onset of activity to occur ~1/2 hr later every day, causing a phase delay of ~3.5 hrs accrued during the 7-day study.

the usual age of onset. Please note that many adolescents function quite well despite an apparent circadian delay. Only those individuals whose delayed schedules are associated with impaired function should be considered to have the pathologic disorder.

Delayed sleep phase disorder is associated with a variety of predisposing psychiatric factors. Affective disorders are especially prevalent, with

three-quarters of patients reporting past or current depression (29). Psychopathology indices, such as the Minnesota Multiphasic Personality Inventory-2, show high scores in depression, psychoasthesia, and hypochondriasis (30). Psychosocial factors, such as social withdrawal, intellectual aspirations, and psychopathology, may steer patients to "self-select" jobs or pastimes that reinforce their maladaptive behaviors, thus promoting a mutually reinforcing pattern of poor circadian adjustment (31). Personality disorders, especially schizophreniform or other asocial subtypes, are found in higher incidence among hospitalized adolescent psychiatric patients with delayed sleep phase disorder than those with normal sleep patterns, further reinforcing the notion that sleep patterns and coping mechanisms form a vicious circle in predisposed individuals (32). Some individuals self-medicate with alcohol or other sedative hypnotics in order to overcome the initial insomnia or use stimulants to overcome morning "sleep drunkenness."

Pathophysiology of Delayed Sleep Phase Disorder

Psychosocial reinforcement and developmental shifts in circadian regulation have been discussed above. The circadian defect in delayed sleep phase disorder has been postulated variously as prolonged circadian periods (exceeding 24 hour) or defects in the phase response curve to light, conferring an inability to phase advance. Most current evidence demonstrates the presence of a pure phase delay in most circadian markers such as sleep onset, melatonin, and body temperature (33–35).

Growing evidence shows a genetic predisposition to delayed sleep phase disorder. Although no clear inheritance patterns have been described, behavioral aspects of the disorder appear to run in rare families in an autosomal-dominant pattern with incomplete penetrance (36). Recent studies have disclosed polymorphisms in clock genes (human *Per2* and *Per3*, a homologue to the *Drosophila* clock gene *Per*) associated with the disorder (although it may be too early to assign causation) (37–39). Other reported inheritable factors include arylalkylamine *n*-acetyltransferase (a component of melatonin synthesis) (40), HLA subtypes (30), and the *Clock* gene (41).

Differential Diagnosis and Evaluation of Delayed Sleep Phase Disorder

The Horne–Östberg sleep phase questionnaire serves as a useful screening device and is often used in research protocols (28). Individuals with delayed sleep phase disorder score as definite evening types. Beyond evaluation of sleep hygiene and possible contributing psychological or psychiatric factors, documenting a sustained pattern of delayed sleep onset and awakening, usually with weekend "catch-up" sleep, is appropriate to make the diagnosis. This can be done with sleep logs of at least seven days duration (27)

or with serial actigraphy. Serial actigraphy, rather than polysomnography, is better suited to document phases of rest and activity (42) corroborating long-term sleep diaries (see Chap. 2 for more details).

Detailed polysomnography and continuous core body temperature measurements show that these patients have increased sleep latency, total sleep time, wakefulness after sleep onset, and greater relative amounts of stage 1 sleep than controls. Additional measurements such as a delayed early morning temperature nadir or dim light melatonin onset may aid in diagnosis.

Treatment of Delayed Sleep Phase Disorder

Treatment centers on using appropriate zeitgebers to re-entrain the patient to a more socially appropriate 24-hour schedule. Most trials use a program of scheduled forced activity–rest cycles supplemented with chronophototherapy or melatonin in single or combination therapy. No comparative clinical trials exist by which to judge the effectiveness of different programs. However, one blinded placebo-controlled study demonstrated the efficacy of short-term melatonin administration. In this protocol, 5 mg of melatonin was administered five hours before the nightly dim light melatonin onset calculated for each patient (mean onset time = 23.17 hr) for a 2-week period. Although core temperature rhythms did not show a phase shift, actigraphy demonstrated significant phase advances in sleep–wake activity and patients reported subjective improvements in morning alertness (43).

Another treatment option involves timed exposure to bright light, also known as chronophototherapy. This treatment modality requires the use of morning bright light (>2500 lx) on a regular schedule. Compliance and disturbance of sleep are two factors that limit its effectiveness, but several reports document short-term success (44–46). One report documents the successful use of a light-therapy mask that provides morning illumination through closed eyes. With this device, low-level illumination starts approximately 4 hours before the desired awakening time and is ramped up to full intensity (2700 lx) in the first hour. This treatment resulted in significant phase advances in melatonin rhythms and improvements in subjective self-assessments (47). Of note, both melatonin and chronophototherapy should be accompanied by scrupulous sleep hygiene and avoidance of evening bright light.

Several different forced-activity protocols are available (48). The least intrusive but longest duration protocol consists of progressive 15–30 minute daily advances in bedtimes and awakenings. Bright light exposure is used with the patient initially exposed to light in the late morning and gradually shifted to the time of awakening (48). Depending on the phase delay severity, this protocol can take 2–3 weeks to accomplish. Other protocols include daily 3–4-hour phase delays until the patient completely cycles back to the desired sleep–wake cycle, or prolonged forced wakefulness for one night followed by

a 90-minute advance of the sleep period the next day. This pattern is repeated once per week until the desired shift is accomplished (48). Although there are reports of unpleasant side effects in forced activity protocols (49), the biggest problem remains the high rate of relapse.

The public health aspects of delayed sleep phase disorder have recently gained attention in school systems. The high incidence of a delayed phase preference in adolescents (50), along with evidence that late bedtimes correlate with poor school performance (51), has lead some school systems to shift school opening times to later morning hours to allow better matching with adolescents' later vigilance peaks.

Other basic sleep hygiene recommendations aid the relapsing patient. In general, regular exercise, beyond the basic health benefits, promotes sleep onset and improves sleep depth if not performed too close to sleep onset. Indeed, the timing of exercise is important as it induces phase delays in a phase-dependent fashion. The closer to the onset of the nocturnal melatonin peak, the more significant the subsequent phase delay (52,53). Therefore, morning exercise upon awakening probably provides the most benefit to these patients.

The use of stimulants in delayed sleep phase disorder has not been systematically studied. These medications improve subjective alertness and task performance following sleep deprivation and appear to have no effect on underlying circadian phase. For example, modafinil has no effects on core body temperature, or the rhythms of melatonin, cortisol, or growth hormone secretion (54). Therefore, stimulants may be used to counter inappropriate morning sleepiness, but will not treat the underlying rhythm disorder. Caffeine overcomes circadian phase-dependent declines in performance (55) and is commonly used for a "morning jumpstart." Patients with delayed sleep phase disorder often recognize this, and unregulated self-medication with nocturnal sedatives and morning stimulants frequently exacerbates rather than helps their circadian problem. Physicians should counsel patients with this disorder to limit caffeine and stimulant use to before noon. Physicians should understand that prescription of controlled substances under less-than-ideal indications might lead to problems outside the purely circadian realm. No matter what the initial course of treatment, most clinicians agree that combination therapy with a disciplined patient has the best chance to overcome symptoms of this disorder.

ADVANCED SLEEP PHASE DISORDER

Definitions and Clinical Features

Advanced sleep phase disorder is the opposite of delayed sleep phase disorder (Fig. 4). These patients present with an intractable pattern of irresistible evening sleepiness and early morning awakening with an inability to return to sleep. Recent reports of familial advanced sleep phase disorder demonstrate that these individuals go to sleep 2–4 hours earlier than unaffected family members

and awaken early as well (39,56–58). The circadian period—normally 24.18 hour (2)—is 1 hour shorter in the only measured pedigree of advanced sleep phase disorder (58). As with delayed sleep phase disorder, sleep is otherwise normal unless there is sufficient conflict with more conventional outside schedules. Although the incidence of advanced sleep phase disorder in the general population is unknown, it is rarer than delayed sleep phase disorder and does not carry the same psychiatric disease associations as this disorder.

Pathophysiology of Advanced Sleep Phase Disorder

Increasing age is associated with earlier sleep times and awakenings, a tendency to "morning larkness," and advances in phase of peak secretions of melatonin and cortisol (59). Although it appears that the elderly are susceptible to advanced sleep phase disorder, studies show a poor correlation between preferred sleep times and other markers of circadian phase (60). Instead, in this population, early morning awakening may be more the result of defects in the depth and maintenance of sleep, with early sleep onset compensating for sleep loss (60,61).

The best documented cases occur in families in which the trait is inherited in an autosomal dominant manner (39,56–58). One pedigree has a mutation in the human clock gene *Per2* (39). Two unrelated pedigrees, however, have no evidence of a similar mutation, suggesting that similar phenotypes may occur from different clock gene defects (56).

Differential Diagnosis and Evaluation of Advanced Sleep Phase Disorder

The evaluation is similar to that of delayed sleep phase disorder. Features of mood and interest in other activities are helpful distinguishing features. Early morning awakening ("terminal insomnia") is common in depression, and the physician must distinguish advanced sleep phase disorder from this and other mood disorders. Early bedtimes and early awakenings occurring without social dysfunction do not require intervention (some authorities have even declared such habits supportive of health, wealth, and wisdom) (62). Like delayed sleep phase disorder, advanced sleep phase disorder can be designated as predominately psychological or physiological in origin (27).

Treatment of Advanced Sleep Phase Disorder

Because the syndrome is rare, treatment regimens have not been reported. Despite this, many clinicians utilize a program consisting of small phase delays augmented by chronophototherapy. As opposed to delayed sleep phase disorder, bright light exposure is given in the evening. The human

phase response curve shown in Figure 1 demonstrates the impact of light timing on circadian phase.

As in delayed sleep phase disorder, melatonin administration, exercise, and judicious stimulant use provide a multimodal treatment plan. Due to timing issues, these adjunctive treatments are more difficult to administer in advanced sleep phase disorder. Theoretically, evening bright light should suppress the phase-advanced secretion of melatonin, but there are no studies documenting the success of administration of exogenous melatonin to provide a more phase-appropriate peak. Therefore, exogenous melatonin should be given after sleep onset to coincide with the more appropriate midnight peak. Thus, the phase-advanced patient should be awakened for timed nocturnal melatonin, similar to the midsleep administration of gamma hydroxybutyrate for narcolepsy/cataplexy. Lastly, evening exercise may delay circadian phase by working as a zeitgeber and eliminating evening sedentary drowsiness (52,53).

IRREGULAR SLEEP–WAKE RHYTHM DISORDER

Definitions and Clinical Features

The ''irregularity'' in irregular sleep–wake rhythm disorder stems from the randomness and lack of circadian organization in sleep–wake patterns of affected individuals (Fig. 4). The severity of the syndrome can range from the clustering of short naps within a favored phase to complete disorganization or inversion of normal sleep–wake cycles.

Although total sleep time may be normal when tallied over a 24-hour interval, the depth or duration of sleep may not be sufficient, thus leaving subjects sleep deprived.

Pathophysiology of Irregular Sleep–Wake Rhythm Disorder

The institutionalized elderly are particularly susceptible to irregular sleep–wake rhythm disorder, especially if acute illness disturbs an otherwise regular routine. In these individuals, psychiatric or psychological factors contribute to desocialization and a lack of zeitgebers, which in turn exacerbate alterations in circadian phase (63).

Lack of circadian rhythmicity implies a lesion of the suprachiasmatic nuclei or of their efferent connections to hypothalamic targets. Thus, a variety of heterogeneous etiologies, most causing multifocal lesions of the central nervous system, contribute to this disorder. Some typical examples include neurodegenerative diseases and other dementias, static encephalopathy/mental retardation, and multifocal demyelinating diseases. Regarding neurodegenerative diseases, patients with Alzheimer's dementia demonstrate greater irregularity in rest–activity rhythms than age-matched, undemented controls. Pathological studies of Alzheimer patients show plaque involvement and

neuronal loss within the suprachiasmatic nuclei (64). Alzheimer's patients demonstrate reduced amplitudes, larger variation of circadian phases, and diminished total secretion in melatonin rhythms (65). ''Sundowning,'' a recurring pattern of late afternoon agitation, may be a related phenomena (66).

Because some efferent pathways are affected while others are spared, some circadian rhythms may not be completely abolished. For example, in studies of circadian regulation in neuronal ceroid lipofucinosis (67), the majority of patients had irregular fragmented sleep episodes with irregular phasic distribution. Half the patients had alterations in circadian variations in body temperature, while only a few with advanced disease had alterations in daily cortisol or nocturnal melatonin peaks. Similarly, patients with severe epilepsy and mental retardation (Lennox–Gastaut syndrome) vary widely in degrees of disturbances in sleep–wake, temperature, cortisol, and melatonin rhythms (68). These disorders show that disturbances of the central nervous system may manifest as disruption of circadian function.

Differential Diagnosis and Evaluation of Irregular Sleep–Wake Rhythm Disorder

As in both advanced and delayed sleep phase disorder, voluntary irregular sleep habits and poor sleep hygiene must be distinguished from involuntary activities. Fragmented and inadequate sleep from obstructive sleep apnea, parasomnias, or medical disorders such as congestive heart failure should be evaluated in susceptible individuals, as the resulting sleep impairment may cause excessive sleepiness, resulting in frequent random naps.

Although circadian aspects are not well characterized, there is a growing appreciation of Parkinson's disease-related sleep disorders. Like irregular sleep–wake rhythm disorder, patients with Parkinson's disease present with excessive daytime sleepiness. Abrupt sleep attacks, akin to narcolepsy, may punctuate the day, and nighttime sleep is often interrupted by dyskinesias and sleep maintenance dysfunction related to dopamine system pathology (69). Thus, the pattern of frequent nocturnal arousals and recurrent daytime sleep can mimic patterns of random rest activity characteristic of irregular sleep–wake rhythm disorder.

The draft classification of circadian disorders allows for designating some as secondary to a known medical disorder. Since most irregular sleep–wake rhythm disorders are secondary to known neurological disease, the value of separate classifications remains debatable.

Treatment of Irregular Sleep–Wake Rhythm Disorder

Many of these subjects have diseases rendering them incapable of self-care. Therefore, reviewing the institutional environment and educating caregivers are important to initiating and maintaining a socially acceptable schedule for these patients. Encouragement of stimulating daytime activities and limitation or strict scheduling of naps helps consolidate sleep. Patients benefit

from appropriate zeitgeber timing and consistent schedules maximizing the circadian system's ability to maintain rhythmicity.

Other therapies may also be helpful. Chronophototherapy consisting of evening bright light exposure (19:00–21:00 for one week) in those with sundowning or irregular sleep cycles improves sleep and wakefulness as rated by caregivers. Chronophototherapy also improves the amplitude of locomotor activities measured by actigraphy (70). Melatonin appears to improve sleep quality and entrainment and may even slow cognitive impairment (71).

NONENTRAINED OR FREE-RUNNING RHYTHM DISORDER

Definitions and Clinical Features

Synonyms for nonentrained circadian disorder include non-24-hour sleep–wake rhythm disorder and hypernycthemeral syndrome (Greek: *hyper*—over, *nuctos*—night, *hemeral*—day). This disorder, usually affecting the blind, involves an intact circadian rhythm that "free runs" unentrained to the local solar cycle (Fig. 4). About 50% of totally blind subjects have free-running circadian rhythms (72). If the circadian period is less than or greater than 24 hours, patients will gradually cycle in and out of phase with conventional sleep–wake schedules. Patients adopting a conventional pattern may still complain of excessive daytime sleepiness or nocturnal insomnia at intervals when endogenous and external cycles are most mismatched. Thus, sleep–wake pattern variability, punctuated by recurrent periods of insomnia or excessive sleepiness as cycles mesh and unmesh, is characteristic of this disorder (73). Frequent daytime napping is a common complaint in affected subjects (74).

Pathophysiology of Nonentrained Disorder

Lack of entrainment of otherwise intact circadian regulation implies a disorder of afferent stimuli to the suprachiasmatic nucleus. Accordingly, most subjects with nonentrained disorder are totally blind from lesions anterior to the optic tract. Note that even total blindness is not sufficient to cause this disorder, as vision pathways and circadian photic pathways involve different retinal cells and anatomical pathways. Thus, subjects with cortical blindness or those with isolated loss of rods and cones are not susceptible to this disorder. Patients unable to suppress melatonin secretion with light exposure, implying lack of a functioning retinohypothalamic tract, are at greatest risk of developing the disorder (75).

Most human subjects when placed in temporal isolation free run with rest–activity cycles greater than 24 hours (1,2). Therefore, the slow period cycle of insomnia and excessive sleepiness is due to the slow precession of the endogenous circadian cycle through the 24-hour day. As demonstrated

in Figure 4, a subject with a circadian period of 24.5 hour will fall behind 1/2 hour each day, creating a periodic return to normal phase every 48 days. Insomnia and sleepiness occur because depth and duration of sleep are limited by the underlying circadian phase (74).

Differential Diagnosis and Evaluation of Nonentrained Disorder

Other circadian disorders, such as delayed sleep phase disorder, have properties similar to nonentrained disorder because they gradually and progressively delay subsequent cycles. However, periodic symptoms such as insomnia or daytime sleepiness are not characteristic of these other disorders. Although blindness is the usual predisposing condition, sighted patients occasionally present with nonentrainment. In these cases, ophthalmologic evaluation is necessary for the rare retinal or perichiasmatic lesions that spare visual pathways but affect circadian photic afferents.

Because small mismatches between endogenous and external circadian cycles may take months to demonstrate periodicity, prolonged sleep logs are required to document the characteristic pattern. For example, a subject with a free-running period of 24.5 hours will require two full cycles (over three months) in order to demonstrate the slow periodicity of symptoms.

Treatment of Nonentrained Disorder

Regular nocturnal melatonin administration (5 mg at 21:00) is effective in re-entrainment of sleep–wake cycles and endogenous hormonal rhythms. This effectiveness is aided by a lack of competition from the light zeitgeber in these patients (76).

JET LAG DISORDER

Definitions and Clinical Features

Unlike previous syndromes, which often carry an association with other diseases, jet lag is a circadian disorder provoked by air travel. Its high incidence and perceived detriment to work-related productivity have generated huge amounts of public interest. Indeed, a recent Google™ search on "jet lag productivity loss" yielded 11,000 hits from sites ranging from business information pages to natural herb vendors.

Jet lag disorder usually arises after crossing three or more time zones (48). Symptoms worsen and incidence rises with increasing age (77). Fatigue, nocturnal insomnia, and daytime sleepiness are often present along with impaired cognitive performance, worse athletic performance, and gastrointestinal symptoms. Although jet lag disorder is transient, chronic jet lag has subtle but real consequences on homeostasis and cognition (78).

Interest in even subtle dysfunction from jet lag is high in professional athletics due to the thin margins that separate winning from losing. Accordingly, the number of hits in baseball (79), the number of wins and points scored in football (80), and the number of points in basketball (81) all correlate with transcontinental travel and the time of day during which games are scheduled.

Pathophysiology of Jet Lag Disorder

The abrupt desynchronization of the internal clock with the local solar cycle is the direct cause of jet lag disorder. The stress associated with air travel as well as physical discomfort and alcohol ingestion act to exacerbate fatigue, dehydration, and inactivity. These factors worsen sleep deprivation and contribute to the malaise of transmeridian air travel. Consider the following example of how air travel affects circadian rhythms. An individual who flies from New York to Stockholm, thus traveling eastward, finds himself with a circadian rhythm that is 6 hours delayed in comparison to the new local environment. To adjust, that individual's circadian clock must undergo a phase advance. Conversely, the passenger upon a westward flight from Stockholm to New York finds that the circadian rhythm of the person is advanced 6 hours relative to local time, and the circadian clock of that person must delay 6 hours.

Although the phase response curve (Fig. 1) suggests that light stimuli can abruptly shift phases by more than 3 hours, practical issues limit real-world adjustments to about 1 hour per time zone crossed. The phase response curve also predicts that phase shifts and re-entrainment are easier for phase delays, in part because the times of day allowing phase delays are more generous than those allowing phase advances.

Most studies of jet lag disorder confirm that eastward travel is less easily tolerated than westward travel. Indeed, the maxim "west is best, east is least" summarizes the relationships neatly. The asymmetry is significant enough to show up in the batting performances of Major League Baseball teams subjected to transcontinental travel. East coast teams traveling westward have over a one-run advantage over west coast teams flying eastward (79). Studies of clock genes investigated with cell cultures taken from the suprachiasmatic nuclei and a variety of peripheral tissues correlate with the asymmetry of transmeridian travel. In vitro rhythms of peripheral clocks respond more quickly and with more synchronization with suprachiasmatic clocks after phase delays than after phase advances (11).

Treatment of Jet Lag Disorder

As the phase response curve in Figure 1 demonstrates, large shifts in circadian phase are possible, but only under ideal circumstances. Variations in activity, light exposure, mealtimes, and sleep duration all act to limit the extent of phase adjustment. Jet lag disorder treatment centers on common

sense limitations in activities that exacerbate symptoms stemming from stress and sleep deprivation independent of circadian factors. Thus, proper hydration, limitation of caffeine and alcohol ingestion, and a sensible diet significantly improve the symptomatology.

To address the symptoms attributable to circadian mismatch, most advise outdoor light exposure, daytime activity, and concerted attempts to maintain socially appropriate activities for the new local time zone. In other words, embracing the local zeitgebers—light, exercise, mealtimes, and social interactions—facilitates adjustment, whereas maintaining behaviors inappropriate to the local schedule prolong the adjustment.

Knowledge of the phase response curve aids the adjustment. For example, after eastward travel (a phase advance), bright light exposure in the morning and avoidance of bright light in the evening has the best chance of placing the local zeitgeber within the portion of the phase response curve favoring phase advances. The converse strategy is followed after westward travel, with bright light exposure in the evening and limitation of bright light early in the morning. Reports of more quantitative methods using bright light exposure to treat jet lag disorder show favorable but minor improvements in function and circadian parameters (82,83).

Drug treatment of jet lag disorder centers on melatonin, stimulants, or sedative-hypnotic medications. Anecdotal reports note the benefit of timed melatonin, but results are less impressive in double-blinded studies. For example, subjects were given morning caffeine for five postflight days, evening melatonin for the preflight and subsequent four days, or placebo for five days (84). Patients on caffeine reported some amelioration of daytime sleepiness but had negative effects on slow-wave sleep, whereas both placebo and melatonin groups had paradoxical findings of improved slow-wave sleep and worsened subjective sleepiness.

SHIFT WORK DISORDER

Definitions and Clinical Features

Shift work disorder is by far the most common circadian rhythm sleep disorder. An estimated 25 million workers—25% of the full-time U.S. workforce—are susceptible to at least occasional deviations from typical "9-to-5" daytime work hours. Although most workers maintain usual work hours between 06:00 and 18:00, more than 15 million (16.8% of all full-time and salaried workers) worked alternative shifts (85). The most prevalent alternative shift is the evening shift, with work hours between 14:00 and midnight (4.6% of all workers), followed by irregular shifts (3.9%), which change constantly to meet business needs. Night shifts (21:00–08:00, 3.5%) and rotating shifts (regularly rotating day, evening, and night shifts, 2.9%) account for the remainder (85).

The public health consequences of shift work are potentially large. Night-shift train operators report a 6–14 times higher rate of severe sleepiness during work hours than their day-shift colleagues (86). Factory workers report that work-related accidents occur twice as often when they work temporary rotating day shifts as opposed to steady day shifts (87). Motor vehicle accidents, perhaps attributable to worsened sleep or to higher rates of alcohol use, occur more frequently in shift workers (88).

Shift workers experience morbidities thought to result from chronic maladaptation and sleep deprivation. Heart disease, peptic ulcer disease, and complications of pregnancy have the strongest associations with night-shift work (89). In a study of the metabolic consequences of shift work in a sample of 27,485 full-time workers, obesity, high triglycerides, and low high-density lipoprotein levels were more prevalent in shift workers than in day workers (90). Metanalyses have concluded that night-shift workers have a 40% increased cardiovascular risk (91).

The effect of age on shift work is more complex than that for jet lag. Young age allows quicker physiological and psychological adaptations to abrupt changes in shift, an advantage that decreases when shift work becomes chronic (92). Older shift workers, however, may perform some tasks better or have fewer subjective complaints (86,93,94), an observation possibly explained by self-selection or better discipline at acquiring missed sleep.

Pathophysiology of Shift Work Disorder

Shift work shares with jet lag the common pathophysiology of a mismatch between the phase of the endogenous clock and the local environment. However, unlike jet lag disorder, symptoms of shift work disorder persist as long as shift work continues, especially if the individual attempts to live with differing activity–rest cycles simultaneously or sequentially (e.g., working night shift during the week and resuming daytime activities on the weekend).

Treatment of Shift Work Disorder

Given that many services and industries require 24-hour capabilities, the elimination of shift work is unlikely. However, several studies reveal basic measures that can minimize at least the short-term effects of shift work. Use of zeitgebers such as light is helpful, but consistency of the timing of light exposure may have more overall effect than its phase-appropriate timing, as predicted by the human phase response curve (Fig. 1). For example, when subjected to a simple protocol of exposure to natural morning light for 20 minutes at the end of their shift (time = 07:00, picked to mimic exposure to light while driving home after a night shift), and then allowed to sleep from 08:00 until spontaneous awakening, workers' cognitive performance and sleep efficiency improves over a week's time after an abrupt change to night

shift. Furthermore, melatonin profiles show appropriate phase delays despite exposure to light at a point in the phase response curve that would predict phase advances (95). The authors attribute the success of circadian adaptation to the regularity of schedule and an experimental protocol that promoted daytime sleep in a light- and soundproof environment. Chronophototherapy with the use of artificial light shows similar success (96). These results suggest that when sleep loss is minimized and light exposure standardized, adaptation of performance can occur in conjunction with circadian adaptation. On the other hand, data suggest that circadian adaptation does not occur when conditions are not ideal, such as when sleep is not maintained on a regular schedule or when light exposure is not controlled (97–99).

Exogenous melatonin may be beneficial. Indeed, melatonin administration in a crossover, placebo-controlled study of night-shift adaptation shows significant improvements in sleep time but only marginal boosts in nocturnal alertness and no effects on performance (100).

Considering the difficulties of "real-world" treatment, the physician's main strategy includes basic counseling to maintain regular sleep–wake patterns and avoidance of self-medication with alcohol as a sedative and caffeine as a stimulant. Employers should promote adaptation by avoiding rapid-cycling rotating shifts and using bright lights within the workplace. As in jet lag disorder, in which phase delays are better tolerated than phase advances, the use of forward rotating shifts (day to evening to night to day) rather than reverse rotations (day to night to evening to day) may improve employee adjustment.

CONCLUSION

Circadian sleep disorders represent maladaptations of the biological clock to the local solar environment arising from social, psychiatric, genetic, or medical etiologies. The pattern of sleep–wake cycles compared to light–dark cycles provides the means of characterization and diagnosis. Delayed and advanced sleep phase disorder patients chronically lag or precede conventional daily schedules. Irregular sleep–wake rhythm disorder patients generally have multifocal or degenerative central nervous system disease and display irregular, random patterns of sleep–wake activities due to loss of circadian regulation. Nonentrained disorder patients, typically those with blindness from lesions anterior to the optic tract, slowly precess unentrained to 24-hour cycles, displaying periodic bouts of insomnia and excessive sleepiness. Subjects susceptible to the effects of jet lag and shift work experience a variety of symptoms that are attributable to acute and chronic mismatches between internal and external clocks.

Employers and government officials are beginning to show a greater appreciation of the public health advantages of working with, rather than against, the circadian clock. Careful attention to sleep hygiene, sleep–wake scheduling, and bright light exposure are the mainstays of therapy,

and supplementary measures including melatonin and sedative or stimulant administration are being evaluated for efficacy.

REFERENCES

1. Czeisler C. The effect of light on the human circadian pacemaker. CIBA Found Symp 1995; 183:254–290.
2. Czeisler CA, Duffy JF, Shanahan TL, Brown EN, Mitchell JF, Rimmer DW, et al. Stability, precision, and near-24-hour period of the human circadian pacemaker. Science 1999; 284(5423):2177–2181.
3. Johnson CH. An Atlas of Phase Response Curves for Circadian and Circatidal Rhythms. Nashville, Tennessee: Department of Biology, Vanderbilt University, 1990.
4. Borbély AA. Sleep homeostasis and models of sleep regulation. In: Kryger M, Roth T, Dement W, eds. Principles and Practice of Sleep Medicine. 2nd ed. Philadelphia: W. B. Sanders, 1994:309–320.
5. Campbell S, Zulley J. Napping in time-free environments. In: Dinges D, Broughten R, eds. Sleep and Alertness: Chronobiological, Behavioral, and Medical Aspects of Napping. New York: Raven Press, 1989:121–138.
6. Dijk D, Czeisler C. Contribution of the circadian pacemaker and the sleep homeostat to sleep propensity, sleep structure, electroencephalographic slow waves, and sleep spindle activity in humans. J Neurosci 1995; 15(5): 3526–3538.
7. Schwartz WJ, Reppert SM, Eagan SM, Moore-Ede MC. In vivo metabolic activity of the SCN: a comparative study. Brain Res 1983; 274:184–187.
8. Inouye SIT, Kawamura H. Characteristics of a circadian pacemaker in the suprachiasmatic nucleus. J Comp Physiol 1982; 146:153–160.
9. Ralph MR, Foster RG, Davis FC, Menaker M. Transplanted suprachiasmatic nucleus determines circadian period. Science 1990; 247:975–978.
10. Young MW, Kay SA. Time zones: a comparative genetics of circadian clocks. Nat Rev Genet 2001; 2:702–715.
11. Albrecht U, Eichele G. The mammalian circadian clock. Curr Opin Genet Dev 2003; 13:271–277.
12. Yamazaki S, Numano R, Michikazu A, Akiko H, Takahashi R, Ueda M, et al. Resetting central and peripheral circadian oscillators in transgenic rats. Science 2000; 288:682–685.
13. Yoo S-H, Yamazaki SM, Lowrey PL, Shimomura K, Ko CH, Buhr ED et al. Period2: Luciferase real-time reporting of circadian dynamics reveals persistent circadian oscillations in mouse peripheral tissues. Proc Natl Acad Sci USA 2003; 101:5339–5346.
14. Stokkan KA, Yamazaki S, Tei H, Sakaki Y, Menaker M. Entrainment of the circadian clock in the liver by feeding. Science 2001; 291(5503): 490–493.
15. Hattar S, Liao HW, Takao M, Berson DM, Yau KW. Melanopsin-containing retinal ganglion cells: architecture, projections, and intrinsic photosensitivity. Science 2002; 295(5557):1065–1070.
16. Berson DM, Dunn FA, Takao M. Phototransduction by retinal ganglion cells that set the circadian clock. Science 2002; 295(5557):1070–1073.

17. Moore RY, Lenn NJ. A retinohypothalamic projection in the rat. J Comp Neurol 1972; 146:1–14.
18. Lucas RJ, Freedman MS, Lupi D, Munoz M, David-Gray ZK, Foster RG. Identifying the photorecceptive inputs to the mammalian circadian system using transgenic and retinally degenerate mice. Brain Res 2001; 125:97–102.
19. Hall JC. Cryptochromes: sensory reception, transduction, and clock functions subserving circadian systems. Curr Opin Neurobiol 2000; 10(4):456–466.
20. Campbell S, Murphy P. Extraocular circadian phototransduction in humans. Science 1998; 279:396–399.
21. Ruger M, Gordijn MC, Beersma DG, de Vries B, Daan S. Acute and phase-shifting effects of ocular and extraocular light in human circadian physiology. J Biol Rhythms 2003; 18(5):409–419.
22. Silver R, LeSauter J, Tresco PA, Lehman MN. A diffusible coupling signal from the transplanted suprachiasmatic nucleus controlling circadian locomotor rhythms. Nature 1996; 382(6594):810–813.
23. Nave R, Herer P, Haimov I, Shlitner A, Lavie P. Hypnotic and hypothermic effects of melatonin on daytime sleep in humans: lack of antagonism by flumazenil. Neurosci Lett 1996; 214(2–3):123–126.
24. Dawson D, Encel N. Melatonin and sleep in humans. J Pineal Res 1993; 15: 1–12.
25. Reppert SM, Weaver DR, Ebisawa T. Cloning and characterization of a mammalian melatonin receptor that mediates reproductive and circadian responses. Neuron 1994; 13:1177–1185.
26. Pang S, Lee P, Chan Y. Melatonin secretion and its rhythms in biological fluids. In: Reiter R, Yu H, eds. Melatonin: Biosynthesis, Physiological Effects, and Clinical Applications. Boca Raton: CRC Press, 1993:130–153.
27. Anonymous. ICSD-2: proposed sleep disorders categories and individual sleep disorders. AASM Bull 2003; 10:13–14.
28. Horne JA, Ostberg O. A self-assessment questionnaire to determine morningness–eveningness in human circadian rhythms. Int J Chronobiol 1976; 4(2):97–110.
29. Regestien QR, Monk TH. Delayed sleep phase syndrome: a review of clinical aspects. Am J Psychiatry 1995; 152:602.
30. Takahashi Y, Hohjoh H, Matsuura K. Predisposing factors in delayed sleep phase syndrome. Psychiatry Clin Neurosci 2000; 54(3):356–358.
31. Shirayama M, Shirayama Y, Iida H, Kato M, Kajimura N, Watanabe T, et al. The psychological aspects of patients with delayed sleep phase syndrome (DSPS). Sleep Med 2003; 4(5):427–433.
32. Dagan Y, Stein D, Steinbock M, Yovel I, Hallis D. Frequency of delayed sleep phase syndrome among hospitalized adolescent psychiatric patients. J Psychosom Res 1998; 45(1 Spec No):15–20.
33. Shibui K, Uchiyama M, Okawa M. Melatonin rhythms in delayed sleep phase syndrome. J Biol Rhythms 1999; 14(1):72–76.
34. Watanabe T, Kajimura N, Kato M, Sekimoto M, Nakajima T, Hori T, et al. Sleep and circadian rhythm disturbances in patients with delayed sleep phase syndrome. Sleep 2003; 26(6):657–661.
35. Uchiyama M, Okawa M, Shibui K, Kim K, Tagaya H, Kudo Y, et al. Altered phase relation between sleep timing and core body temperature rhythm in

delayed sleep phase syndrome and non-24-hour sleep–wake syndrome in humans. Neurosci Lett 2000; 294(2):101–104.
36. Ancoli-Israel S, Schnierow B, Kelsoe J, Fink R. A pedigree of one family with delayed sleep phase syndrome. Chronobiol Int 2001; 18(5):831–840.
37. Archer SN, Robilliard DL, Skene DJ, Smits M, Williams A, Arendt J, et al. A length polymorphism in the circadian clock gene *Per3* is linked to delayed sleep phase syndrome and extreme diurnal preference. Sleep 2003; 26(4):413–415.
38. Ebisawa T, Uchiyama M, Kajimura N, Mishima K, Kamei Y, Katoh M et al. Association of structural polymorphisms in the human period 3 gene with delayed sleep phase syndrome. EMBO Rep 2001; 2(4):342–346.
39. Toh KL, Jones CR, He Y, Eide EJ, Hinz WA, Virshup DM, et al. An hPer2 phosphorylation site mutation in familial advanced sleep phase syndrome. Science 2001; 291(5506):1040–1043.
40. Hohjoh H, Takasu M, Shishikura K, Takahashi Y, Honda Y, Tokunaga K. Significant association of the arylalkylamine *N*-acetyltransferase (AA-NAT) gene with delayed sleep phase syndrome. Neurogenetics 2003; 4(3):151–153.
41. Iwase T, Kajimura N, Uchiyama M, Ebisawa T, Yoshimura K, Kamei Y, et al. Mutation screening of the human *Clock* gene in circadian rhythm sleep disorders. Psychiatry Res 2002; 109(2):121–128.
42. Ancoli-Israel S, Cole R, Alessi C, Chambers M, Moorcroft W, Pollak CP. The role of actigraphy in the study of sleep and circadian rhythms. Sleep 2003; 26(3):342–392.
43. Nagtegaal JE, Kerkhof GA, Smits MG, Swart AC, Van Der Meer YG. Delayed sleep phase syndrome: a placebo-controlled cross-over study on the effects of melatonin administered five hours before the individual dim light melatonin onset. J Sleep Res 1998; 7(2):135–143.
44. Watanabe T, Kajimura N, Kato M, Sekimoto M, Takahashi K. Effects of phototherapy in patients with delayed sleep phase syndrome. Psychiatry Clin Neurosci 1999; 53(2):231–233.
45. Alvarez B, Dahlitz MJ, Vignau J, Parkes JD. The delayed sleep phase syndrome: clinical and investigative findings in 14 subjects. J Neurol Neurosurg Psychiatry 1992; 55(8):665–670.
46. Akata T, Sekiguchi S, Takahashi M, Miyamoto M, Higuchi T, Machiyama Y. Successful combined treatment with vitamin B12 and bright artificial light of one case with delayed sleep phase syndrome. Jpn J Psychiatry Neurol 1993; 47(2):439–440.
47. Cole RJ, Smith JS, Alcala YC, Elliott JA, Kripke DF. Bright-light mask treatment of delayed sleep phase syndrome. J Biol Rhythms 2002; 17(1): 89–101.
48. Aldrich MS. Chronobiologic disorders. In: Aldrich MS, ed. Sleep Medicine. New York: Oxford University, 1999:186–199.
49. Yanagida H, Nakajima T, Kajimura N, Kato M, Watanabe T, Hori T, et al. Physical symptoms under forced-phase advance treatment in a patient with delayed sleep phase syndrome: a case report. Psychiatry Clin Neurosci. 2002; 56(3):219–220.
50. Carskadon MA, Vieira C, Acebo C. Association between puberty and delayed phase preference. Sleep 1993; 16(3):258–262.

51. Wolfson AR, Carskadon MA. Sleep schedules and daytime functioning in adolescents. Child Dev 1998; 69(4):875–887.
52. Barger LK, Wright KP Jr, Hughes RJ, Czeisler CA. Daily exercise facilitates phase delays of circadian melatonin rhythm in very dim light. Am J Physiol Regul Integr Comp Physiol 2004; 286(6):R1077–R1084.
53. Buxton OM, Lee CW, L'Hermite-Baleriaux M, Turek FW, Van Cauter E. Exercise elicits phase shifts and acute alterations of melatonin that vary with circadian phase. Am J Physiol Regul Integr Comp Physiol 2003; 284(3): R714–R724.
54. Brun J, Chamba G, Khalfallah Y, Girard P, Boissy I, Bastuji H, et al. Effect of modafinil on plasma melatonin, cortisol and growth hormone rhythms, rectal temperature and performance in healthy subjects during a 36 h sleep deprivation. J Sleep Res 1998; 7(2):105–114.
55. Wyatt JK, Cajochen C, Ritz-De Cecco A, Czeisler CA, Dijk DJ. Low-dose repeated caffeine administration for circadian-phase-dependent performance degradation during extended wakefulness. Sleep 2004; 27(3):374–381.
56. Satoh K, Mishima K, Inoue Y, Ebisawa T, Shimizu T. Two pedigrees of familial advanced sleep phase syndrome in Japan. Sleep 2003; 26(4): 416–417.
57. Reid KJ, Chang AM, Dubocovich ML, Turek FW, Takahashi JS, Zee PC. Familial advanced sleep phase syndrome. Arch Neurol 2001; 58(7):1089–1094.
58. Jones CR, Campbell SS, Zone SE, Cooper F, DeSano A, Murphy PJ, et al. Familial advanced sleep-phase syndrome: a short-period circadian rhythm variant in humans. Nat Med 1999; 5(9):1062–1065.
59. Dijk DJ, Duffy JF. Circadian regulation of human sleep and age-related changes in its timing, consolidation and EEG characteristics. Ann Med 1999; 31(2):130–140.
60. Duffy JF, Czeisler CA. Age-related change in the relationship between circadian period, circadian phase, and diurnal preference in humans. Neurosci Lett 2002; 318(3):117–120.
61. Tozawa T, Mishima K, Satoh K, Echizenya M, Shimizu T, Hishikawa Y. Stability of sleep timing against the melatonin secretion rhythm with advancing age: clinical implications. J Clin Endocrinol Metab 2003; 88(10):4689–4695.
62. Franklin B. Poor Richard's Almanack. Mount Vernon, New York, Peter Pauper Press. 1937; p. 46.
63. Yamadera H, Takahashi K, Okawa M. A multicenter study of sleep–wake rhythm disorders: clinical features of sleep–wake rhythm disorders. Psychiatry Clin Neurosci 1996; 50(4):195–201.
64. Stopa EG, Volicer L, Kuo-Leblanc V, Harper D, Lathi D, Tate B, et al. Pathologic evaluation of the human suprachiasmatic nucleus in severe dementia. J Neuropathol Exp Neurol 1999; 58(1):29–39.
65. Mishima K, Tozawa T, Satoh K, Matsumoto Y, Hishikawa Y, Okawa M. Melatonin secretion rhythm disorders in patients with senile dementia of Alzheimer's type with disturbed sleep–waking. Biol Psychiatry 1999; 45(4): 417–421.
66. Volicer L, Harper DG, Manning BC, Goldstein R, Satlin A. Sundowning and circadian rhythms in Alzheimer's disease. Am J Psychiatry 2001; 158(5):704–711.

67. Heikkila E, Hatonen TH, Telakivi T, Laakso ML, Heiskala H, Salmi T, et al. Circadian rhythm studies in neuronal ceroid-lipofuscinosis (NCL). Am J Med Genet 1995; 57(2):229–234.
68. Laakso ML, Leinonen L, Hatonen T, Alila A, Heiskala H. Melatonin, cortisol and body temperature rhythms in Lennox–Gastaut patients with or without circadian rhythm sleep disorders. J Neurol 1993; 240(7):410–416.
69. Paus S, Brecht HM, Koster J, Seeger G, Klockgether T, Wullner U. Sleep attacks, daytime sleepiness, and dopamine agonists in Parkinson's disease. Move Disord 2003; 18:659–667.
70. Satlin A, Volicer L, Ross V, Herz L, Campbell S. Bright light treatment of behavioral and sleep disturbances in patients with Alzheimer's disease. Am J Psychiatry 1992; 149(8):1028–1032.
71. Cardinali DP, Brusco LI, Liberczuk C, Furio AM. The use of melatonin in Alzheimer's disease. Neuroendocrinol Lett 2002; 23(suppl 1):20–23.
72. Sack RL, Lewy AJ, Blood ML, Keith LD, Nakagawa H. Circadian rhythm abnormalities in totally blind people: incidence and clinical significance. J Clin Endocrinol Metab 1992; 75(1):127–134.
73. Klein T, Martens H, Dijk DJ, Kronauer RE, Seely EW, Czeisler CA. Circadian sleep regulation in the absence of light perception: chronic non-24-hour circadian rhythm sleep disorder in a blind man with a regular 24-hour sleep–wake schedule. Sleep 1993; 16(4):333–343.
74. Lockley SW, Skene DJ, Butler LJ, Arendt J. Sleep and activity rhythms are related to circadian phase in the blind. Sleep 1999; 22(5):616–623.
75. Czeisler CA, Shanahan TL, Klerman EB, Martens H, Brotman DJ, Emens JS, et al. Suppression of melatonin secretion in some blind patients by exposure to bright light. N Engl J Med 1995; 332(1):6–11.
76. Sack RL, Lewy AJ, Blood ML, Stevenson J, Keith LD. Melatonin administration to blind people: phase advances and entrainment. J Biol Rhythms 1991; 6(3):249–261.
77. Moline ML, Pollak CP, Monk TH, Lester LS, Wagner DR, Zendell SM, et al. Age-related differences in recovery from simulated jet lag. Sleep 1992; 15(1):28–40.
78. Cho K, Ennaceur A, Cole JC, Suh CK. Chronic jet lag produces cognitive deficits. J Neurosci 2000; 20(6):RC66.
79. Recht L, Lew R, Schwartz W. Baseball teams beaten by jet lag. Nature 1995; 377:583.
80. Smith RS, Guilleminault C, Efron B. Circadian rhythms and enhanced athletic performance in the National Football League. Sleep 1997; 20(5): 362–365.
81. Steenland K, Deddens JA. Effect of travel and rest on performance of professional basketball players. Sleep 1997; 20(5):366–369.
82. Boulos Z, Campbell SS, Lewy AJ, Terman M, Dijk DJ, Eastman CI. Light treatment for sleep disorders: consensus report. VII. Jet lag. J Biol Rhythms 1995; 10(2):167–176.
83. Boulos Z, Macchi MM, Sturchler MP, Stewart KT, Brainard GC, Suhner A, et al. Light visor treatment for jet lag after westward travel across six time zones. Aviat Space Environ Med 2002; 73(10):953–963.

84. Beaumont M, Batejat D, Pierard C, Van Beers P, Denis JB, Coste O, et al. Caffeine or melatonin effects on sleep and sleepiness after rapid eastward transmeridian travel. J Appl Physiol 2004; 96(1):50–58.
85. Beers TM. Flexible schedules and shift work: replacing the 9–5 workday? Mon Labor Rev 2000; 123:33–41.
86. Harma M, Sallinen M, Ranta R, Mutanen P, Muller K. The effect of an irregular shift system on sleepiness at work in train drivers and railway traffic controllers. J Sleep Res 2002; 11(2):141–151.
87. Ohayon MM, Lemoine P, Arnaud-Briant V, Dreyfus M. Prevalence and consequences of sleep disorders in a shift worker population. J Psychosom Res 2002; 53(1):577–583.
88. Richardson GS, Miner JD, Czeisler CA. Impaired driving performance in shiftworkers: the role of the circadian system in a multifactorial model. Alcohol Drugs Driving 1989; 5–6(4–1):265–273.
89. Knutsson A. Health disorders of shift workers. Occup Med (Lond) 2003; 53(2):103–108.
90. Karlsson B, Knutsson A, Lindahl B. Is there an association between shift work and having a metabolic syndrome? Results from a population based study of 27,485 people. Occup Environ Med 2001; 58(11):747–752.
91. Boggild H, Knutsson A. Shift work, risk factors and cardiovascular disease. Scand J Work Environ Health 1999; 25(2):85–99.
92. Harma MI, Hakola T, Akerstedt T, Laitinen JT. Age and adjustment to night work. Occup Environ Med 1994; 51(8):568–573.
93. Akerstedt T, Knutsson A, Westerholm P, Theorell T, Alfredsson L, Kecklund G. Work organisation and unintentional sleep: results from the WOLF study. Occup Environ Med 2002; 59(9):595–600.
94. Akerstedt T, Fredlund P, Gillberg M, Jansson B. Work load and work hours in relation to disturbed sleep and fatigue in a large representative sample. J Psychosom Res 2002; 53(1):585–588.
95. Lamond N, Dorrian J, Roach GD, McCulloch K, Holmes AL, Burgess HJ, et al. The impact of a week of simulated night work on sleep, circadian phase, and performance. Occup Environ Med 2003; 60(11):e13.
96. Czeisler C, Johnson M, Duffy J, Brown E, Ronda J, Kronauer R. Exposure to bright light and darkness to treat physiologic maladaptation to night work. N Engl J Med 1990; 322:1253–1259.
97. Knauth P, Emde E, Rutenfranz J, Kiesswetter E, Smith P. Re-entrainment of body temperature in field studies of shift work. Int Arch Occup Environ Health 1981; 49:137–149.
98. Horowitz TS, Cade BE, Wolfe JM, Czeisler CA. Efficacy of bright light and sleep/darkness scheduling in alleviating circadian maladaptation to night work. Am J Physiol Endocrinol Metab 2001; 281(2):E384–E391.
99. Yoon IY, Jeong DU, Kwon KB, Kang SB, Song BG. Bright light exposure at night and light attenuation in the morning improve adaptation of night shift workers. Sleep 2002; 25(3):351–356.
100. Yoon IY, Song BG. Role of morning melatonin administration and attenuation of sunlight exposure in improving adaptation of night-shift workers. Chronobiol Int 2002; 19(5):903–913.

10

Sleep Problems in Children

O'Neill F. D'Cruz

Departments of Neurology and Pediatrics,
University of North Carolina–Chapel Hill,
Chapel Hill, North Carolina, U.S.A.

Symptoms of Sleep Problems in Children

Sleepiness
Excessive napping
Difficulty sleeping at night
Agitation
Irritability
Nighttime behaviors

Diagnoses

Sleep-onset disorders
- *Sleep-onset association disorder*
- *Limit-setting sleep disorder*
- *Circadian rhythm sleep disorders*
  - *Advanced sleep phase disorder*
  - *Delayed sleep phase disorder*
- *Transition parasomnias*

Sleep period disorders
- *Sleep-disordered breathing*
- *Periodic limb movement disorder*
- *Parasomnias*
- *Nocturnal seizures*

Sleep offset disorders
- *Nightmare disorder*
- *Recurrent isolated sleep paralysis*
- *Sleep inertia*

INTRODUCTION

The cardinal manifestations of sleep disorders in the pediatric age group differ from adults and are easily overlooked. Anticipatory guidance during well-child visits requires an understanding of age-appropriate sleep characteristics. Sleep problems in childhood are a common source of distress to caregivers and can be especially challenging for clinicians. For effective assessment, the physician must use an organized approach to assess sleep-related complaints. This chapter presents an overview of normal sleep patterns in children, an outline of sleep disorders linked to the sleep–wake cycle, and a clinical approach to the evaluation and intervention of pediatric sleep disorders.

THE NORMAL SLEEP–WAKE CYCLE

In humans, wakefulness and sleep are noted during any 24-hour period. Sleep, often considered a unitary state, actually consists of periods of nonrapid eye movement (NREM) and rapid eye movement (REM) sleep (Table 1). NREM sleep is further classified into four stages. Stage 1 occurs at sleep onset and during transitions between sleep cycles, stage 2 is noted

Table 1 Sleep Stages: Clinical and Electroencephalographic Characteristics

Sleep stage		Clinical features	EEG characteristics
REM sleep		Rapid eye movements Low muscle tone Irregular respirations	REMs on eye leads Low-voltage EEG/EMG
Non-REM sleep	Stage 1	Drowsiness	Attenuated posterior dominant rhythm
		Slow eye movements	Increased central theta and beta activity
		Regular respirations Low arousal threshold	Vertex sharp waves
	Stage 2	Sustained sleep No eye movements Regular respirations Moderate arousal threshold	Sleep spindles K-complexes
	Stages 3–4	Deep sleep	Delta waves (slow EEG waves)
		Regular respirations	Stage 3—moderate delta activity
		High arousal threshold	Stage 4—high delta activity

Abbreviations: EEG, electroencephalography; EMG, electromyography.

during sustained sleep, and stages 3 and 4 (slow-wave or delta sleep) are observed during the early portions of the sleep period. REM sleep is usually noted during the latter portion of the sleep period. Sleep stages follow characteristic patterns of evolution during the sleep period, forming the basis of age-appropriate sleep architecture. The amount and quality of normal sleep change with age. These sleep architecture concepts are covered in greater detail in Chapter 2.

Pediatric Sleep Patterns

Sleep patterns are an aggregate of sleep time (phase), duration (amount), and efficiency (quality) that vary according to age and physiologic maturity. Newborn infants sleep approximately 18 hours a day and have differentiated active and quiet sleep stages, with nearly half of sleep time spent in active (REM) sleep. As toddlers, children have a well-regulated circadian rhythm, and REM sleep resembles adult patterns. Adolescence is characterized by delayed sleep phase, but sleep need is unchanged from preteen years. A summary of normal pediatric sleep patterns is included in Table 2 (1).

Sleep in Infancy

During the neonatal period, the sleep–wake cycle consists of short periods of sleep alternating with wakefulness throughout a 24-hour period. State differentiation is a marker of biologic maturation, with normal newborns demonstrating sustained states of active sleep (equivalent to REM sleep), quiet sleep (NREM sleep), and indeterminate sleep (mixed features). Newborns frequently enter sleep in the indeterminate or active states and cycle between quiet and active sleep. Indeterminate sleep is gradually replaced by differentiated sleep states during infancy.

Infant sleep has several distinct characteristics (2). Sleep is consolidated into longer nocturnal sleep periods between six weeks and three months of age, associated with the development of sleep spindles on electroencephalography (EEG). At three months, total sleep time ranges from 10 to 19 hours

Table 2 Sleep Patterns in Childhood and Adolescence[a]

Age	Phase	Amount (hrs)	Quality/efficiency
Neonates	None	18+	Brief, frequent sleep periods
Early infancy	Irregular	10–18	3+ naps, longer night sleep
Late infancy	Regular	11–16	2+ naps, 1–2 night-sleep periods
Preschool	Early	10–15	1+ naps, sustained night sleep
Middle childhood	Regular	9–12	No naps, excellent night sleep
Adolescents	Delayed	9–12	Lower efficiency than 1st decade

[a]Sleep amounts modified from Ref. 1.

per 24-hour period. Total sleep duration averages about 14 hours between six months and one year of age. Daytime sleep, included in the total sleep time, decreases from 3-1/2 hours at six months of age to 2-1/2 hours by one year of age. REM sleep in infants occurs at sleep onset and has a short period of 50–60 minutes.

Sleep in Childhood

Sleep phase is well established in the majority of children by six months of age, with daytime naps decreasing in duration and number in the preschool years. Indeed, the number of children taking daytime naps decreases from over 90% at one year of age to around 35% by four years of age. REM sleep decreases from nearly 50% of sleep in the newborn state to 25% of sleep in the toddler. NREM sleep continues to include high percentages of slow-wave sleep, even being apparent during daytime naps. In addition to sleep, rapid changes in physical and neurological developmental along with achievement of social milestones make 1–5-year-old children susceptible to sleep disruption. School-aged children have excellent biologic sleep parameters, with sustained efficient nocturnal sleep lasting 10–11 hours. Daytime naps are unusual at this age. Hence, sleep complaints during this period are often secondary to environmental or physical causes.

Sleep in Adolescence

Adolescence is a period of rapid physical, emotional, and social maturation. Sleep during adolescence reflects the impact of several of these factors. Teenagers experience a physiologic delay in sleep phase (see below, and Chap. 9). While sleep need generally decreases with age, sleep need during adolescence is unchanged from preteen years, even increasing during periods of rapid growth. This age group is also vulnerable to impaired sleep quality from poor sleep habits and sleep disorders. This age group of the pediatric population is most likely to have a multifactorial origin of sleep complaints.

BIOLOGIC–ENVIRONMENTAL INTERACTIONS

The initiation of sleep requires a sequential and voluntary disengagement from the environment in response to biologic cues of sleepiness. Hence, attention to biologic and environmental factors is necessary for optimal sleep. In children, biologic maturation influences all aspects of sleep and is governed by the factors outlined below. In addition, environmental influences, including caregivers and adults, must be considered when evaluating sleep complaints in otherwise healthy children. A summary of biologic and environmental factors affecting sleep is outlined in Table 3.

Table 3 Factors Affecting Sleep in Children

Biologic factors:
Gender
Incidence and prevalence of specific parasomnias/sleep disorders
Growth phase
Age
Neuro-developmental phase
Genetics
Sleep phase
Parasomnias
Environmental factors:
Setting
Sleep deprivation or disruption
Changes in sleep schedule
Change in sleep environment
Social dynamics
Parent–child interaction
Vulnerable child syndrome
Parental factors: domestic abuse, psychiatric
Stressors (intrinsic)
Acute febrile illness
Medications—sedatives, beta-blockers, opiates, TCA/SSRI
Withdrawal effects—medications, drugs, or alcohol
Acute pain syndromes—somatic, visceral, or neurological
Stressors (extrinsic)
Changes in day care, school, or home setting
Anxiety-provoking life events (sibling or family issues, peer interactions, natural or social/political catastrophes)

Abbreviations: TCA, tricyclic antidepressants; SSRI, selective serotonin reuptake inhibitors.

Biological Factors Affecting Sleep

Genetic Influences on Sleep

Genes lay the foundation of our neuronal makeup. It is not uncommon for families to note a child sleeping in a manner similar to one of the parents during their childhood. Familial traits have been described for sleep length, sleep phase, and even sleep characteristics. Primary sleep disorders or other disorders that manifest during sleep may also be influenced by genetics. Disorders such as narcolepsy, parasomnias, and periodic limb movement disorder demonstrate a marked familial preponderance. Nocturnal seizure disorders, including benign epilepsy with centrotemporal spikes (benign rolandic epilepsy) and autosomal dominant nocturnal frontal lobe epilepsy, are state-dependent expressions of a genetic tendency. Fatal familial insomnia is associated with sleep disorders at the onset of a neurodegenerative disorder.

Gender Influences on Sleep

Genetic and hormonal factors can influence sleep in a gender-specific manner. Indeed, several sleep disorders exhibit a gender difference in adults. Obstructive sleep apnea and REM sleep behavior disorder are predominantly seen in males, while restless legs syndrome presents earlier in women. Sleep disorders due to affective disorders are more common in women and some disorders are gender specific (e.g., menstrual-related hypersomnia). In prepubertal children, there are no significant differences in the prevalence of common sleep disorders (including sleep apnea), although referral patterns may influence frequency of diagnosis. Some parasomnias, including sleep enuresis, sleep-related rhythmic movement disorder, and sleep terrors are more common in males, while sleep-related bruxism, sleep talking (somniloquy), and nightmares are equally prevalent in boys and girls.

Growth Phase Influences on Sleep

Maturation of the sleep–wake cycle and consolidation of sleep state features occur gradually over months to years in healthy children. Abnormal psychomotor development adversely affects sleep maturation, leading to persistence of infantile sleep patterns into childhood. These children often have coexisting medical and neurological disorders that affect sleep. In addition, social and language development influences the interaction between caregivers and children. These factors predispose to sleep disturbances in young children with developmental disorders. Indeed, prematurity, autistic spectrum disorders, severe mental retardation, and static encephalopathy are associated with a high incidence of sleep disorders and consolidated sleep may not occur in the first year of life in these children. The resulting sleep disruption often adversely affects quality of life. Lastly, clinicians should be aware that parasomnias might persist well beyond early childhood.

Environmental Factors Influencing Sleep

Transition from wakefulness to sleep, as well as sustained nocturnal sleep, are influenced by a variety of environmental factors. Children are more likely to fall asleep in a dark, quiet, comfortable environment if they associate sleep onset with that environment. Disruption of sleep setting, social dynamics, or introduction of stressors can adversely affect sleep (Table 3). Attention to these factors facilitates the sleep transition and reduces bedtime struggles (the acronym SLEEP is outlined in Table 4). When the sleep disorder is due to environmental factors, the intensity of environmental changes parallels the severity of the sleep disturbance. The occurrence or resolution, of sleep disorders after a change in the environment is a strong clue to environmental factors contributing to the sleep disorder.

Table 4 Suggestions for Improving the Sleep–Wake Transition in Children: The Mnemonic *SLEEP*

• **S**low down (avoid vigorous play and environmental stimulation)
• **L**imit intake (avoid caffeinated beverages, excessive fluids, spicy foods)
• **E**ase up (on loud sounds, bright lights)
• **E**nable transition (consistent bed-time routine; adjust three Hs—heat, humidity, "hum"[a])
• **P**rovide for comfort (transition objects, age-appropriate sleep area)

[a]Hum refers to white noise, e.g., a fan.

The Importance of the Sleep Setting

A child's ability to settle down to sleep is a learned behavior involving disengagement from the caregivers in a secure, comfortable sleep environment. Parenting styles, social and cultural expectations, and sleeping arrangements are among the environmental determinants of sleep patterns in children. A consistent set of environmental cues is needed to promote sleep onset and maintain sleep after transient arousals.

Socioeconomic Factors and Sleep

A child's sleep environment varies widely based on the socioeconomic status of the family. Among the lower socioeconomic classes, inadequate sleeping areas, lack of electricity, overcrowding, and a noisy environment contribute to the child's sleep difficulties. Conversely, easy access to television, computers, and video games and numerous social engagements or after-school activities may predispose children in more affluent families to insufficient or disrupted sleep. Consumption of caffeinated beverages, inadequate or inappropriate food intake, and poor sleep hygiene also affect sleep in children.

Environmental Stressors and Sleep

Sleep disorders are precipitated by extrinsic and intrinsic stressors. Extrinsic stressors affect sleep based on their duration and severity. The impact may be mild and self-limited in some instances (e.g., prior to travel or a test) or may last several weeks to months (e.g., changing schools or residential settings). Other social stressors including domestic or societal violence, geopolitical events, and major environmental disasters affecting entire segments of society can induce long-term changes in children's sleep patterns, ranging from mild sleep avoidance to post-traumatic stress disorder. Intrinsic stressors such as fever, systemic illness, chronic pain, and medical disorders may also disturb sleep due to the inherent pathophysiology of the stressor and secondary discomfort.

THE CARDINAL SYMPTOMS OF SLEEP DISORDERS IN CHILDREN

Children frequently display the classic symptoms of falling asleep at inappropriate times or having trouble sleeping at night (Table 5). However, if symptoms differ from those commonly seen in adults, sleep disorders are often overlooked with the symptoms incorrectly attributed to other causes. The child may be blamed for the functional limitations that occur due to inadequate or disrupted sleep. Poor sleep can lead to adverse health outcomes in children with medical and neurological disorders.

Daytime sleep in young children is limited to naps in preschool-aged children, with vigorous activity in between. Sleep disorders should be suspected when naps increase in duration or number in younger children or napping recurs in school-aged children, especially napping at unusual times and places. School-aged children may forego social functions, withdraw from sports or play activities, and take naps in busy or noisy surroundings. While awake, sleepy children often appear glassy-eyed and seem unmotivated in school. They often stare off unless actively engaged and are unable to sustain the attention and concentration necessary for schoolwork.

Conversely, children may attempt to resist sleep, exhibiting signs of paradoxical hyperactivity, agitation, and off-task behavior. They may also be irritable and moody, especially after sleep offset or if asked to perform activities requiring sustained attention. If the child attempts to sleep at home and resists sleep in school, parents and school personnel describe markedly different symptoms that sometimes contradict each other. It is important to be aware of the common origin of these apparently paradoxical reports.

Sleep and neurological disorders exhibit a bidirectional effect. In children with migraine and epilepsy, an increase in the frequency of headaches and seizures is often noted following sleep deprivation or disruption. Similarly, neurological disorders and pharmacologic therapy may impair the quality and amount of sleep in these children. Children with cerebral palsy, muscular dystrophy, and airway disorders are among the special populations who should undergo a sleep assessment when devising treatment plans for their primary disorders.

Table 5 Daytime Symptoms of Sleep Disorders in Children

- Motor disorders—hyperactivity, agitation
- Mood disorders—irritability, social withdrawal, affective symptoms
- Cognitive dysfunction—impaired school performance, inattention
- Inappropriate/excessive napping
- Neuro-endocrine dysfunction—altered growth patterns, hypertension

Table 6 The Relationship of Sleep Disorders to the Sleep–Wake Cycle

Sleep—onset disorders
Sleep-phase disorders
Sleep-onset association disorder
Limit-setting sleep disorder
Transition parasomnias
Sleep period disorders
Sleep-disordered breathing
Periodic limb movements
Arousal parasomnias
Systemic illness—pain, gastrointestinal, neurological
Sleep dysregulation disorders
Sleep offset disorders
Sleep paralysis
Sleep inertia
REM parasomnias
Sleep phase disorders

Understanding that these symptoms represent sleep disruption is crucial to diagnosing sleep disorders in children. Ultimately, the clinician must appreciate that children manifest sleep disruption, in an age distinct manner. Astute clinicians who utilize these subtle symptoms as clues to sleep disruption are well on their way to effectively treating sleep disorders in children.

SLEEP DISORDERS IN RELATION TO THE SLEEP–WAKE CYCLE

In general, sleep difficulties can be categorized by their relationship to the sleep–wake cycle (Table 6). Sleep difficulties occurring during a specific phase of the sleep–wake cycle suggest certain diagnoses. Some sleep disorders do not demonstrate this relationship, thus requiring a broader perspective for an accurate diagnosis (3).

Sleep-Onset Disorders

Several disorders are characterized by their occurrence at sleep onset. Distinguishing these disorders helps avoid unnecessary conflicts and improper interventions. A key clinical aspect of assessing sleep-onset related disorders is to establish the optimal sleep-onset sequence with respect to time and interventions.

Sleep-Onset Association Disorder

Sleep onset in infants is often facilitated by the parents. Feeding, rocking, and cuddling are common antecedents to sleep onset in infancy. Later, these interventions are replaced with transitional objects (e.g., pacifiers, bottles,

blankets). The place and setting of sleep in children become environmental reinforcements for the transition to sleep. Children who learn to sleep using one or more of these aids develop a sleep-onset association with the transitional object, place, or person. These children seek the same aids to return to sleep after nocturnal arousals. The lack of these sleep aids during the night leads to prolonged periods of arousal during which the child attempts to restore the environment that facilitated the onset of sleep. If the sleep-onset association involves parental interaction or a place other than the child's customary sleeping area, parents have to intervene before the child can return to sleep. The frequency and duration of these interventions lead to sleep disruption for the caregivers and are often the reason for seeking medical advice. A new set of nondisruptive sleep-onset associations need to be cultivated for resolution of the sleep-onset association disorder. This process may take several days to weeks.

Limit-Setting Sleep Disorder

Voluntary disengagement from the environment is an initial step before going to sleep. In children, this process requires parental supervision and reinforcement. Children often postpone bedtimes by making repeated requests for minor interventions. If caregivers do not consistently reinforce limits, this behavioral pattern delays sleep onset, leading to insufficient sleep for the preschool-aged child. Older children may lack the self-discipline to go to bed at an appropriate time, and adolescents often choose to sleep on an irregular schedule. In all cases, there is no difficulty after sleep onset. Based on the age and temperament of the child, a variety of behavioral techniques (positive reinforcement, consistent expectations, parental guidance and supervision) are available to manage this disorder. Sleep-related complaints resolve after a consistent sleep schedule is enforced.

Circadian Rhythm Sleep Disorders (Sleep Phase Disorders)

Sleep phase is primarily determined by intrinsic chronobiological factors that influence the timing of sleep during the 24-hour period. Recent research outlines genetic influences that determine the propensity for sleep onset. Environmental factors also play an important role in sleep phase disorders (hence, these disorders have physiologic and behavioral subtypes in the International Classification of Sleep Disorders—2). These disorders are covered in detail in Chapter 9.

Advanced sleep phase disorder is associated with sleep onset in the early evening hours, followed by early morning awakening. Since sleep onset in children is usually early compared to adults, there are rarely any clinical concerns relating to an early sleep onset assuming the child can complete the day's tasks. Inability to stay awake during homework may be misinterpreted as sleep deprivation or school avoidance. When allowed to choose their own

sleep–wake schedule (e.g., on vacation or weekends), children with advanced sleep phase disorder often prefer to wake up earlier, reflecting their chronophysiological predisposition. If the child awakens earlier than other family members, caregivers may request medications or evaluation for insomnia. If the child is able to function well during the day, there is rarely any need for further evaluation.

Delayed sleep phase disorder is typically observed in the adolescent population, and is partly related to a physiologic phase delay evident in the early teen years. An inability to fall asleep until the early morning hours is a consistent feature in this disorder. Attempts to induce sleep with the use of sedatives are generally unsuccessful. Parents may report an increase in social activities during the late evening hours or working late at after-school activities as contributing to the phase delay. Since delayed sleep phase disorder is also associated with a delay in awakening, the sleep period often extends into the morning hours, often overlapping with the start of the school day. Compensating for sleep deprivation during the school week by sleeping late on weekends compounds the problem, introducing a further phase delay at the start of the school week. When allowed to sleep on a self-dictated schedule, most adolescents with this disorder will choose a sleep period mimicking the sleep–wake schedule for ''second-shift'' workers.

Transition Parasomnias

Transitions from wakefulness to sleep and between sleep stages lead to these disorders, which are generally benign, occurring in otherwise healthy children. Rhythmic movements may represent self-comforting behaviors or occur as a sleep-inducing behavior. Head banging, body rolling, and to-and-fro rocking are among the more commonly observed behaviors associated with rhythmic movement disorder. These movements can rarely cause facial or soft tissue injury. Sleep starts are often single, abrupt motor or sensory phenomena that occur during sleep–wake transitions, causing transient arousals. Vocalizations during sleep (including talking, giggling, and neologisms) are disruptive to those sharing the sleep environment in much the same way as rhythmic movements. Nocturnal leg cramps are associated with painful sensations in the lower extremities and may result in sleep disruption or insomnia.

Sleep Period Disorders

Sleep need changes throughout childhood. Therefore, the amount of sleep needed by an individual child must be monitored and adjusted accordingly. A 2-week sleep diary is the key to determining average sleep need. Adequate nocturnal sleep is determined by spontaneous awakening at the end of the sleep period and normal daytime functioning. Once the sleep need is established, the sleep period can be arranged to suit the child and family's

Table 7 Sleep Amount by Age—Rule of Threes

Sleep amount decreases by: Rule 1: 1 hr/yr till age 3 Rule 2: 1 hr/3 yr, after age 3 Rule 3: Each rule can be applied three times.
Mean sleep at age (by Rule of Threes) 1 yr/0 → 14 hr; 2 yr/0 → 13 hr; 3 yr/0 → 12 hr 6 yr/0 → 11 hr; 9 yr/0 → 10 hr; 12 yr/0 → 9 hr

preferences. The mean amount of sleep at various ages may be recalled using the "rule of threes" (Table 7).

If a child functions well with less than an average amount of sleep, he/she is at risk for increased arousals (resulting in sleep fragmentation) when the time-in-bed exceeds sleep time. On the other extreme, sleep deprivation results from an inadequate sleep period in children with above-average sleep. Both groups of children may appear poorly rested in the morning. It is often necessary to enlist the help of more than one caregiver in assisting the child to maintain a regular sleep schedule, especially in children with below-average sleep need.

The nocturnal sleep period, if matched closely to sleep need, is generally consolidated into sustained sleep, with infrequent and brief arousals. Primary sleep disorders increase the number and duration of arousals in children. Recurrent or prolonged arousals after sleep onset lead to sleep fragmentation and nonrestorative sleep for children and their caregivers. Disorders occurring at sleep onset (as described above) may be observed as the child attempts to return to sleep.

Sleep-Disordered Breathing

Obstructive sleep apnea is characterized by sleep-related respiratory disturbance ranging from increased resistance to airflow during sleep (upper airway resistance syndrome) to reduction (hypopnea) or cessation (apnea) of airflow. The absence of effort during a respiratory event is characteristic of central apneas, distinguishing them from obstructive apneas and hypopneas. Sleep-disordered breathing in childhood is associated with conditions affecting respiratory control during sleep (e.g., central hypoventilation syndrome), craniofacial structural abnormalities (macroglossia, micrognathia), and abnormal airway tone (cerebral palsy) or structure (adenotonsillar hypertrophy). Systemic disorders (e.g., sickle cell disease) may be associated with a higher risk of complications due to obstructive sleep apnea. Children with neurological disorders often have a multifactorial etiology to their sleep-disordered breathing.

Table 8 American Academy of Pediatrics Practice Guidelines for Obstructive Sleep Apnea

Screening:
• Screen all children for snoring/symptoms of obstructive sleep apnea
• Refer complex, high-risk patients to a specialist
Evaluation:
• Urgent evaluation for cardio-respiratory failure
• Diagnostic evaluation for snoring versus obstructive sleep apnea
• Polysomnography is the gold standard for diagnosis
Treatment:
• Adenotonsillectomy-treatment of choice
• Inpatient post-operative monitoring
• Re-evaluate for residual obstructive sleep apnea (polysomnography with continuous positive airway pressure titration)

Source: From Ref. 4.

Clinical guidelines have recently been formulated for the diagnosis and management of obstructive sleep apnea in children (Table 8) (4). A history of snoring, presence of adenotonsillar hypertrophy, and sleep disturbance provide clinical clues to the presence of obstructive sleep apnea. Overnight polysomnography is the diagnostic study of choice and should be interpreted using age-appropriate criteria for sleep-disordered breathing. In older children with repeated arousals and sleep fragmentation due to sleep-disordered breathing (upper airway resistance syndrome), the multiple sleep latency test is helpful in assessing the impact of sleep disturbance on daytime alertness.

Adenotonsillectomy is often adequate treatment for uncomplicated obstructive sleep apnea in children. Continuous positive airway pressure (CPAP) therapy and bi-level positive airway pressure (BiPAP) therapy are necessary in selected individuals (see Chap. 6). High-risk patients with craniofacial structural abnormalities or concomitant medical or neurological disorders should be evaluated by sleep disorder specialists for residual or refractory sleep problems.

Periodic Limb Movement Disorder

Periodic limb movement disorder is characterized by intermittent, stereotypical movements of one or more extremities occurring after sleep onset, often resulting in insomnia or excessive daytime sleepiness. The disorder has a genetic predisposition and is influenced by age, medical problems (iron deficiency status), and medications (tricyclic antidepressants, selective serotonin reuptake inhibitors, and withdrawal from sedatives and anticonvulsants). A history of restless legs syndrome is often reported in adult first-degree relatives. Periodic limb movement disorder may also coexist with other primary sleep disorders, including narcolepsy and obstructive sleep apnea. Children

with this disorder are noted to have similar daytime symptoms to attention deficit-hyperactivity disorder. Sometimes, the soreness or discomfort in the extremities experienced by children with periodic limb movement disorder is attributed to growing pains. Indeed, caregivers and clinicians must maintain a high index of suspicion to diagnose periodic limb movement disorder in children presenting with attention deficit-hyperactivity disorder, growing pains, or a family history of restless legs syndrome.

A diagnosis of periodic limb movement disorder is confirmed by overnight polysomnography. Study accuracy can be increased by utilizing additional electromyography (EMG) recordings, since the movements show considerable variation in location and frequency between sides and extremities. Severity of disease correlates with low serum and cerebrospinal fluid ferritin levels. Decreased dopaminergic transmission is postulated, as iron is a cofactor in dopamine synthesis. Iron supplementation, both in oral or parenteral forms, reduces the severity of the disorder. Dopamine agonists are also used in the treatment of this disorder. Please see Chapter 4 for more details on periodic limb movement disorder.

Parasomnias

Parasomnias are reviewed at length in Chapter 8. In general, disorders of arousal are the most common parasomnia in children, decreasing in intensity and frequency with age (5). Enuresis and bruxism (teeth grinding) are examples of non-state-specific parasomnias, while night terrors, confusional arousals, and nightmares are state-specific with characteristic features (Table 9).

Parasomnias may be precipitated in susceptible individuals (secondary parasomnias) by arousals or state transitions due to obstructive sleep apnea and periodic limb movement disorder, with reduction or resolution of symptoms after treatment of the underlying primary sleep disorder. Nocturnal seizures, headaches, dystonic disorders, and acid-reflux disease should also be considered in the differential diagnosis of secondary parasomnias.

Table 9 Nocturnal Arousals: Clinical Features of Common Parasomnias

Nightmares	Confusional arousals	Night terrors
Later in sleep period	Early to mid sleep period	Early to mid sleep period
Occur in preschool/ schoolage children	Common in preschool and school age children	Occur in toddlers and preschool age children
Occur in REM sleep	Occur in NREM sleep	Occur in NREM sleep
Lucid on awakening	Confused on awakening	Difficult to arouse
Vivid dream imagery	Disoriented and agitated	Screaming, terrified look
Easily comforted	Increased agitation with comfort measures	Unable to comfort

Abbreviations: REM, rapid eye movement; NREM, nonrapid eye movement.

Table 10 Indications for Polysomnography in Patients with Parasomnias

- Violent sleep-related behavior with potential for injury
- Atypical or unusual parasomnias
- Suspicion of nocturnal seizures
- Failure of conventional therapy
- Excessive daytime sleepiness
- Suspicion of sleep disorder (obstructive sleep apnea or periodic limb movement disorder)

Parasomnias are often more distressing to the parent than the child. In such situations, education and reassurance may suffice, since most parasomnias resolve with increasing age. In some instances, however, further evaluation is indicated (Table 10). In patients with coexisting medical or neurological disorders, a low threshold for evaluation is appropriate, since the underlying disorders and/or the medical treatment may affect or be influenced by sleep.

Nocturnal Seizures

Seizures occurring during sleep pose special challenges at all ages (Chap. 8). A clear description of the events is the key feature to the diagnosis. However, most children are not under direct observation at the time of the seizure, and hence, there may be few, if any, witnesses to the actual onset of the event. Typically, the child may not recall anything unusual but appears tired on awakening. Sleep-related injury, intermittent enuresis, or headaches are other clues to nocturnal seizures. Two childhood-related forms of nocturnal epilepsy are benign epilepsy with centrotemporal spikes (benign rolandic epilepsy) and benign occipital epilepsy of childhood.

Children with benign epilepsy with centrotemporal spikes present with a characteristic sequence of symptoms. They awaken from sleep with facial twitching or grimacing associated with increased salivation, choking sounds, and slurred speech. They appear alert during the event. The child may signal to the caregivers during the event, and can recall the episode afterward. Occasionally, the child wakes up in the morning, notes excessive drooling on the pillow, and appears to have difficulty talking. Rarely, generalized convulsive seizures are noted. The diagnosis is confirmed with an EEG (Fig. 1), which has a characteristic pattern of sleep-related epileptic abnormalities in the centrotemporal regions. A familial tendency is well recognized, and the seizures usually subside in the teenage years. Antiepileptic therapy (carbamazepine, gabapentin) is individualized based on frequency and type of seizures.

In benign occipital epilepsy of childhood, the nocturnal seizures often resemble, and are thus mistaken, for migraine headaches. The child may

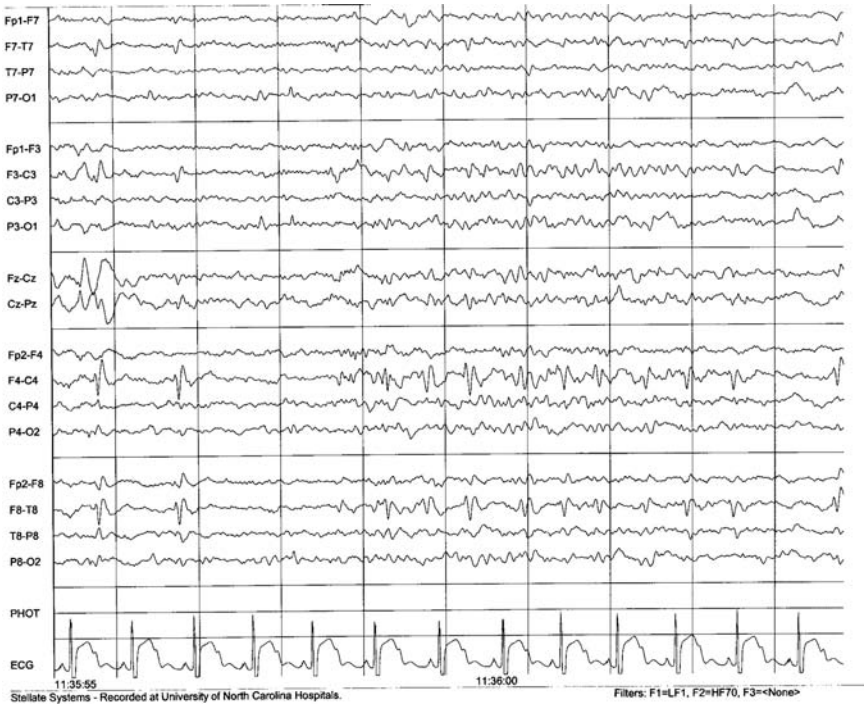


Figure 1 Epileptiform pattern in benign epilepsy with centrotemporal spikes (benign rolandic epilepsy).

wake up from sleep with nausea and emesis, reporting visual hallucinations and headaches. Following the event, the child returns to sleep. Unlike migraines, however, children with this type of nocturnal seizure will exhibit epileptic abnormalities in the occipital region, with the discharges being more evident after sustained eye closure or after sleep onset. The seizures subside with age, and are generally responsive to antiepileptic medications used for partial-onset seizures (e.g., carbamazepine).

Sleep Offset Disorders

The transition between sleep and wakefulness usually occurs over a brief period of time. If sleep is insufficient or fragmented, sleep offset may be delayed or associated with a variety of symptoms. The child's mood, behavior, and activity in the initial hour after awakening are key clinical clues to the restorative effects of the overnight sleep period.

Sleep offset disorders may also hint at underlying primary sleep disorders. Nightmares and sleep paralysis are REM-sleep-related disorders that occur at sleep offset. Children with periodic limb movement disorder report

soreness or stiffness in the limbs after awakening. Headaches at sleep offset may be related to hypoventilation during sleep.

Nightmare Disorder

Most children experience occasional frightening dreams, and respond to reassurance and comforting measures by caregivers. Common features of nightmares are outlined in Table 9. If children experience frequent nightmares, attention to potential triggers as well as behavioral therapy may be needed. In children with sleep apnea, nightmares may signal REM-related respiratory events causing disturbing dreams and arousals. Nightmares and sleep disturbances can persist in children with severe psychopathology or post-traumatic stress disorder, making referral to a specialist necessary.

Recurrent Isolated Sleep Paralysis

Sleep paralysis is the persistence of REM atonia into wakefulness, causing a transient inability to move. This experience often frightens the child. Recurrent isolated sleep paralysis occurs occasionally in young children. Since REM atonia does not affect respirations or vision during wakefulness, the child is unable to communicate the distress associated with sleep paralysis. Fortunately, sensory stimulation (touch, voice) terminates the event. Sleep paralysis is likely to occur more often at sleep offset in the normal sleep cycle, but is observed at sleep onset in narcolepsy, due to sleep-onset REM periods. Pharmacotherapy is usually not necessary.

Sleep Inertia

The process of sleep offset occurs over several minutes, leading to a gradual increase in alertness, interaction, and physical activity. Normally, children who are well rested resume activities within a relatively brief period after arousal. If sleep phase, amount, or quality is altered, sleep inertia persists into the waking period. Despite repeated attempts at arousal, the child tries to return to sleep, either in the usual sleeping area or during morning activities. The persistence of sleep inertia into the waking hours is often accompanied by wake-period dysfunction, as noted below. The treatment of sleep inertia is individualized based on the cause of the sleep disturbance. For instance, increasing sleep amount will reduce sleep inertia in a child with inadequate sleep, and attention to sleep phase will reduce sleep inertia in delayed sleep phase disorder.

CLINICAL APPROACH: THE INBED PROTOCOL

A busy practitioner can rapidly evaluate sleep disorders using a protocol with broad clinical applications. The INBED protocol is a clinical aid addressing the various components of a sleep disorders evaluation (Table 11). The acronym is designed to take into account individual sleep characteristics,

Table 11 The INBED Protocol

I—Individual sleep features (memory aid: FAQ)
Sleep phase (F)
Sleep amount (A)
Sleep quality (Q)
If a sleep disorder is present, proceed to next step:
N—nature → Biologic factors → Behavioral interventions
N—nurture → Environmental factors → Environmental modifications
N—neither → Diagnostic studies → Diagnosis and treatment

biologic–environmental interactions, and various treatment approaches. It also functions as a screening tool for office management and referral decisions.

I—Individual Sleep Assessment (Sleep Phase, Amount, and Quality)

The first step of the clinical evaluation is focused on assessing the child's sleep patterns. The three major aspects of sleep (phase, amount, and quality) are reviewed along with the impact of the sleep disturbance on daytime functioning. Sleep questionnaires, sleep diaries and logs, and caregiver/school personnel reports are useful aids in this portion of the assessment. If this part of the evaluation does not disclose any significant problems, a sleep disorder may not exist and efforts should be geared toward education of caregivers regarding normal pediatric sleep patterns.

A common clinical situation uncovered during this stage of the evaluation is a mismatch between parental expectations and age-appropriate sleep patterns in young children. In children who require below average amounts of sleep, parents should be counseled to restrict bed times to match sleep need. A sleep log is initially used to calculate average sleep need and sleep phase. After determining family preferences, time in bed and sleep period are determined. The sleep pattern can be reinforced with environmental modifications (activities/meals/medications). An example of this approach is outlined in Figure 2. If a parental concern is validated, the clinician can proceed to the next aspect of sleep evaluation.

N—Nature and Nurture (Biologic and Environmental Influences on Sleep)

Sleep complaints arising from biologic factors, as outlined above, may be related to gender, growth phase, and genetic factors that determine the

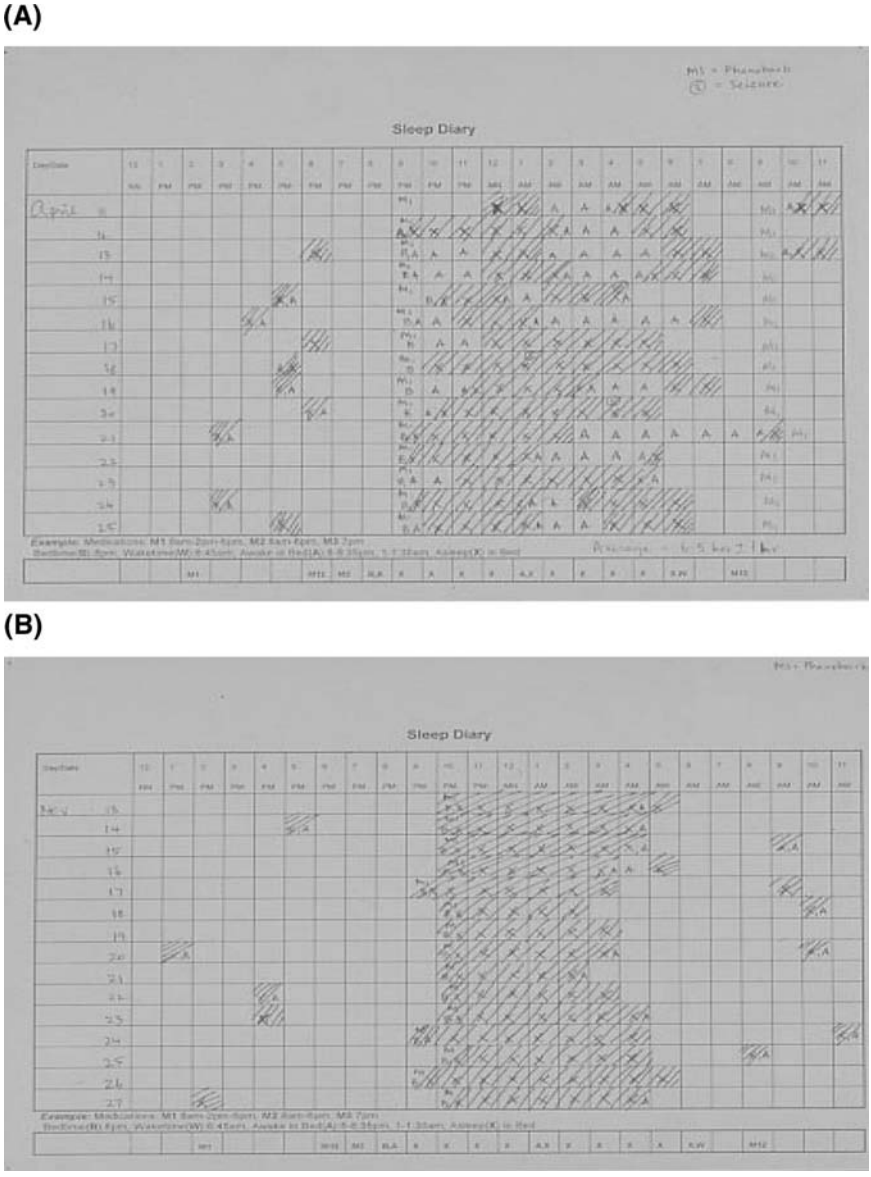


Figure 2 (**A**) Sleep patterns in a child with a below-average sleep need (6.5 ± 1 hr). (**B**) Effect of matching sleep period to sleep need.

maturation of the sleep–wake cycle. If the disorder is primarily biologic in nature, the natural history of the disorder is helpful in determining both the need for, and duration of, the intervention (e.g., treatment of nocturnal

enuresis). Environmental influences of sleep setting, socioeconomic factors, and stressors can be recognized and modified when they play a major role in the sleep disorder (e.g., sleep-onset association disorder is amenable to modification of sleep transition sequence and environment). If neither the biologic nor the environmental factors explain the clinical concerns, the clinician can proceed to further diagnostic evaluation and treatment or refer the patient to a specialist. The next aspect of the INBED protocol focuses on the treatment approaches available for management of sleep disorders.

B—Behavioral Therapy

Behavioral therapy is useful in several pediatric sleep disorders. The clinician can provide office-based services for simple interventions and utilize pediatric psychological and counseling services in complex disorders.

Among the behavioral approaches used in managing sleep disorders, anticipatory (scheduled) awakening and some counseling services can be performed by clinicians, whereas biofeedback and desensitization techniques often require additional expertise.

Anticipatory awakening is a nonpharmacologic technique to manage arousal parasomnias in young children, particularly those with frequent sleep terrors. The caregivers document the time of occurrence of the sleep terrors in a diary. After the pattern of arousals is established, the caregivers awaken the child 15–30 minutes before the expected time of the event. The child may return to sleep afterward. The behavioral intervention is maintained for several nights, reducing the arousal parasomnias. The mechanism is thought to possibly function due to learned self-arousals and the resetting of the arousal patterns. The effect of the intervention is variable in efficacy and duration, but may be repeated if an initial positive response is noted.

Several other behavioral interventions are available, but detailed descriptions are beyond the scope of this chapter. Biofeedback has been used in the management of anxiety disorders, migraine headaches, and pain syndromes that interfere with sleep. Although this service may not be widely available, certain aspects of biofeedback are utilized in devices that are commonly available, e.g., bell-and-pad systems for enuresis. Biofeedback is often combined with some form of counseling regarding attention to sleep hygiene and elimination of sleep-disruptive behavioral patterns. Desensitization techniques may be utilized in specific situations, including setting up sleep studies and the use of face masks for obstructive sleep apnea.

E—Environmental Modifications

If the clinical assessment reveals normal biologic function and uncovers environmental influences accounting for the sleep disorder, treatment is geared to modifying the sleep environment. Often these modifications involve

the entire family's schedules and preferences, requiring parental counseling and cooperation for a successful outcome.

Sleep setting is a largely modifiable environmental influence that can assist or hinder sleep. Attention to sleep surface, ambience (heat, humidity, and "hum"), and comfort is essential to promoting sleep onset. In addition, parental roles in sleeping arrangements (co-sleeping, sleep-onset associations) can be addressed to minimize sleep disruption for children.

Social dynamics may result in disruptive environmental influences. Choice of diet and entertainment, sleep times, late-evening activities, and other aspects of sleep hygiene are often modeled after peer or parental choices. These issues are best addressed by education and counseling of the entire family unit. Changes in school, daycare, or domestic schedules are often a precipitating factor for sleep disruption in children, and parents should be advised accordingly. The child's sleep maybe adversely affected in households with issues of domestic violence, drug abuse, and unsafe housing, and social support services may need to be mobilized to address these influences.

D—Diagnostic Evaluation of Sleep Disorders

When the child's sleep disorder does not involve readily identifiable biologic or environmental factors, the clinician can choose to proceed with a diagnostic evaluation or referral to a specialist. The choice of diagnostic studies is dictated by the type and timing of clinical symptoms that require evaluation. In children with disruption of the nocturnal sleep period, overnight polysomnography is the diagnostic procedure of choice (see Chap. 2). The overnight polysomnogram helps to assess sleep architecture (stages, cycles, and continuity of sleep) and is the study of choice for the diagnosis of obstructive sleep apnea and periodic limb movement disorder. In children with symptoms of obstructive sleep apnea that persist after upper airway surgical evaluation and intervention (e.g., adenotonsillectomy), CPAP titration can be performed during polysomnography (see Chap. 6). The study can also be modified to assess parasomnias and nocturnal seizures in specific instances. Some circumstances require combining the polysomnogram with a multiple sleep latency test.

The multiple sleep latency test is an objective measure of sleepiness during the day, and has been validated in older children and adolescents (see Chap. 2). It consists of 5 naps at two-hour intervals, with the first nap commencing two hours following awakening. In addition to assessing the presence and extent of daytime sleepiness, the test documents patterns of sleepiness across the day. It is used to confirm the impact of nocturnal sleep disruption and support a diagnosis of narcolepsy.

Video monitoring of the child is helpful, both at home and during evaluation for seizures and parasomnias. The videos can help uncover subtle clinical manifestations, support parental observations, identify sleep disorder

severity, and provide additional details in events with partial or poor recall. In some cases, the videos are helpful for educating parents regarding the importance of sleep environmental modification (e.g., sleep disruption due to cosleeping). In the sleep laboratory, infra-red cameras are used to minimize sleep disruption due to video monitoring.

Actigraphy is helpful in the evaluation of certain sleep disorders (see Chap. 2). In this procedure, a "wrist-watch"-type device is used to assess rest–activity patterns in children with irregular sleep patterns. Actigraphy is helpful in objective documentation of sleep patterns over an extended period of time. It documents sleep phase, sleep amount, and sleep continuity. Actigraphy may also be used to assess the effect of an intervention. Since this is a noninvasive procedure, it is well-tolerated by all age groups.

CONCLUSION

The maturation of the sleep–wake cycle and the influence of biologic and environmental influences play a role in understanding normal childhood sleep patterns. Transition from wakefulness to sleep may be facilitated by utilizing the approach described in the SLEEP acronym (Table 4). A systematic approach to sleep disorders in children can distinguish between children who need diagnostic evaluation from those who are likely to respond to behavioral or environmental therapy. The INBED protocol (Table 11), outlined above, is a useful clinical tool for busy practitioners who need to make decisions about appropriate office-based intervention and referrals to sleep specialists in specific instances.

REFERENCES

1. Iglowstein I, Jenni, OG, Molinari L, Largo RH. Sleep duration from infancy to adolescence: reference values and generational trends. Pediatrics 2003; 111: 302–307.
2. Anders TF, Sadeh A, Appareddy V. Normal sleep in neonates and children. In: Ferber R, Kryger M, eds. Principles and practice of sleep medicine in the child. Philadelphia: W. B. Saunders, 1995:7–18.
3. American Academy of Sleep Medicine. International Classification of Sleep Disorders: Diagnostic and Coding Manual. 2nd ed. Westchester, Illinois: American Academy of Sleep Medicine, 2005.
4. Section on Pediatric Pulmonology, Subcommittee on Obstructive Sleep Apnea Syndrome. American Academy of Pediatrics. Clinical practice guideline: diagnosis and management of childhood obstructive sleep apnea syndrome. Pediatrics 2002; 109:704–712.
5. D'Cruz OF, Vaughn BV. Parasomnias—an update. Semin Pediatr Neurol 2001; 8(4):251–257.

11

Special Topics in Sleep

Maha Alattar

Department of Neurology,
University of North Carolina–Chapel Hill,
Chapel Hill, North Carolina, U.S.A.

Special Topics	***Diagnoses***
Sleep and women: menarche, menopause, and pregnancy	*Alzheimer's disease and other dementias*
Sleep and the elderly	*Down syndrome*
Sleep and dementia	*Depression*
Sleep and Down syndrome	*Generalized anxiety disorder*
Sleep and psychiatric illness	*Nocturnal panic attack*
	Posttraumatic stress disorder

INTRODUCTION

This chapter covers sleep disturbances in special populations such as women and the elderly, as well as special topics including sleep in dementing illness, Down syndrome, depression, anxiety and panic attacks, and posttraumatic stress disorder. Although the symptoms are diverse, these disorders share a common approach to their management and treatment.

Difficulty initiating and maintaining sleep as well as excessive daytime sleepiness and fatigue are common symptoms of sleep disorders in these populations. This diverse symptomatology represents physiological alterations in sleep–wake mechanisms due to age, hormonal changes, psychosocial issues, and central nervous system disease. These alterations, in turn, result in disorders such as obstructive sleep apnea, restless legs syndrome, circadian rhythm disturbances, and insomnia. Therefore, the initial approach to the diagnosis and treatment of sleep disorders in these populations should focus on symptoms as a basis for a differential diagnosis. For example, difficulty initiating sleep may be due to a host of issues, including mood disorders, restless legs syndrome, pain, or poor sleep hygiene. Treatment and management would therefore be driven by symptoms.

Throughout this chapter, reference will be to abnormalities in respiration during sleep. The term *sleep-disordered breathing*, encompasses a wide variety of disorders characterized by abnormal nocturnal respiration, including snoring, obstructive sleep apnea (''sleep apnea''), upper airway resistance syndrome, central sleep apnea, central hypoventilation, and other nonobstructive hypoventilation disorders. For the purposes of this chapter, sleep-disordered breathing, obstructive sleep apnea, and sleep apnea are used interchangeably.

SLEEP AND WOMEN: MENARCHE, MENOPAUSE, AND PREGNANCY

Gender and age significantly influence sleep and perception of sleep. This is likely due to hormonal and psychosocial influences. Gender differences become more obvious with the onset of puberty but continue even into the senior years. Table 1 lists general sleep disorders that affect women. Younger women experience sleep changes across their menstrual cycle. These changes are most notable during premenstruation and menstruation. The most remarkable gender influence on sleep occurs during the perimenopausal and postmenopausal states, in which sleep complaints indicating disorders of sleep physiology become most prevalent. Sleep awareness is also important when considering women's sleep because the ovulatory cycle is associated with changes in perception of sleep quality. Indeed, women are more likely to present with insomnia in the setting of preserved sleep architecture.

Table 1 Common Sleep Disorders in Women by Menstrual/Reproductive Phase and Symptom

	Symptom	
Menstrual/ reproductive phase	Hypersomnia	Insomnia
Menarche	Depression or social anxiety	Delayed sleep phase disorder
	Substance abuse (alcohol, drugs)	Depression or social anxiety
	Insufficient sleep syndrome	Substance abuse (nicotine, drugs)
	Obstructive sleep apnea	Poor sleep hygiene (late bedtime)
		Obstructive sleep apnea
Pregnancy	Obstructive sleep apnea	Restless legs syndrome
	Nocturnal hypoventilation	Obstructive sleep apnea
	Periodic limb movements in sleep	Disrupted sleep (discomfort, emesis, nocturia)
	Disrupted sleep (discomfort, emesis, nocturia)	
Menopause	Obstructive sleep apnea	Obstructive sleep apnea
	Depression	Restless legs syndrome
	Periodic limb movements in sleep	Depression
	Medications side effects	Generalized anxiety disorder
	Hot flashes	Substance abuse (nicotine, caffeine)
	Generalized anxiety disorder	Medications (bronchodilators,
	Substance abuse (alcohol)	beta-blockers, corticosteroids)

Gender difference in sleep physiology is demonstrated by sleep-disordered breathing. Women have more subtle presentations of obstructive sleep apnea and are less likely than men to exhibit the classic presentation of the disorder (witnessed apneas and heavy snoring). Rather, fatigue and mood changes are often the only manifestations of the disease in women (1). Certain features of sleep apnea demonstrate gender bias. For instance, women's respiratory disturbances cluster in rapid eye movement (REM) sleep more than men (2). Although the frequency and severity of sleep apnea remains higher in men than women (3), its prevalence increases in post-menopausal women reaching that of men. Indeed, the menopausal transition is significantly associated with an increased risk of the disorder, independent of age, body mass index, smoking, and other lifestyle factors (4).

The quality of sleep at menopause is affected by a number of factors, including hormonal, vasomotor, and psychosocial issues. Hormonal changes likely have the strongest influence on breathing physiology during sleep. Both progesterone and estrogen contribute to the regulation of hypoxic ventilatory drive and stimulation of inspiratory muscles (5). These hormones also play a role in modulating central nervous system neurotransmitters that are part of normal sleep physiology. Therefore, declining levels of these hormones may compromise respiratory physiology and other sleep mechanisms. Although a number of small clinical trials reported a beneficial effect of hormone replacement therapy on sleep-disordered breathing, these effects were minimal and long-term effects are unknown (6–8). Therefore, hormone replacement therapy is not an alternative treatment to the mainstream treatment of sleep apnea in postmenopausal women.

In this section, we discuss sleep changes relating to the female population. Sleep complaints vary depending on age. A young woman's sleep complaints often relate to the menstrual cycle or pregnancy. Older women, on the other hand, typically experience sleep disturbance as a result of aging and hormonal changes during menopause. It's important to note the social setting of each age population, since this plays a significant causative role in sleep disturbance. The management of each group requires recognition of hormonal influences that tend to fluctuate, or in the case of the menopausal population, attenuate or diminish. Treatment may involve more than sleeping pills. Management of secondary causes of sleep disturbances through nonpharmacological interventions, as is often the case with pregnancy-related discomfort or menopausal insomnia, is an important part of a comprehensive treatment plan. Therefore, treatment is multifactorial and includes a multidisciplinary approach with attention to social circumstances, age, and hormonal changes.

Sleep Across the Menstrual Cycle

Sleep is influenced by the phases of the menstrual cycle (menstruation, follicular, early luteal, and late luteal). Mood and subjective sleep fluctuate throughout the menstrual cycle. Women may note sleepiness during the early luteal phase, but during the late luteal phase, they present with insomnia that is often exacerbated during menses. Ovulation is also characterized by a transient insomnia. These changes may be related to cyclic changes in the sleep–wake rhythm. Metabolic rate and body temperature affect sleep during different phases of the cycle. In a healthy individual, sleep quality is dependent on circadian fluctuations of amplitude and phase of core body temperature. In the luteal phase, core body temperature amplitude is decreased and phase is delayed, explaining the decreased alertness observed late in this phase (9). Increased sleepiness in the early luteal phase is associated with increased slow-wave sleep and melatonin levels during the

day (10) and decreased slow-wave sleep during the night (11). The effect of progesterone as a respiratory stimulant is believed to have a protective effect among premenopausal women from apnea during sleep. Although significant changes in progesterone levels are present across the menstrual cycle, there are no significant changes in breathing parameters (12).

Sleep and Menarche

The onset of menarche elicits many changes in young women, resulting in alterations in sleep propensity and habits. The clinician should inquire about sleep patterns, daytime sleepiness, classroom performance, and parent's observations and expectations. Poor academic performance can provide clues to an underlying sleep disorder. Indeed, shortened total sleep time, irregular sleep/wake schedules, late bed and rise times, and poor sleep quality are negatively associated with academic performance in adolescents from middle school through the college years (13).

Delayed sleep phase syndrome, common amongst adolescents, is characterized by difficulty falling asleep at desired times. Once removed from a strict schedule (e.g., on weekends), these individuals demonstrate a normal sleep length and pattern and wake up refreshed. These people are known as evening types. The desired wake time is often delayed, occurring at noon or later and causing significant social difficulty on school days. These individuals tend to nap frequently and complain of daytime sleepiness. They also have difficulty paying attention in class, poor school achievement, increased physical injuries, and emotional problems (14). The clinician should counsel the patient on proper sleep hygiene, including strict bed and wake times, avoidance of after-school naps, warm evening showers, and stimulant avoidance (caffeine and nicotine). Bright light therapy in the morning is especially helpful to reset the biological clock by progressively advancing the teenager's sleep tendency.

Depression in young girls increases as compared to boys with the onset of puberty and menarche (15). This often leads to sleep problems such as sleep onset or maintenance insomnia or hypersomnia. Psychosocial influences and changes in hormonal physiology play causative roles. Counseling and psychiatric evaluation is warranted before starting antidepressants in teenagers. The rise of obesity occurring during the menarche years confers an increased risk of sleep-disordered breathing, making obesity prevention important during the teenage years. A sleep evaluation should be part of the routine check up of pubertal females.

Sleep and Pregnancy

Pregnancy is associated with sleep disturbances such as insomnia, frequent awakenings, sleepiness, snoring, and restless legs syndrome. Contributing factors include hormonal alterations and physical changes from the growing

Table 2 Measures to Improve Sleep in Pregnancy

- Sleep on the side
- Warm foot bath in the evening or prior to bedtime
- Avoid eating or drinking close to bedtime to avoid reflux and frequent urination
- Sound therapy (music) for relaxation
- Avoid sleeping aids (medications)

fetus. Psychosocial factors and anticipatory issues can play a role. During the first trimester, women complain of insomnia and decreased sleep.

Sleep is normalized during the second trimester, with resumption of poor sleep in the third trimester. Both sleep-disordered breathing and restless legs syndrome are most notable during the third trimester, a time when clinicians should pay particular attention to sleep issues. Daytime symptoms of fatigue, tiredness, and excessive sleepiness as well as nighttime insomnia, frequent awakenings, and pain are common complaints (16). Primagravidae women have a higher risk of fatigue and sleep disturbances than their multigravidae counterparts (17). Frequent urination, hip or lower back pain, heartburn, and nausea/vomiting are frequent complaints contributing to sleep disturbance in pregnancy, especially during the third trimester. Other underlying medical conditions contributing to sleep disruption, including pain and nausea or vomiting, should be managed accordingly. General sleep measures in pregnancy can facilitate sleep onset and maintenance and alleviate discomfort associated with pregnancy (Table 2).

Sleep-Disordered Breathing in Pregnancy

Pregnancy is associated with significant changes in respiratory physiology that can worsen existing sleep disorders. Indeed, there is a well-documented increased incidence of snoring during pregnancy (18). During the third trimester, alterations in functional residual capacity, residual volume, and increased alveolar–arterial oxygen differences account for these changes. Reduction in supine cardiac output leads to maternal oxygen desaturation during sleep, putting these patients at risk for nocturnal hypoventilation (19). These changes are related to hormonal influences, increased uterine size, and weight gain. Habitual snoring is more common than fulminant apneas or hypopneas. Although sleep-disordered breathing has been reported in pregnant women, the true incidence of obstructive sleep apnea is unknown due to a lack of longitudinal epidemiological studies. Clinicians must recognize sleep apnea in pregnancy, as maternal and fetal complications such as pre-eclampsia, maternal hypertension, and intrauterine growth retardation (20) can be avoided with the use of continuous positive airway pressure (CPAP) therapy (21). Pregnant women with pre-existing obesity are

at higher risk of developing sleep apnea than women with normal weight prior to conception (22). Weight gain during pregnancy has unknown effects on sleep apnea risk.

Management of pregnant patients with sleep apnea begins by inquiring about changes in sleep patterns, levels of sleepiness, insomnia, and nocturnal awakenings. Special attention should be given to those with significant pregnancy-related weight gain or maternal–fetal complications such as pre-eclampsia. In these cases, clinicians should refer to a sleep center for clinical and polysomnographic evaluation. If obstructive sleep apnea is present, then nasal CPAP a safe and effective therapy in pregnancy, should be instituted (23). Six weeks following delivery, a repeat baseline polysomnogram is indicated to evaluate for persistent sleep apnea.

Restless Legs Syndrome in Pregnancy

Restless legs syndrome prevalence increases to 20% during pregnancy (24), significantly higher than the general population (25). This disorder is associated with sleep-onset insomnia, and treatment involves ruling out associated conditions in pregnancy, most notably iron deficiency anemia. In the general population, 80% of people with restless legs syndrome have associated periodic limb movements in sleep. Therefore, pregnant women should be questioned regarding nocturnal leg jerks or daytime sleepiness. If present, polysomnography is warranted to look for associated arousals and sleep disruption indicative of periodic limb movement disorder. Pharmacological treatment options are limited, as specific recommendations regarding the safety of dopaminergic medications (pramipexole, pergolide, ropinirole) in pregnancy do not exist (26).

Sleep Postpartum

The postpartum period affects the sleep of both the mother and father. New parents can be reassured that sleep will return to normal three months after delivery (27). Short-term hypnotics can be helpful during this time. New parents may take child care ''shifts,'' allowing each parent some dedicated sleep time. New parents may also utilize family or close friends to assume some of the child care burden allowing them to meet their sleep needs.

Sleep and Menopause

Peri- and postmenopausal women report more dissatisfaction with their sleep than premenopausal women (28). Indeed, menopause is associated with increased sleep disruption as well as daytime fatigue and sleepiness. These complaints are more significant among women not taking hormone replacement therapy (29). The most common clinical complaints are difficulty falling asleep and frequent awakenings, although vasomotor symptoms and psychosocial issues are also problematic. The perimenopausal

state is associated with psychosocial stressors and life changes such as children leaving home, caring for aging parents, and the death of a parent or spouse. The menopausal transition is associated with changes in ovarian function and fluctuations in hypothalamic–pituitary–ovarian hormones. Decreased estrogen and progesterone exerts effects on circadian rhythms and respiratory physiology. As always, the clinician should be vigilant for occult sleep disorders, such as obstructive sleep apnea, periodic limb movement disorder, and restless legs syndrome.

Menopause and Insomnia

Insomnia, as identified by difficulty both falling and staying asleep, affects many women in midlife. Perimenopausal women experience more frequent awakenings and disturbed sleep than premenopausal women (30). Contributing factors include psychosocial stressors, increased prevalence of mood disorders, medication side effects (Table 3), emergence of sleep-disordered breathing, and hot flashes. Evaluating sleep-onset insomnia requires assessment for restless legs syndrome, mood disorders, stimulant abuse (caffeine, nicotine), hot flashes, and poor sleep hygiene. Treatment should be tailored to the cause. Counseling, behavioral therapy, and sleep hygiene recommendations comprise the first line of therapy (Table 4). Short-term sedative-hypnotic medications can break the cycle of insomnia. Short-acting non-benzodiazepine, benzodiazepine receptor agonists such as zolpidem, zaleplon, and eszopiclone are helpful in this regard. Obstructive sleep apnea must be ruled out in patients with frequent awakenings at night prior to initiation of medications. In women with hot flashes and insomnia, consider treatment with hormone replacement therapy, selective serotonin reuptake inhibitors (paroxetine, fluoxetine), or gabapentin. Table 5 provides some helpful hints when approaching the patient with intractable insomnia.

Sleep-Disordered Breathing During Menopause

Women are generally protected from sleep-disordered breathing during their reproductive years. Following menopause, levels of progesterone, a

Table 3 Substances and Medications that Affect Sleep

- Stimulants: caffeine, nicotine, theophylline, fluoxetine, bupropion
- Sedatives: antidepressants (venlafaxine, amitriptyline, doxepin, mirtazapine)
- Hypnotics: benzodiazepines (alprazolam) and non-benzodiazepines (zolpidem, zaleplon, eszopiclone)
- Antihypertensives: beta-blocking agents
- Antiepileptics: topiramate, carbamazepine, valproic acid, zonisamide, phenytoin
- Withdrawal from stimulants can cause sleepiness, while withdrawal from sedative-hypnotics may cause insomnia

Table 4 Management of Insomnia in Postmenopausal Women

- Morning exercise
- Social interaction during the day
- Bright light (sunlight or artificial) during the day
- Hot bath in the evening
- Stimulant avoidance (caffeine, nicotine)
- Hot flashes: hormone replacement therapy, fluoxetine, paroxetine, gabapentin, venlafaxine, clonidine
- Non-benzodiazepine hypnotics (adjunctive, brief treatment): zolpidem, zaleplon, eszopiclone

respiratory stimulant, decrease, making women more susceptible to the disorder. Other contributing factors include increased age, weight gain, and midlife changes in facial and oral morphology. A polysomnogram should be performed when symptoms of obstructive sleep apnea are present, such as snoring, daytime sleepiness, frequent awakenings, leg jerks, night sweats, and nocturnal gasping. Continuous positive airway pressure remains the mainstream therapy of choice for sleep apnea. Although data on hormone replacement therapy for sleep-disordered breathing are promising, currently it is not an alternative to CPAP treatment as the long-term effects are unknown (8).

Hot Flashes and Sleep

Hot flashes are thermoregulatory disturbances causing major sleep disruption in menopausal women. Hypothalamic temperature and sleep-regulating centers are closely related, allowing concurrent disruption by hormonal changes. Hot flashes and resulting night sweats are associated with arousals and waking episodes on polysomnography. Treatment with hormone replacement therapy alleviates the vasomotor symptoms, improving subjective

Table 5 Clinical Assessment of Intractable Insomnia

- Assess for inadequate treatment of the psychiatric illness
- Assess for underlying secondary illness (fibromyalgia, chronic obstructive pulmonary disease)
- Review medication list (Table 3)
- Review sleep hygiene
- Review sleep schedule for insufficient sleep
- Assess for substance abuse (alcohol)
- Perform polysomography to rule out sleep disorders (obstructive sleep apnea, periodic limb movement disorder, parasomnia)
- Obtain a sleep diary and wrist actigraphy to confirm the sleep schedule

sleep quality. Other beneficial nonhormonal agents include clonidine, venlafaxine, paroxetine, fluoxetine, and gabapentin. These treatments are helpful in patients with contraindications to hormone replacement therapy (31).

SLEEP AND THE ELDERLY

Sleep problems are common in the elderly (>65 years), largely due to the increased prevalence of sleep disorders with age. Age-dependent changes in sleep quality occur in the context of changing brain physiology with resultant medical/neuropsychiatric illness, ultimately affecting psychosocial interactions and well being. Total sleep time is decreased and both nighttime awakenings and daytime napping increase. Unfortunately, elderly people often fail to mention sleep problems to their primary care provider, believing it's a natural part of the aging process and that treatment is futile.

Sleep disturbance in the elderly is associated with poor health, depression, angina, cardiovascular morbidity and mortality, limitation of activities of daily living, and the use of hypnotics (32). Nighttime sleep problems and daytime sleepiness are associated with an increased risk of falling. Given that obstructive sleep apnea is a known risk factor for vascular pathology and disrupted sleep is associated with daytime dysfunction, early recognition and treatment of sleep disorders in the elderly will not only improve quality of life but also decrease the risk of developing or worsening an already present cardiovascular or cerebrovascular disease.

Age changes both sleep physiology and sleep architecture. Delta (sleep stages 3 and 4) frequency waves in slow-wave sleep decrease both in number and amplitude. This phenomenon has many potential causes, including neurotransmitter loss, alterations in neuronal synchronization, or changes in skull thickness. Sleep architecture reveals reduced REM sleep and increased sleep fragmentation due to frequent arousals or awakenings. Discrepancies between subjective and objective measures of sleep emerge. Overall, sleep in the elderly retains its ultradian nature, cycling between REM and non-REM (NREM), although the cycles become less robust. With aging, nighttime sleep is decreased from the 7.5 hours of the average adult to 5.5–6.5 hours (33). However, the total sleep time during a 24-hour period remains unchanged due to daytime naps.

The most common sleep complaints among the elderly include trouble falling asleep, frequent awakenings, early awakening, awakening unrefreshed, and daytime fatigue or tiredness. Factors contributing to this sleep disturbance include social stressors (living alone, death of spouse, economical hardship), psychiatric illness (depression, anxiety), physical disability, medical illness (pain, cardiovascular and cerebrovascular disease), underlying sleep-disordered breathing, and use of alcohol or medications such as hypnotics or stimulants (Table 3). Insomnia is very common in the elderly, with a prevalence of 36% in men and 54% in women (34). Most

insomnia symptoms are associated with depression, anxiety, or chronic pain, and appropriate recognition and management of the associated medical or psychiatric illness often alleviates the insomnia (35). Sleep-disordered breathing is also very common, affecting >25% of the elderly (36) compared to 4–6% of the general population. The diagnosis may be delayed if symptoms such as frequent daytime napping, poor concentration, fatigue, memory lapses, nocturia, and sexual dysfunction are incorrectly attributed to the aging process. Other sleep disorders of concern in this population include restless legs syndrome and periodic limb movement disorder, as both dramatically increase with age. Epidemiological studies demonstrate a prevalence of 9–20% for restless legs syndrome and 4–11% for periodic limb movement disorder in the elderly (37). Circadian rhythm disorders, including sundowning, as well as parasomnias, such as REM sleep behavior disorder, also increase in prevalence with age.

Assessment of Sleep in the Elderly

The general approach to sleep complaints is described in Chapter 1. This section deals with assessment issues relevant to the elderly with special focus on the impact of comorbid conditions and illnesses. The clinical assessment begins with the sleep history, which allows formulation of a differential diagnosis and provides direction for testing and treatment. The history should ascertain the presence of comorbid illnesses (chronic obstructive pulmonary disease, heart disease, dementia, and pain syndromes) and current medications. Table 6 outlines typical comorbid conditions affecting sleep in the elderly. Common daytime manifestations of sleep disruption include memory impairment, fatigue, and poor concentration. Physical examination should involve both the general and neurological exam with special attention to weight, height, body mass index, neck size, blood pressure, and appearance of the pharyngeal anatomy. The neurological examination should assess for peripheral neuropathy, particularly when restless legs syndrome or periodic limb movement disorder is suspected.

Table 6 Comorbid Conditions Affecting Sleep in the Elderly

- Metabolic: chronic renal insufficiency, liver disease
- Nutritional: B12/folate/iron deficiency
- Neurological: stroke, Parkinson's disease, Alzheimer's disease
- Psychiatric: depression, anxiety
- Cardiac: ischemia, congestive heart failure
- Pulmonary: chronic obstructive pulmonary disease, asthma
- Pain: arthritis, headaches, lower back pain, peripheral neuropathy
- Genitourinary: polyuria, nocturia

Objective sleep evaluations in the elderly include sleep diaries, questionnaires, polysomnography, and occasionally the multiple sleep latency test. The sleep diary is especially relevant in patients complaining of insomnia. Elderly patients often fail to accurately recall their recent sleep habits. By using a sleep diary, patients record information regarding bedtime, rise time, sleep latency, sleep onset, wakefulness, nighttime awakenings, and daytime napping. This information helps the clinician diagnostically and to monitor progress during treatment.

Standardized and validated questionnaires are useful tools to sort out sleep complaints in a primary care setting. The Pittsburgh Sleep Quality Index (Table 7) is a simple and valid tool to assess both sleep quality and disturbance in a clinical setting over a 1-month period (38). A global score of 5 can be used to distinguish good from poor sleepers: the higher the score, the worse the sleep. The Epworth Sleepiness Scale is a validated questionnaire that assesses the likelihood of falling asleep in various situations (see Chap. 1) (39). The Insomnia Severity Index assesses the presence and severity of insomnia (40). Finally, the Minnesota Multiphasic Personality Inventory-2 can be utilized to identify insomnia patients requiring psychotherapeutic intervention (41).

Polysomnography is most relevant in patients suspected of having sleep-disordered breathing. This test should be performed in any elderly patient complaining of snoring, restless sleep, waking up multiple times at night, leg jerking, intractable insomnia, or dream enactment, suggesting an underlying parasomnia. Table 8 provides a symptom-based approach to the differential diagnosis and testing of sleep disorders in the elderly.

Management of Sleep Disorders in the Elderly

Treatment and management of sleep complaints in the elderly should be tailored to the specific disorder. The clinician must engage the patient in the treatment plan and set realistic expectations. Patients requesting medications should understand that they might not be warranted in specific situations. Although general practitioners often use pharmacological interventions when treating sleep disorders, the inappropriate use of sedative-hypnotic medications as first-line treatments can delay the proper diagnosis and produce unwanted side effects such as respiratory depression and daytime drowsiness. An attempt should always be made to diagnose the appropriate sleep disorder before prescribing medications.

Initial management should consider nonpharmacological approaches, not only to avoid unwanted medication side effects, but also to optimize treatment effects. Indeed, elderly patients with primary or psychiatric insomnia often benefit most when psychopharmacological therapy is combined with cognitive-behavioral approaches. Close follow-up to monitor side effects and assess treatment efficacy is crucial to successful therapy. Constant

Table 7 The Pittsburgh Sleep Quality Index

Instruction: The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all the questions.

During the past month:

1. When have you usually done to bed? _____
2. How long (in minutes) has it usually taken you to fall asleep each night? _____
3. When have you usually gotten up in the morning? _____
4. How many hours of actual sleep did you get on a usual night? _____
   (*Note*: This may be different than the number of hours you spend in bed).

5. During the past month, how often have you had trouble sleeping because you	Not during the past month (0)	Less than once a week (1)	Once or twice a week (2)	Three or more times a week (3)
a. Cannot get to sleep within 30 min	0	1	2	3
b. Wake up in the middle of the night or early morning	0	1	2	3
c. Have to get up to use the bathroom	0	1	2	3
d. Cannot breathe comfortably	0	1	2	3
e. Cough or snore loudly	0	1	2	3
f. Feel too cold	0	1	2	3
g. Feel too hot	0	1	2	3
h. Have bad dreams	0	1	2	3
i. Have pain	0	1	2	3
j. Other reason(s) please describe: (include how often you have had trouble sleeping for each reason)	0	1	2	3
6. During the past month, how often have you taken medication (prescribed or "over the counter") to help you sleep?	0	1	2	3
7. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?	0	1	2	3
8. During the past month, how much of a problem has it been for you to keep up enthusiasm to get things done?	No problem at all (0)	Only a slight problem (1)	Somewhat of a problem (2)	A very big problem (3)
9. During the past month, how would you rate your sleep quality overall?	Very good (0)	Fairly good (1)	Fairly bad (2)	Very bad (3)

Table 8 Differential Diagnosis and Testing of Sleep Disruption in the Elderly

Symptoms	Differential diagnosis	Diagnostic tests
Snoring Witnessed apneas Frequent awakenings Night sweats Dry throat Morning headaches Fatigue Daytime sleepiness	Obstructive sleep apnea Upper airway resistance syndrome Central sleep apnea Hypoventilation Cheyne–Stokes respiration	Polysomnography Multiple sleep latency test
Nocturnal leg jerks Daytime sleepiness Insomnia	Periodic limb movement disorder Obstructive sleep apnea	Polysomnography
Urge to move the legs: • Associated with uncomfortable or unpleasant sensations • Occurring when sedentary • Worse at night • Relieved by movement	Restless legs syndrome Neuropathic pain	For restless legs syndrome: Iron indices B12/folate/magnesium For neuropathy: CBC, ESR, CRP, VDRL, ANA, RF, Cryoglobulins, SPEP, UPEP, TSH, HgB A1C Fasting glucose level Oral glucose tolerance test Urinalysis

Abbreviations: CBC, complete blood count; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; VDRL, venereal disease research laboratory test; ANA, antinuclear antibody test; RF, rheumatoid factor test; SPEP, serum protein electrophoresis; UPEP, urine protein electrophoresis; TSH, thyroid stimulating hormone; HgB, hemoglobin.

attention must be paid to the unique physiology of advancing age. Table 9 provides a general approach to improving sleep in the elderly.

Sleepiness in the Elderly

Elderly patients with sleepiness or fatigue often report frequent daytime naps. They often deny their sleepiness, either due to poor recollection or because they believe napping is normal. Hypersomnia often indicates an underlying sleep disturbance causing sleep fragmentation and a reduced total sleep time and sleep efficiency. Failure to recognize sleep disorders in the elderly results in missed opportunities to improve quality of life and cardiovascular, cognitive, and psychiatric health. Prescribing stimulants

Table 9 General Approach to Improving Sleep in the Elderly

- Identify and treat underlying disorders (obstructive sleep apnea, depression, restless legs syndrome, parasomnias)
- Proper sleep hygiene
  - Strict bedtime and wake time
  - Avoid stimulants (caffeine and nicotine)
  - Avoid alcohol and sedative-hypnotics
  - Avoid eating or drinking 3 hr prior to bedtime, except for a light snack
- Relaxation techniques (Yoga) and stress prevention
- Gentle daily daytime exercise
- Bright light exposure during the day (natural sun or increased luminance at home)
- Warm bath in the evening
- Avoidance of bright light close to bedtime

without a good faith effort to investigate for causes of sleepiness is not an acceptable clinical practice.

The medical history of the sleepy elderly patient should search for signs of obstructive sleep apnea including snoring, witnessed apneas, frequent awakenings, night sweats, dry throat, morning headaches, and daytime sleepiness or fatigue. Other relevant questions include poor concentration, memory problems, frequent urination, sexual dysfunction, and depression. The physical exam should focus on the body mass index, neck circumference, and oropharyngeal anatomy. If restless legs syndrome or periodic limb movement disorder is suspected, query the patient regarding leg discomfort and restlessness, nocturnal leg jerks, daytime sleepiness or fatigue, poor concentration, memory problems, or depression. If insufficient sleep is suspected, consider sleep-onset insomnia as a cause and ask about underlying depression, anxiety, and poor sleep hygiene (staying up too late watching TV, frequent late afternoon daytime naps, caffeine consumption). A sleep diary can help establish the habitual sleep schedule.

The clinician should also consider underlying medical illness as the cause of sleepiness in the elderly. Examples include arthritic pain, underlying cardio-pulmonary disease (chronic obstructive pulmonary disease), or neurological disorders (Parkinson's disease). Other contributing factors may include weight gain, menopause, divorce, and death of a spouse. Medication side effects should always be considered in a sleepy elderly subject. Prescription medications such as benzodiazepines or other nonprescription hypnotics (alcohol, benadryl) are commonly used by the elderly with sleep disturbances and often lead to daytime drowsiness. These medications should be avoided in this population. Polysomnography or a multiple sleep latency test may be warranted for diagnostic purposes. Treatment is directed at the underlying pathology. Daytime stimulants such as modafinil and methylphenidate are helpful in compliant sleep apnea patients with residual sleepiness on CPAP.

Monitoring of blood pressure and cardiovascular parameters are important when using these medications.

Insomnia in the Elderly

Insomnia is common in the elderly, especially women. These patients often complain of difficulty initiating sleep at the desired time with frequent awakenings and trouble falling back asleep. Early morning awakenings may also be problematic. Identification of the type and etiology of insomnia is important when prescribing medications. Individuals with insomnia experience high levels of stress with a heightened arousal system when they attempt to sleep. In this section, we divide the symptoms of insomnia into three categories and discuss the differential diagnosis for each. Chronic insomnia will be the focus, as this population is more apt to seek medical attention. Several factors, including medical illness, medications, and psychological and social issues arising with age, often contribute to or exacerbate insomnia. Treatment should be tailored to the individual patient (42).

Sleep-Onset Insomnia

According to the Diagnostic and Statistical Manual of Mental Disorders-IV, insomnia is a frequent symptom of major depression, and treatment often improves the sleep disturbance. Depression is not a natural part of aging; therefore, the goal of treatment is full remission. This can be achieved with appropriate medications and cognitive-behavioral therapy (see Chap. 3) (43). The long-term use of sedative-hypnotics is not advised due to side effects and dependency issues. The elderly who present with benzodiazepine dependency should be tapered off these medications in conjunction with cognitive-behavioral therapy (44). Applying this type of multidisciplinary approach helps reduce benzodiazepine use.

Psychophysiological insomnia is another important cause for sleep disturbance in the elderly. These patients experience racing thoughts and excessive worry regarding their sleep. Poor sleep hygiene often occurs in retirement, a result of late bedtimes (TV viewing, hobbies, etc.) and frequent daytime naps. Problems with the sleep environment, such as excessive noise, a snoring bed partner, and uncomfortable bedding, can also disrupt sleep in the elderly. Sleeping in separate bedrooms, although not optimal for many patients, can resolve some of these issues.

Restless legs syndrome is highly prevalent in the elderly, with severity increasing with age. Dopamine agonists are the treatment of choice and are well tolerated by the geriatric population (see Chap. 4). Benzodiazepines should be avoided, and opiates should be prescribed with caution due to their addictive potential. Arthritic and lower back pain can also cause insomnia, and treatment should focus on pain management rather than

sedative-hypnotics. Table 10 provides a differential diagnosis and treatment strategies for sleep-onset insomnia in the elderly.

Special attention must be paid to the untoward effects of pharmacotherapy in the geriatric population when treating insomnia. The use of hypnotics in the elderly may lead to daytime drowsiness, increasing the risk of cognitive impairment, falls, and motor vehicle accidents. Because of these issues, nonpharmacological interventions such as optimizing sleep hygiene and cognitive-behavioral therapy should always be tried before medications (Table 9). Cognitive-behavioral therapy requires patience and often takes weeks to show an effect. Short-term non-benzodiazepine hypnotics (zolpidem, zaleplon, eszopiclone) can be helpful to bridge this treatment gap. Stress prevention techniques alleviating emotional problems are an integral part of treatment. Comfortable bedding, cool ambient temperature, and noise reduction are important environmental modifications. Gentle daily exercise, preferably in the morning, should be encouraged as it reduces stress and improves sleep architecture (45). Phototherapy is helpful, preferably through natural sun exposure (exercise and eating lunch outdoors, yard work). An alternative means to phototherapy is artificial luminance by using a light therapy box, also known as a Lux Lamp (Lux being a measurement of light). This treatment is effective in patients with seasonal affective disorder. Warm relaxing baths in the evening consolidate sleep and decrease arousals promoting sleep onset and maintenance.

Pharmacological intervention is necessary when treating short-term insomnia, chronic insomnia unresponsive to nonpharmacological therapy, and patients with medical issues such as pain, depression, or anxiety (Table 11). Sedative-hypnotics are useful during the initial phase of cognitive-behavioral therapy. Other medications such as selective serotonin reuptake inhibitors and tricyclic antidepressants are effective in certain patients. Side effects must be monitored as they can cause memory impairment, daytime drowsiness, falls, and motor vehicle accidents. The ideal sedative-hypnotic has a rapid onset of action, duration of effect ending upon awakening, and no effect on respiratory drive. Longer acting medications increase fall risk and hip fractures. Appropriate recommendations include utilizing the lowest dose available for a short period of time (3–4 weeks) with intermittent dosing (2–4 times per week). Discontinuation should involve a slow taper to avoid rebound insomnia. The short-acting rapidly eliminated non-benzodiazepine hypnotics such as zaleplon, zolpidem, and eszopiclone are effective and safe first-line agents for sleep-onset insomnia. Antidepressants including trazodone, nefazodone, and paroxetine can alleviate depression-related sleep disturbance (46). Benzodiazepines such as flurazepam and quazepam have long half-lives (36–120 hours), providing advantageous daytime anxiolytic effects in selected patients with insomnia and anxiety. Caution should be exercised as long-term use may lead to daytime sleepiness, depression, and cognitive impairment. Routine clinic visits are needed

Table 10 The Approach to Sleep-Onset Insomnia in the Elderly

Causes of insomnia (diagnosis)	Management
Depression	Venlafaxine, mirtazapine
	Psychiatric evaluation
Generalized anxiety disorder	Psychiatric evaluation
	Cognitive therapy
	Caffeine avoidance
	Non-benzodiazepine hypnotics (zolpidem, zaleplon, eszopiclone)
	Paroxetine
Psychophysiological insomnia	Exercise and bright light during the day
	Relaxation techniques
	Routine bedtime and wake time
	Keep a written "worry" diary or a to-do list
	Cognitive-behavioral therapy
Inadequate sleep hygiene	Routine bedtime and wake time
	Avoid daytime naps
	Avoid caffeinated beverages especially in the late afternoon
	Gentle morning exercise
	Warm bath in the evening
Restless legs syndrome	Check for:
	Peripheral neuropathy (Table 8)
	Radiculopathy
	B12/folate/magnesium deficiency
	Uremia
	Avoid:
	Selective serotonin reuptake inhibitors
	Tricyclic antidepressants
	Lithium
	Rapid withdrawal from benzodiazepines or hypnotics
	Treatment:
	Dopamine agonists pramipexole and pergolide
	Gabapentin
Pain (arthritis, lower back)	Optimize pain management
	Avoid hypnotics if possible unless pain persists despite treatment then use trazodone or mirtazapine
	Intermittent use of non-benzodiazepine hypnotics (zaleplon, zolpidem, eszopiclone)
Environmental sleep disorder	Limit noise
	Comfortable bedding
	Cool ambient room temperature
Substance abuse	Avoid alcohol, nicotine, caffeine
Other comorbid sleep disorders (obstructive sleep apnea, periodic limb movement disorder, etc.)	Optimize management of comorbid condition

Table 11 Pharmacotherapy of Insomnia in the Elderly

Rule out secondary sleep disorders before initiating medications (obstructive sleep apnea, periodic limb movement disorder)
• Non-benzodiazepine hypnotics
– Zaleplon
– Zolpidem
– Eszopiclone
• Antidepressants
– Trazodone
– Mirtazapine
– Amitriptyline
– Doxepin
• Benzodiazepines
– Clonazepam
– Flurazepam
– Quazepam
Routine clinic visits to monitor progress of treatment and follow side effects

when prescribing medications for insomnia to monitor the side effects. Unfortunately, data regarding the long-term efficacy of pharmacological treatments for insomnia are not available.

Sleep-Maintenance Insomnia

Disruption of sleep during the night implies excessive internal or external stimuli or difficulty with sleep mechanisms. The sleep environment should be assessed for sleep disrupting stimuli. Questions should identify the presence of obstructive sleep apnea, restless legs syndrome, periodic limb movement disorder, and sleep impairing medications (Table 3). Patients complaining of difficulty staying asleep and sleep disruption should be evaluated for snoring, witnessed apneas, night sweats, daytime sleepiness, and fatigue. In this case, polysomnography is helpful to rule out sleep apnea. Weight control and CPAP are first-line therapies, with surgery and dental appliances providing other options. The surgical treatment option should be chosen with caution in the elderly due to increased surgical complications in this group. Periodic limb movement disorder is suffered by an estimated 44% of subjects 65 years or older, significantly fragmenting sleep. In this disorder, the patient's bed partner usually notes leg jerks during sleep while the unknowing patient complains of daytime fatigue and sleepiness. Polysomnography is the diagnostic study of choice. Treatment options include gabapentin or dopamine agonists. Associated conditions should be ruled out, including peripheral neuropathy, radiculopathy, iron deficiency anemia, and B12/folate/magnesium deficiency.

Parasomnias, such as REM sleep behavior disorder and confusional arousals, can cause significant sleep disruption. These patients should be referred to a sleep specialist for an evaluation, which may include brain imaging, electroencephalography, and polysomnography (parasomnia protocol) to rule out seizure disorders and identify the specific parasomnia (see Chap. 8). Treatment with clonazepam is often effective. Pain and nocturia, along with medical disorders such as congestive heart failure, diabetes mellitus, and chronic renal insufficiency, are also common sleep disrupters that should be considered in patients with sleep-maintenance insomnia.

Early Morning Awakenings

Early morning awakenings are distressing to the elderly. Shifts in the circadian rhythm causing advanced sleep phase disorder are often the causative mechanism (see Chap. 9). Treatment involves evening bright light exposure delaying the onset of sleepiness from the early evening hours, allowing the patient to awaken later in the morning. Short-acting non-benzodiazepine hypnotics (zaleplon) are effective when used cautiously. The patient should take the pill upon awakening, allowing for extra morning sleep. Since early morning awakenings characterize depression, mood disorders should be considered in these patients. In addition, obstructive sleep apnea or periodic limb movement disorder can disrupt sleep at anytime during the night, necessitating polysomnography when these disorders are suspected.

SLEEP AND DEMENTIA

Sleep disturbance affects 20–44% of patients with degenerative brain diseases such as Alzheimer's disease, Lewy body disease, and multi-infarct dementia (47). Sleep disruption is a major source of stress for caregivers and the main reason for institutionalization in dementia. Clinical manifestations of poor sleep in these patients include insomnia, motor restlessness, and frequent daytime napping. Nightmares and hallucinations are also common symptoms, and nocturnal wandering and aggressive daytime behaviors are particularly distressing to caregivers. Clinicians who manage this population face a challenging task, but familiarity with the complex nature of these illnesses goes a long way in helping alleviate caregiver burden. Indeed, comorbidities and medications can exacerbate sleep disorders, and sleep disturbance complicates many aspects of dementia. For example, sleep apnea exacerbates nocturnal agitation and restlessness and is associated with vascular disease, which may contribute to further cognitive dysfunction. Similarly, patients with Alzheimer's disease treated with donepezil may experience side effects such as insomnia and fatigue.

In this section, we discuss the common sleep disorders and complaints of demented patients with special focus on diagnostic approaches and clinical

management. Any patient with dementia and sleep complaints such as daytime sleepiness, insomnia, or frequent awakenings should be evaluated for sleep disorders such as obstructive sleep apnea, periodic limb movement disorder, insomnia, and parasomnias. Psychiatric illness should always be considered when evaluating sleep disorders in this population. Anxiety and nighttime awakenings are highly inter-related in patients with moderate dementia with Alzheimer's disease (48). A careful medication review often reveals sedatives or stimulants with negative consequences on sleep (Table 3). Sedative-hypnotics are not the most viable treatment for sleep disturbance in dementia patients. Basic nonpharmacological interventions can greatly improve the sleep of patients with dementia (Table 9). Clinicians must have realistic expectations regarding treatment compliance, given the patients' cognitive dysfunction. For example, nasal CPAP may not be tolerated in this population, and alternative measures should be sought with the help of a sleep medicine specialist.

Dementia-related neuronal degeneration can affect cerebral and brainstem sleep promoting centers, altering sleep physiology. This degeneration causes decreased mental and physical activity and changes in social interactions. Impaired perception of environmental synchronizers and damage to circadian control centers such as the suprachiasmatic nucleus contributes to disturbed sleep–wake cycles. Additional damage occurs to sleep–wake rhythms when degeneration extends to hypothalamic and cortical regions responsible for wakefulness and alertness. Indeed, melatonin, a neurohormone secreted by the pineal gland that regulates circadian rhythms, is decreased in the cerebrospinal fluid of Alzheimer's disease patients and the elderly. Sleep–wake disturbances in dementia increase in severity with progression of the disease. The disturbance also increases with age as evidenced by decreased slow-wave and REM sleep and increased nighttime arousals and awakenings over time.

Sundowning

Sundowning, or sundown syndrome, consists of evening or late afternoon increased motor activity, confusion, restlessness, and aggressiveness in the context of dementia. Precipitants include forced awakening, environmental noise, and caregiver shift changes (Table 12). Polypharmacy, bladder catheterization, fecal impaction, and underlying medical illness contribute to the syndrome (49). The symptoms can worsen with the use of psychotropic medications that affect daytime cognition. This phenomenon is most often seen in institutionalized patients. Caretakers suffer from chronic fatigue and sleepiness due to nighttime attendance to the patient's sleep disturbance. The cyclic nature of the symptoms points to a disruption of circadian control of the sleep–wake cycle.

Treatment of sundowning depends on recognizing the precipitants. Alleviating uncomfortable medical or environmental situations, such as

Table 12 Precipitants of Sundown Syndrome

- Forced awakening from sleep
- Environmental noise
- Caregiver shift change
- Polypharmacy
- Psychotropic medications
- Bladder catheterization
- Fecal impaction
- Comorbid illnesses

fecal impaction, bed sores, and nocturnal noise, is critical to successful treatment. Secondary sleep disorders, such as obstructive sleep apnea, periodic limb movement disorder, and parasomnias, must be ruled out or diagnosed and treated. Nonpharmacological interventions improve sleep quality while avoiding the untoward side effects of medications. Behavioral techniques such as sleep hygiene protocols are useful when taught to caregivers, as they help re-establish the patient's normal sleep–wake cycle. Maintenance of a consistent bedtime and rise time, nap restriction, and increased daytime activity all are helpful. Additional strategies include walking, social interactions, and listening to music or watching TV during the day. Increasing light exposure during the day, either by natural sun or by improving the luminance in the patient's room is critical. Opening the blinds or taking the patient to outdoor settings is helpful. During the night, a quiet environment and diminished light exposure decreases agitation. Caregivers should be given written descriptions of sleep hygiene rules with specific guidance regarding napping and activities. Realistic expectation of these routines should be discussed, given the compliance difficulties of this population.

Pharmacological treatment is effective in treating sundowning but should only be considered once nonpharmacological measures have been exhausted. Three milligrams of melatonin exhibits a hypnotic effect and increases total sleep time, decreases nighttime activity, and ameliorates sundowning (50,51). Melatonin also has a more favorable side-effect profile than benzodiazepines, which may cause daytime sleepiness and nighttime delirium. Non-benzodiazepine hypnotics such as zolpidem, zaleplon, and eszopiclone are often effective. Newer antipsychotics, including clozapine, olanzapine, quetiapine, and risperidone, are preferred over traditional neuroleptics due to their more favorable side-effect profile. Clozapine is associated with agranulocytosis, mandating white blood cell count measurement during its use. Medications used to treat Alzheimer's disease also have effects on sleep. Galantamine improves sleep quality, while donepezil is associated with insomnia. Table 13 summarizes the pharmacological and nonpharmacological treatments of sundowning.

Table 13 Management of Sundown Syndrome

- Alleviation of uncomfortable medical or environmental situations
  - Fecal impaction
  - Bed sores
  - Nighttime noise
- Rule out secondary sleep disorders (obstructive sleep apnea, periodic limb movement disorder, parasomnia)
- Utilize behavioral techniques
  - Consistent bedtime and rise time
  - Restrict naps
  - Increase daytime activities (walking, social interactions, watching TV, music)
  - Increase daytime light exposure
    - Natural sun (opening blinds and curtains to allow sun)
    - Improving luminance in patient's room
    - Diminish nighttime exposure to light or noise
- Pharmacotherapy
  - Melatonin 3 mg at night
  - Non-benzodiazepine hypnotics (eszopiclone, zolpidem, zaleplon)
  - Newer antipsychotics
    - Olanzapine, quetiapine, and risperidone
    - Clozapine (use mandates frequent white blood cells counts)

Dementia and Sleep Apnea

Patients with multi-infarct dementia, the second most common cause of dementia after Alzheimer's disease, are predisposed to developing sleep-disordered breathing in direct proportion to their dementia severity (52). In contrast, patients with Alzheimer's disease have similar sleep apnea prevalence as controls. Alzheimer's patients with nocturnal desaturations experience morning confusion, and those with sleep apnea exhibit greater agitation, which improves following treatment (53). This improvement can reduce caregiver burden, allowing patients to live at home longer (54). Therefore, when obstructive sleep apnea is suspected, diagnostic polysomnography is warranted and nasal CPAP therapy should be implemented when appropriate. Unfortunately, patients with moderate to severe dementia often do not tolerate CPAP. In this instance, consultation with a sleep medicine specialist is advised. Oxygen and acetazolamide, along with non-benzodiazepine hypnotics such as zolpidem, zaleplon, and eszopiclone, are other therapeutic options. Benzodiazepines should be avoided to prevent further aggravation of the sleep apnea.

Dementia and Insomnia

Dementia patients have increased psychiatric comorbidities including depression and anxiety, resulting in difficulty initiating and maintaining

sleep. When identified, these psychiatric illnesses should be the focus of treatment, as the patient's sleep complaints often resolve with management of the primary disorder. Secondary causes for nighttime awakenings, such as obstructive sleep apnea, periodic limb movement disorder, or parasomnias, should be ruled out as causes. First-line treatment of insomnia encompasses behavioral strategies including improved sleep hygiene, consistent bed and wake times, and avoidance of napping. The caregiver should be involved in this process. If sedative-hypnotics are needed, they should only be prescribed in the short term. Non-benzodiazepine hypnotics such as zolpidem, zaleplon, and eszopiclone are preferred. Other options include melatonin and antidepressants such as trazodone, mirtazapine, or doxepin.

Dementia and Parasomnias

REM sleep behavior disorder is a common parasomnia among patients with dementia, especially Lewy body dementia. These patients should be evaluated with polysomnography to rule out other sleep or seizure disorders. When seizure disorders are suspected, referral to an epilepsy center and video electroencephalographic monitoring are warranted for diagnostic purposes. Treatment involves bedroom safety measures and clonazepam, a highly effective medication for REM sleep behavior disorder. When parasomnias are suspected, the patient should be referred to a sleep specialist.

SLEEP AND DOWN SYNDROME

Patients with Down syndrome may demonstrate subtle symptoms indicating sleep disruption, including irritability, cognitive decline, and behavioral problems. The prevalence of sleep-disordered breathing in Down syndrome is high (20–50%), especially in boys with tonsillar hyperplasia (55). Snoring and restlessness are common manifestations. The severity of sleep apnea depends on factors such as age, obesity, upper airway abnormalities, and the extent of brainstem dysfunction. Clinicians should maintain a high index of suspicion for underlying sleep-disordered breathing in this population. Polysomnography and referral to a sleep specialist are necessary. Treatment includes nasal CPAP and possible adeno-tonsillectomy.

SLEEP AND PSYCHIATRIC ILLNESS

Stress and sleep have always coexisted, and patients with psychopathology often complain of excessive sleepiness, insomnia, and disrupted sleep. Further, many psychiatric medications have untoward effects on sleep. Conversely, patients with primary sleep disorders may exhibit symptoms consistent with psychiatric illnesses such as depression and anxiety. Clinicians should recognize and isolate sleep disturbance associated with

psychopathology in order to optimize patient management. Insomnia is a risk factor for the development of psychiatric disorders, and sleep disturbance may be a risk factor for mania. However, most patients with primary sleep disorders do not have intrinsic mood disorders.

In this section, we discuss major depression, generalized anxiety disorder, nocturnal panic attacks, and posttraumatic stress disorder. These disorders are often seen in the primary care setting coincident with sleep complaints. Insomnia is a common complaint in this population, and, although this is often a symptom of the primary psychiatric disorder, the clinician should maintain a high index of suspicion for sleep disorders as well, since treatment may improve the affective symptoms. The general view of managing sleep disorders in patients with psychiatric illnesses is represented in Table 14. Managing these patients is challenging, and referral to a sleep specialist is often necessary, particularly if the patient fails to respond to conventional psychiatric treatment. Nonpharmacological intervention is effective either alone or in combination with medications. Psychotherapy and cognitive-behavioral therapy should be emphasized as a treatment option not only for affective symptoms but also for sleep complaints such as sleep-onset insomnia. A multidisciplinary approach with frequent communication occurring between the primary care

Table 14 Management of Sleep Disturbances in Patients with Psychiatric Illness

Disorder	Management
Major depression with insomnia	Psychiatric evaluation Consider secondary sleep disorders (obstructive sleep apnea, periodic limb movement disorder) Pharmacotherapy: mirtazapine, trazodone, amitriptyline Hypnotics: zaleplon, zolpidem, eszopiclone Bright light therapy
Generalized anxiety disorder with insomnia	Psychiatric evaluation Cognitive-behavioral therapy Pharmacotherapy: paroxetine, venlafaxine, mirtazapine, amitriptyline Anxiolytics: clonazepam, flurazepam Hypnotics: zaleplon, zolpidem, eszopiclone Warm bath in the evening
Nocturnal panic attack	Psychiatric evaluation Cognitive-behavioral therapy Pharmacotherapy: paroxetine, buspirone
Posttraumatic stress disorder	Psychiatric evaluation with intensive psychotherapy Pharmacotherapy: prazosin, nefazodone, trazodone, fluvoxamine Dream rehearsal therapy for nightmares

physician, psychiatrist, and sleep medicine specialist provides the best avenue for optimizing therapy.

Depression

Patients with sleep disturbance have increased rates of major depression. Indeed, prior insomnia is a significant predictor of subsequent major depression (56). Depressed patients have many sleep complaints, including difficulty falling asleep, nighttime awakenings, early morning awakening, decreased total sleep time, and bothersome dreams. Daytime symptoms of fatigue, decreased energy, and sleepiness are notable. Nonspecific polysomnographic features are often seen in patients with major depression. These include decreased slow-wave sleep, frequent awakening and arousals, prolonged sleep latency, and early REM latency, with the latter being strongly associated with depression. Obstructive sleep apnea or periodic limb movement disorder may exacerbate coexistent major depression, and, therefore, clinicians treating depression should consider sleep disorders in their differential diagnosis.

Epidemiologic studies have shown a strong association between insomnia and depressive symptoms, suggesting that insomnia might be a risk factor for the development of affective disorders (57,58). Chronic insomnia worsens any associated mood disorder, impairing daytime functioning and decreasing quality of life. Insomnia has many different causes, making diagnosis a challenge, especially when psychiatric illness is present. Insomnia results from secondary sleep disorders such as obstructive sleep apnea, restless legs syndrome, periodic limb movement disorder, cardiorespiratory disorders, medications, substance abuse, pain, and circadian rhythm disturbances. Successful management of insomnia depends on the underlying cause(s).

Treating depression in patients with sleep complaints involves multiple steps. Treatment should focus on the depression, with sleep disturbances often improving thereafter. Consultation with a psychiatrist is often warranted. The choice of antidepressant depends on the specific sleep complaint. If insomnia persists, the depression may be refractory to treatment, or other causes such as underlying medical disorders (pain, chronic obstructive pulmonary disease), idiopathic insomnia, and poor sleep hygiene may be contributing. Persistent insomnia should be treated aggressively, given its adverse effect on depression outcome. Although pharmacotherapy provides rapid insomnia relief, cognitive-behavioral therapy produces greater long-term benefit.

The initial focus should be on healthy sleeping habits. The use of caffeine, alcohol, and nicotine should also be discouraged. Stimulus control therapy and relaxation techniques should be discussed (see Chap. 3). When sleep-onset insomnia persists, pharmacotherapy should be initiated. Benzodiazepines and non-benzodiazepine hypnotics demonstrate the best efficacy, although sedating antidepressants are often prescribed. The unfavorable

side-effect profile of medications (tolerance, dependence, daytime drowsiness, further impairment of sleep) should be considered, especially when prescribing benzodiazepines. Zaleplon, a fast-acting, non-benzodiazepine hypnotic, is advantageous in promoting sleep with minimal daytime residual sedation (59). Trazodone, nefazodone, mirtazapine, or low doses of tricyclic antidepressants such as amitriptyline or doxepin (60) may provide benefit if taken in the evening. Depressed patients with daytime sleepiness can be treated with morning doses of stimulating antidepressants such as fluoxetine or bupropion, which can be taken in the morning.

Clinicians should always rule out obstructive sleep apnea and periodic limb movement disorder via polysomnography, particularly when a history of snoring, witnessed apneas, leg jerking, frequent awakenings, fatigue, and sleepiness is obtained. A review of the patient's medication profile is helpful in avoiding activating medications that exacerbate insomnia, such as theophylline and albuterol.

Generalized Anxiety Disorder

Insomnia is common in patients with generalized anxiety disorder, and approximately 25–40% of the insomniacs complain of anxiety (58). Typical insomnia complaints in generalized anxiety disorder include restless sleep, difficulty falling asleep, frequent awakenings, and early morning awakenings. Daytime fatigue, decreased energy, and impaired daytime activities are also common. Multiple sleep complaints, rather than a single complaint, are typical. Polysomnography in these patients shows reduced sleep efficiency, decreased total sleep time, increased arousals during sleep, and more early morning awakening. Insomnia is a source of distress in and of itself, with most patients worrying about their inability to initiate and maintain adequate sleep. In summary, generalized anxiety disorder-associated sleep disturbance is usually sleep-maintenance insomnia, although sleep-onset insomnia can be observed (61).

Clinicians managing patients with generalized anxiety disorder should focus on alleviating the insomnia, as this can impair daytime functioning and well being. Counseling the patient regarding treatment options and coping strategies is critical for good treatment outcomes. Cognitive-behavioral therapy significantly reduces symptoms in these patients (62). Again, because insomnia is commonly encountered in other disorders, clinicians should rule out comorbid conditions or secondary sleep disorders. Polysomnography evaluates obstructive sleep apnea and periodic limb movement disorder, especially in those with frequent awakenings, leg jerks, or snoring.

Pharmacological intervention includes anxiolytics, sedative-hypnotics, or muscle relaxants. Benzodiazepines provide short-term benefits, although unwanted side effects, including dependence and residual daytime drowsiness, may limit their usefulness. Nevertheless, insomnia associated with mild-to-moderate generalized anxiety disorder generally responds to

Table 15 Management of Fatigue and Sleepiness in Psychiatric Illness

- Rule out underlying conditions (obstructive sleep apnea, insufficient sleep)
- Pharmacological treatments
  - Modafinil
  - Methylphenidate
  - Bupropion
  - Fluoxetine
- Exercise
- Bright light during the day (sunlight or artificial bright light)
- Social interactions during the day

psychological treatment and anxiolytic benzodiazepines. The concomitant administration of hypnotic medications can be helpful in patients with severe forms of the disease. Selective serotonin or norepinephrine reuptake inhibitors can also be used as first-line or add-on therapy. The selective serotonin reuptake inhibitor paroxetine is indicated for short-term treatment of generalized anxiety disorder, while the serotonin–norepinephrine reuptake inhibitor venlafaxine results in both short- and long-term improvement of anxiety symptoms and prevention of relapse (63). Citalopram is effective treatment for depression and anxiety, with an excellent safety and tolerability profile (64). Medical therapy should be supplemented with routine clinic visits to follow the progress of treatment and check for side effects, especially for patients prescribed benzodiazepines. Dependence, rebound anxiety, and daytime sedation or memory impairment should be recognized during the follow-up visit. Clinicians should routinely emphasize good sleep hygiene and relaxation techniques. Cognitive-behavioral therapy by a skilled psychiatrist should be attempted in each patient. Exercise should be encouraged.

Nocturnal Panic Attacks

Panic attacks can occur during wake or sleep. Nocturnal panic attacks are common in patients with a daytime panic disorder. Autonomic nervous system dysfunction may contribute to nocturnal panic attacks, while psychological and cognitive factors precipitate daytime panic attacks (65). These patients exhibit sudden arousals from stage 4 sleep and often respond to treatment with carbamazepine and clonazepam (66). The differential diagnosis includes obstructive sleep apnea; therefore, polysomnography is warranted in all patients with nocturnal panic disorder. Patients with a history of sleep panic attacks have significantly higher rates of comorbid generalized anxiety disorder, social phobia, and major depression, and treatment of these conditions can optimize outcomes (67). Minimal data

exist regarding pharmacological intervention of nocturnal panic; however, selective serotonin reuptake inhibitors (paroxetine), anxiolytics (buspirone), or higher potency benzodiazepines (alprazolam, clonazepam) can alleviate symptoms. Cognitive-behavioral therapy can be useful, and psychiatric evaluation by an expert in this field is highly recommended.

Posttraumatic Stress Disorder

Posttraumatic stress disorder is a form of anxiety disorder in which patients suffer from insomnia and nightmares. Phobias, flash backs, and maladaptive ritualistic habits may also be observed. These patients benefit from a multidisciplinary approach to therapy, with intensive psychotherapy being the cornerstone of treatment. Additional treatment options include antidepressants, such as nefazodone, trazodone, and fluvoxamine, and imagery rehearsal therapy (see Chap. 8) (68). Prazosin, a central alpha adrenoreceptor antagonist, is helpful in reducing nightmares and other symptoms of the disorder (69). This medication is thought to act by minimizing cortical noradrenergic activity.

Fatigue or Hypersomnia in Affective Disorders

Patients with depression and anxiety have decreased energy and increased fatigue and daytime sleepiness. Secondary sleep disorders, such as obstructive sleep apnea, periodic limb movement disorder, insufficient sleep, and poor sleep hygiene, should be ruled out. If sleepiness persists, consider wake-promoting agents or stimulants, such as methylphenidate or modafinil (Table 15) (70). Antidepressants with stimulant properties, such as bupropion and fluoxetine, are also beneficial. All stimulant medications should be taken in the morning or no later than early afternoon. Exercise, bright light exposure, and social interactions during the day are helpful measures to improve the patient's energy level and sense of well being.

REFERENCES

1. Collop NA, Adkins D, Phillips BA. Gender differences in sleep and sleep-disordered breathing. Clin Chest Med 2004; 25(2):257–268.
2. O'Conner C, Thornley KS, Hanley PJ. Gender differences in the polysomnographic features of obstructive sleep apnea. Am J Respir Crit Care Med 2000; 161(5):1465–1472.
3. Dancey DR, Hanly PJ, Soong C, Lee B, Shepard J Jr, Hoffstein V. Gender differences in sleep apnea: the role of neck circumference. Chest 2003; 123(5): 1544–1550.
4. Young T, Finn L, Austin D, Peterson A. Menopausal status and sleep-disordered breathing in the Wisconsin Sleep Cohort Study. Am J Respir Crit Care Med 2003; 167(9):1181–1185.

5. Regensteiner JG, Woodard WD, Hagerman DD, Weil JV, Pickett CK, Bender PR, Moore LG. Combined effects of female hormones and metabolic rate on ventilatory drives in women. J Appl Physiol 1989; 66:808–813.
6. Polo-Kantola P, Rauhala E, Helenius H, Erkkola R, Irjala K, Polo O. Breathing during sleep in menopause: a randomized, controlled, crossover trial with estrogen therapy. Obstet Gynecol 2003; 102(1):68–75.
7. Block AJ, Wynne JW, Boysen PG, Lindsey S, Martin C, Cantor B. Menopause, medroxyprogesterone and breathing during sleep. Am J Med 1981; 70(3): 506–510.
8. Shahar E, Redline S, Young T, Boland LL, Baldwin CM, Nieto FJ, O'Connor GT, Rapoport DM, Robbins JA. Hormone replacement therapy and sleep-disordered breathing. Am J Respir Crit Care Med 2003; 167(9):1186–1192.
9. Cagnacci A, Soldani R, Laughlin GA, Yen SS. Modification of circadian body temperature rhythm during the luteal menstrual phase: role of melatonin. J Appl Physiol 1996; 80(1):25–29.
10. Shibui K, Uchiyama M, Okawa M, Kudo Y, Kim K, Liu X, Kamei Y, Hayakawa T, Akamatsu T, Ohta K, Ishibashi K. Diurnal fluctuation of sleep propensity and hormonal secretion across the menstrual cycle. Biol Psychiatry 2000; 48(11):1062–1068.
11. Ito M, Kohsaka M, Honma K, Fukuda N, Honma S, Katsuno Y, Kawai I, Honma H, Morita N, Miyamoto T, et al. Changes in biological rhythm and sleep structure during the menstrual cycle in healthy women. Seishin Shinkeigaku Zasshi 1995; 97(3):155–164.
12. Stahl ML, Orr WC, Males JL. Progesterone levels and sleep-related breathing during menstrual cycles of normal women. Sleep 1985; 8(3):227–230.
13. Wolfson AR, Carskadon MA. Understanding adolescents' sleep patterns and school performance: a critical appraisal. Sleep Med Rev 2003; 7(6): 491–506.
14. Giannotti F, Cortesi F, Sebastiani T, Ottaviano S. Circadian preference, sleep and daytime behaviour in adolescence. J Sleep Res 2002; 11(3):191–199.
15. Born L, Shea A, Steiner M. The roots of depression in adolescent girls: is menarche the key? Curr Psychiatry Rep 2002; 4(6):449–460.
16. Kang MJ, Matsumoto K, Shinkoda H, Mishima M, Seo YJ. Longitudinal study for sleep–wake behaviours of mothers from pre-partum to post-partum using actigraph and sleep logs. Psychiatry Clin Neurosci 2002; 56(3):251–252.
17. Waters MA, Lee KA. Differences between primigravidae and multigravidae mothers in sleep disturbances, fatigue, and functional status. J Nurse Midwifery 1996; 41(5):364–367.
18. Franklin KA, Holmgren PA, Jonsson F, Poromaa N, Stenlund H, Svanborg E. Snoring, pregnancy-induced hypertension, and growth retardation of the fetus. Chest 2000; 117(1):137–141.
19. Prodromakis E, Trakada G, Tsapanos V, Spiropoulos K. Arterial oxygen tension during sleep in the third trimester of pregnancy. Acta Obstet Gynecol Scand 2004; 83(2):159–164.
20. Meurice JC, Paquereau J, Neau JP, Pourrat O, Pierre F. Respiratory disorders during sleep in the pregnant woman. Rev Neurol (Paris) 2003; 159(11 suppl): 6S91–6S94.

21. Blyton DM, Sullivan CE, Edwards N. Reduced nocturnal cardiac output associated with preeclampsia is minimized with the use of nocturnal nasal CPAP. Sleep 2004; 27(1):79–84.
22. Maasilta P, Bachour A, Teramo K, Polo O, Laitinen LA. Sleep-related disordered breathing during pregnancy in obese women. Chest 2001; 120(5):1448–1454.
23. Guilleminault C, Kreutzer M, Chang JL. Pregnancy, sleep disordered breathing and treatment with nasal continuous positive airway pressure. Sleep Med 2004; 5(1):43–51.
24. Suzuki K, Ohida T, Sone T, Takemura S, Yokoyama E, Miyake T, Harano S, Motojima S, Suga M, Ibuka E. The prevalence of restless legs syndrome among pregnant women in Japan and the relationship between restless legs syndrome and sleep problems. Sleep 2003; 26(6):673–677.
25. Phillips B, Young T, Finn L, Asher K, Hening WA, Purvis C. Epidemiology of restless legs symptoms in adults. Arch Intern Med 2000; 160(14):2137–2141.
26. Littner MR, Kushida C, Anderson WM, Bailey D, Berry RB, Hirshkowitz M, Kapen S, Kramer M, Lee-Chiong T, Li KK, Loube DL, Morgenthaler T, Wise M, Standards of Practice Committee of the American Academy of Sleep Medicine. Practice parameters for the dopaminergic treatment of restless legs syndrome and periodic limb movement disorder. Sleep 2004; 27(3):557–859.
27. Hedman C, Pohjasvaara T, Tolonen U, Suhonen-Malm AS, Myllyla VV. Effects of pregnancy on mothers' sleep. Sleep Med 2002; 3(1):37–42.
28. Young T, Rabago D, Zgierska A, Austin D, Laurel F. Objective and subjective sleep quality in premenopausal, perimenopausal, and postmenopausal women in the Wisconsin Sleep Cohort Study. Sleep 2003; 26(6):667–672.
29. Owens JF, Matthews KA. Sleep disturbance in healthy middle-aged women. Maturitas 1998; 30(1):41–50.
30. Baker A, Simpson S, Dawson D. Sleep disruption and mood changes associated with menopause. J Psychosom Res 1997; 43(4):359–369.
31. Sicat BL, Brokaw DK. Nonhormonal alternatives for the treatment of hot flashes. Pharmacotherapy 2004; 24(1):79–93.
32. Newman AB, Enright PL, Manolio TA, Haponik EF, Wahl PW. Sleep disturbance, psychosocial correlates, and cardiovascular disease in 5201 older adults: the Cardiovascular Health Study. J Am Geriatr Soc 1997; 45(1):1–7.
33. Tune GS. The influence of age and temperament on the adult human sleep–wakefulness pattern. Br J Psychol 1969; 60(4):431–441.
34. Maggi S, Langlois JA, Minicuci N, Grigoletto F, Pavan M, Foley DJ, Enzi G. Sleep complaints in community-dwelling older persons: prevalence, associated factors, and reported causes. J Am Geriatr Soc 1998; 46(2):161–168.
35. Benca RM, Ancoli-Israel S, Moldofsky H. Special considerations in insomnia diagnosis and management: depressed, elderly, and chronic pain populations. J Clin Psychiatry 2004; 65(suppl 8):26–35.
36. Ancoli-Israel S, Kripke DF, Klauber MR, Parker L, Stepnowsky C, Kullen A, Fell R. Natural history of sleep disordered breathing in community dwelling elderly. Sleep 1993; 16(8 suppl):S25–S29.
37. Hornyak M, Trenkwalder C. Restless legs syndrome and periodic limb movement disorder in the elderly. J Psychosom Res 2004; 56(5):543–548.

38. Buysse DJ, Reynolds CF III, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. Psychiatry Res 1989; 28(2):193–213.
39. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991; 14(6):540–545.
40. Bastien CH, Vallieres A, Morin CM. Validation of the insomnia severity index as an outcome measure for insomnia research. Sleep Med 2001; 2(4):297–307.
41. Tsushima WT, Ingolfsdottir E. MMPI-2 scores of patients with insomnia. Psychol Rep 2004; 94(1):267–272.
42. Ancoli-Israel S. Insomnia in the elderly: a review for the primary care practitioner. Sleep 2000; 23(suppl 1):S23–S30; discussion S36–S38.
43. Stanley MA, Diefenbach GJ, Hopko DR. Cognitive behavioral treatment for older adults with generalized anxiety disorder. A therapist manual for primary care settings. Behav Modif 2004; 28(1):73–117.
44. Baillargeon L, Landreville P, Verreault R, Beauchemin JP, Gregoire JP, Morin CM. Discontinuation of benzodiazepines among older insomniac adults treated with cognitive-behavioural therapy combined with gradual tapering: a randomized trial. CMAJ 2003; 169(10):1015–1020.
45. Edinger JD, Morey MC, Sullivan RJ, Higginbotham MB, Marsh GR, Dailey DS, McCall WV. Aerobic fitness, acute exercise and sleep in older men. Sleep 1993; 16(4):351–359.
46. Sharpley AL, Cowen PJ. Effect of pharmacologic treatments on the sleep of depressed patients. Biol Psychiatry 1995; 37(2):85–98.
47. Happe S. Excessive daytime sleepiness and sleep disturbance in patients with neurological disease: epidemiology and management. Drugs 2003; 63(24):2725–2735.
48. McCurry SM, Gibbons LE, Logsdon RG, Teri L. Anxiety and nighttime behavioral disturbances. Awakenings in patients with Alzheimer's disease. J Gerontol Nurs 2004; 30(1):12–20.
49. Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized elderly persons. Predictive model and interrelationship with baseline vulnerability. JAMA 1996; 275(11):852–857.
50. Asayama K, Yamadera H, Ito T, Suzuki H, Kudo Y, Endo S. Double blind study of melatonin effects on the sleep–wake rhythm, cognitive and non-cognitive functions in Alzheimer type dementia. J Nippon Med Sch 2003; 70(4):334–341.
51. Cardinali DP, Brusco LI, Liberczuk C, Furio AM. The use of melatonin in Alzheimer's disease. Neuroendocrinol Lett 2002; 23(suppl 1):20–23.
52. Erkinjuntti T, Partinen M, Sulkava R, Telakivi T, Salmi T, Tilvis R. Sleep apnea in multiinfarct dementia and Alzheimer's disease. Sleep 1987; 10(5):419–425.
53. Bliwise DL, Yesavage JA, Tinklenberg JR, Dement WC. Sleep apnea in Alzheimer's disease. Neurobiol Aging 1989; 10(4):343–346.
54. Gehrman PR, Martin JL, Shochat T, Nolan S, Corey-Bloom J, Ancoli-Israel S. Sleep-disordered breathing and agitation in institutionalized adults with Alzheimer disease. Am J Geriatr Psychiatry 2003; 11(4):426–433.
55. de Miguel-Diez J, Villa-Asensi JR, Alvarez-Sala JL. Prevalence of sleep-disordered breathing in children with Down syndrome: polygraphic findings in 108 children. Sleep 2003; 26(8):1006–1009.

56. Breslau N, Roth T, Rosenthal L, Andreski P. Sleep disturbance and psychiatric disorders: a longitudinal epidemiological study of young adults. Biol Psychiatry 1996; 39(6):411–418.
57. Roberts RE, Shema SJ, Kaplan GA, Strawbridge WJ. Sleep complaints and depression in an aging cohort: a prospective perspective. Am J Psychiatry 2000; 157(1):81–88.
58. Ford DE, Kamerow DB. Epidemiologic study of sleep disturbances and psychiatric disorders: an opportunity for prevention? JAMA 1989; 262: 1479–1484.
59. Richardson GS, Roth T, Kramer JA. Management of insomnia—the role of zaleplon. Med Gen Med 2002; 4(1):9.
60. Hajak G, Rodenbeck A, Voderholzer U, Riemann D, Cohrs S, Hohagen F, Berger M, Ruther E. Doxepin in the treatment of primary insomnia: a placebo-controlled, double-blind, polysomnographic study. J Clin Psychiatry 2001; 62(6): 453–463.
61. Monti JM, Monti D. Sleep disturbance in generalized anxiety disorder and its treatment. Sleep Med Rev 2000; 4(3):263–276.
62. Belanger L, Morin CM, Langlois F, Ladouceur R. Insomnia and generalized anxiety disorder; effects of cognitive behavior therapy for gad on insomnia symptoms. J Anxiety Disord 2004; 18(4):561–571.
63. Culpepper L. Generalized anxiety disorder in primary care: emerging issues in management and treatment. J Clin Psychiatry 2002; 63(suppl 8):35–42.
64. Culpepper L. Escitalopram: A new SSRI for the treatment of depression in primary care. Prim Care Companion J Clin Psychiatry 2002; 4(6):209–214.
65. Shapiro CM, Sloan EP. Nocturnal panic: an underrecognized entity. J Psychosom Res 1998; 44:21–23.
66. Dantendorfer K, Frey R, Maierhofer D, Saletu B. Sudden arousals from slow wave sleep and panic disorder: successful treatment with anticonvulsants—a case report. Sleep 1996; 19(9):744–746.
67. Labbate LA, Pollack MH, Otto MW, Langenauer S, Rosenbaum JF. Sleep panic attacks: an association with childhood anxiety and adult psychopathology. Biol Psychiatry 1994; 36(1):57–60.
68. Singareddy RK, Balon R. Sleep in posttraumatic stress disorder. Ann Clin Psychiatry 2002; 14(3):183–190.
69. Raskind MA, Peskind ER, Kanter ED, Petrie EC, Radant A, Thompson CE, Dobie DJ, Hoff D, Rein RJ, Straits-Troster K, Thomas RG, McFall MM. Reduction of nightmares and other PTSD symptoms in combat veterans by prazosin: a placebo-controlled study. Am J Psychiatry 2003; 160(2):371–373.
70. Ninan PT, Hassman HA, Glass SJ, McManus FC. Adjunctive modafinil at initiation of treatment with a selective serotonin reuptake inhibitor enhances the degree and onset of therapeutic effects in patients with major depressive disorder and fatigue. J Clin Psychiatry 2004; 65(3):414–420.

12

The Future of Sleep Medicine

Nathaniel F. Watson

Department of Neurology, University of Washington School of Medicine, Seattle, Washington, U.S.A.

Bradley V. Vaughn

Department of Neurology, The University of North Carolina School of Medicine, Chapel Hill, North Carolina, U.S.A.

INTRODUCTION

Sleep is ubiquitous and considered essential to good health. Although the genuine purpose of sleep still evades us, we know that all mammals and animals totally deprived of sleep die within weeks (1). Sleep is also tightly linked to human physiology and disease. Indeed, healthy sleep is as important to overall well-being as regular exercise and a proper diet. Therefore, one wonders why the optimization of sleep has lagged in conventional medicine and why society still de-emphasizes the importance of sleep. Perhaps this stems from the fact that sleep, from a behavioral perspective, appears to be a passive, quiescent state devoid of function and productivity. This is compounded by the societal perception that sleep complaints are more a nuisance than a true medical problem.

We now know that sleep is, in fact, a dynamic state coupled to the regulation of many important physiological processes such as body temperature, hormone secretion, cardiovascular function, and cognitive processing. We further understand that dysfunctional sleep has many untoward health consequences, as outlined previously in this book. Therefore, physicians must be alert to the obvious and discreet signs of sleep disorders when assessing a patient's overall health. The importance of sleep must be stressed to both our patients and the public. This will not only encourage healthy sleep but also engender a better quality of life and mitigate illness. In the most basic sense, the future of sleep medicine depends on how effectively we, as a society, embrace the relationship between good sleep and good health, for only by understanding this connection will we ever achieve healthy sleep.

SLEEP AND PUBLIC HEALTH

Our notion of healthy sleep and what constitutes normal is continually challenged by our social experience. In order to bring the notion of healthy sleep to the forefront of social consciousness, we must not only hone our understanding of what represents normal sleep but also better define the typical variations of normal. We must also extend our knowledge of the real and potential risks of sleep deprivation and further our efforts at estimating the costs and benefits of sleep.

A normal duration of sleep is a prerequisite for healthy sleep, and current research demonstrates significant detriments associated with sleep deprivation. Unfortunately, voluntary sleep restriction is common, preventing individuals from attaining healthy sleep (2). This self-defeating phenomenon occurs for many reasons. Technological advances have allowed humans to escape the natural environmental confines of the light–dark cycle. Add to this the demands of work and family and social demands, it is no wonder that total sleep times have decreased by 1.5 hours from the turn of the 20th century (3). In 2002, 39% of adults reported sleeping less

than 7 hours a night in the National Sleep Foundation Sleep in America Poll (4). This attests to our changing beliefs and constructs of normal sleep.

Sleep deprivation has important health ramifications and is a major risk factor for motor vehicle accidents (5,6). Several studies have established a relationship between sleep restriction and the risk of developing obesity, diabetes mellitus, coronary heart disease, and increased mortality (7–13). Despite these alarming findings, sleep for many remains an afterthought or luxury.

The forces behind sleep curtailment are complicated and varied. For some, economic influences interfere with good sleep. Shift work and a 24-hour economy increase personal income and corporate profits. This revenue is a major factor dictating policy that perpetuates sleep deprivation in society. For others, social opportunities interfere with good sleep. The 24-hour availability of social activities, entertainment, and transportation causes many to choose leisure activities over sleep. The near ubiquitous availability of caffeinated beverages often provides the crutch needed to function during the day.

As technology has expanded the capabilities of our 24–7 society, we have pushed beyond our physiological capabilities. In our insatiable need to accomplish more within the same amount of time, we have become the preverbal ''kid in a candy store'' unable to appreciate when enough is enough. Indeed, we are now beginning to experience some of the stomach pains wrought by our infatuation with the expansion of available time. Unfortunately, our bodies have yet to evolve at the same rate as our technology, and currently there is no substitute for sleep. Sleep cannot be captured in a pill or compressed beyond one's physiological requirement. Therefore, future public health efforts must include the goal of supplanting the current emphasis on prolonged wakefulness with a focus on optimization of physiological performance. For only by restoring the societal value to natural alertness will we ever again use our bodies and minds to the best of our abilities.

This public health effort must impress upon the public and medical communities that sleep complaints are health issues. Sleep disorders including obstructive sleep apnea, insomnia, and restless legs syndrome are some of the most common diseases (14–16). Unfortunately, these disorders often go undiagnosed for years, resulting in significant morbidity and mortality. Similarly, greater appreciation of sleep disorders in pediatric populations is needed. The importance of healthy sleep and the consequences of poor sleep are not as well defined for children as they are for adults. Poor sleep may have wide ranging behavioral and social consequences, from limiting intellectual development and classroom performance (17) to impacting upon the presence of attention deficit hyperactivity disorder (18). Public health campaigns are needed that alert health care providers, families, and patients alike to the signs, symptoms, and consequences of sleep disorders. Dissemination of this message will be challenging. The National Sleep

Foundation has been active in this regard for many years and no doubt will remain a leader in educating the public regarding current sleep habits and the importance of healthy sleep. Although this is a good start, more education is needed to bridge the societal information gap regarding sleep disorders.

UNDERSTANDING OF SLEEP DISORDERS

A better knowledge of disease pathophysiology is central to fully understand the health impact of sleep disorders. Although great progress has been made in this area in recent years, many more questions need to be answered. Our first challenge is defining and classifying the disorders attributed to sleep. The recent release of the International Classification of Sleep Disorders–2 exemplifies the current effort of the sleep medicine community to refine sleep disorders definitions (19). These definitions will no doubt continue to evolve as we develop a better understanding of disease pathophysiology and etiology. Improving this understanding has enormous potential to alleviate suffering in those with sleep disorders. Through this knowledge, we can specify diseases more clearly and thereby develop targeted therapies.

For example, consider a clinically heterogeneous disease such as narcolepsy. All patients have excessive sleepiness, but the clinical expression of other symptoms including cataplexy, hypnagogic hallucinations, sleep paralysis, and automatic behavior vary from patient to patient. The results of diagnostic procedures are also often variable. Some patients (particularly those with cataplexy) exhibit low cerebrospinal fluid hypocretin-1 levels, while others have normal levels. Some are HLA DQB1*0602 allele positive; others are negative. Some have two or more sleep onset REM periods on the Multiple Sleep Latency Test while others have none. The presence of this clinical heterogeneity begs the question—is the clinical syndrome of narcolepsy due to a single pathophysiological process or multiple different processes? Does the ''true'' narcolepsy phenotype only comprise those with sleepiness with cataplexy, HLA DQB1*0602 positivity, low cerebrospinal fluid hypocretin-1 levels, and sleep-onset REM periods? Do patients with incomplete findings have an etiology and pathophysiology for their disorder that differ from these ''true'' narcolepsy patients? Could this explain the variable success in disease management? Certainly, these concepts are ripe for collaborative study with our colleagues in genetics, epidemiology, and social science.

Successfully addressing the pathophysiology question by mechanistically subdividing sleep disorders based upon etiology has important consequences for sleep medicine. Specific diagnostic procedures could be developed that are more efficient, accurate, and less costly. Targeted therapeutics and pharmacogenetic approaches could optimize therapeutic benefit while minimizing risks (20). Clearly, future basic science efforts

focused on disease etiology and pathophysiology has great potential to improve the lives of our patients.

NEED FOR DIAGNOSTIC EVOLUTION

Diagnosis continues to be a daunting challenge for the field of sleep medicine. The diagnostic challenges involve two primary issues—accuracy and access. Each challenge is unique requiring novel approaches. Accuracy in defining any problem is fundamental to providing a solution. Indeed, routine clinical sleep disorder testing is often unable to distinguish between various disorders. Present-day diagnostic testing only evaluates a limited number of secondary physiological parameters and does not define etiology. For example, polysomnography can reveal a lack of airflow in a patient with obstructive sleep apnea but does not define why the airway collapsed. Similarly, the movements of a patient with restless legs syndrome and periodic limb movement disorder can be recorded, but the neuronal circuitry involved remains unidentified. Therefore, clinical markers are relied upon as surrogates for disease etiology and pathophysiology.

To complicate matters further, some sleep disorders lack a measurable physiological correlate, making diagnosis especially challenging. For example, most patients with insomnia have no clearly defined symptom-generating mechanism. Sleep specialists have tried to classify or subdivide these patients using associated symptoms, but a single unifying root cause for the disorder has not been identified. This will remain the case until we develop diagnostic tools that distinguish pathology and identify etiology. This lack of etiologic certainty is compounded by an extreme overlap of "normal" and "pathological" for studies such as the Multiple Sleep Latency Test and the Maintenance of Wakefulness Test. In this regard, sleep medicine is still in its infancy, attempting to differentiate normal from abnormal.

Because of their common occurrence, the prevalence of sleep disorders currently outpaces available diagnostic resources (21). As a result, patients often go undiagnosed and untreated with significant consequences on quality of life, morbidity, and mortality. Unfortunately, the problem cannot be solved by simply increasing the number of sleep practitioners, as the financial burden of diagnosing and treating these patients has the potential to financially overwhelm society. Our current diagnostic methods are both labor and time intensive requiring expensive equipment. Therefore, in the future, we must develop simplified diagnostic tools that will not only reduce overall cost but also increase patient access. To solve these issues, we must build on our improved understanding of disease pathophysiology to develop better, cheaper diagnostic technologies such as simple serum, urine, or genetic tests. Another avenue to improve sleep diagnostics includes using advanced signal processing techniques to study readily available physiological signals. These

techniques may maximize the amount of information extracted from recorded signals and thus aid in the differentiation of what appear to be similar phenotypic expressions of distinct pathologies. As we further our understanding of the pathophysiology of sleep disorders, identifying more efficient and accurate tests must be a priority. In this manner, we will improve both diagnostic access and accuracy.

TREATMENTS AND PHARMACOLOGY

A greater understanding of pathophysiological mechanisms will also lead to improvements in current therapies. This is particularly important in sleep medicine where current treatments often have intolerable side effects, prohibitive cost, or marginal efficacy. In the future, innovative thinking will be necessary to improve both compliance and patient satisfaction. Achievement of these goals will require special focus on the development of simple, low-cost, minimally invasive therapies with low side-effect profiles.

Obstructive sleep apnea is in need of novel therapies and improved treatment algorithms defining who requires treatment. Identification of specific anatomic or clinical indicators associated with high success rates with specific therapies will ensure that our patients get the best treatment available. Answering these questions will require substratifying the pathophysiology and risk of disease in individual patients, thus providing a more reasoned approach to treatment. Development of these algorithms will require extensive clinical research.

All current therapies for obstructive sleep apnea have limitations. Continuous positive airway pressure, although curative if the device is worn regularly at the proper pressure, is cumbersome and associated with side effects such as mask discomfort, claustrophobia, and aerophagia. Surgical therapies are painful, variable in efficacy, and may be associated with voice-related issues and velopharyngeal insufficiency. Dental appliances may cause jaw discomfort, tooth movement, and sialorrhea. All of these therapies are expensive. Clearly, further development of novel treatments for obstructive sleep apnea is needed. Whether it is a medication that selectively increases pharyngeal dilator muscle tone during sleep, or a device that maintains airway patency without air pressure, or a medication that reduces weight or pharyngeal adipose tissue, the field of sleep medicine and our patients are waiting for better treatments for obstructive sleep apnea.

Patients with difficulty attaining sleep or wake states are also in need of therapeutic advances. A better understanding of the multitude of pathways associated with sleeplessness and excessive sleepiness would improve the treatment of both insomnia and the hypersomnias. As these disorders represent disruption of central nervous system networks, treatments will need to either supplement existing pathways to state attainment or replace the loss of previous networks. The ideal medication would have a rapid onset, last

an appropriate length of time, be devoid of side effects, be safe for indefinite use, and not be habit forming. For insomnia treatment, the nonbenzodiazepine GABA agonist medications zolpidem, zaleplon, and eszopiclone are a step in the right direction with eszopiclone being approved for long-term use (22). For hypersomnia treatment, modafinil is a significant breakthrough with good tolerability and minimal side effects, albeit limited efficacy.

Another potential novel approach involves combination therapy. For example, medical devices and pharmacological therapy applied in tandem could potentially mimic normal brain function. Indeed, deep brain stimulation is currently used to augment cerebral function in patients with certain neurological disorders. In the future, development of devices that sense and deliver specific neurotransmitters may allow for the approximation of the damaged neuronal circuitry associated with sleep disorders. Other combination therapies are currently available although their potential has not been fully realized. For instance, cognitive-behavioral therapy is a proven effective underutilized treatment for insomnia. Although time and labor intensive, this therapeutic modality stresses a patient-centered approach utilizing the brain's inherent ability to relieve symptoms. This method, in combination with novel pharmacological approaches, may provide new inroads to improved quality of life and health in patients not only with insomnia but also with any of the wide range of sleep disorders.

Recent advances elucidating the pathophysiology of narcolepsy may open other doors to treatment in the future. Hypocretin deficiency is observed in association with narcolepsy, pointing to a central role for this neuropeptide in maintaining alertness. Development of hypocretin agonist medications would not only provide a targeted remedy for narcolepsy but also potentially offer an effective modality for maintaining alertness in other hypersomnias and sleep disorders. Research in neuroregeneration continues to explore mechanisms for the re-establishment of neuronal circuitry by using an array of progenitor cells and growth factors. Hypothetically speaking, neural progenitor cells producing hypocretin could be transplanted into the hypothalamus of patients with this disorder (23). Similarly, gene therapy methods may have the potential to stimulate hypocretin production by cells already present (24). These are but three of many hypothetical treatment modalities with the potential to not only treat but also possibly cure the disorder. As we learn more regarding other sleep disorders, such as restless legs syndrome or circadian rhythm disturbances, we may find that these modalities apply to other disorders as well.

The relationship of sleep disorders to systemic illnesses offers clinicians further opportunities to improve the lives of their patients with disordered sleep. Sleep disorders can exacerbate underlying conditions, for example obstructive sleep apnea may worsen congestive heart failure, epilepsy, and depression. A better understanding of these relationships and the positive impact that sleep disorders treatment has on these illnesses is an important

task for sleep medicine in the future. All clinicians, regardless of discipline, must recognize that worsening of medical, neurological, or psychiatric disorders can indicate the presence of sleep disorders. Patients often diminish the importance of sleep symptoms unaware of its connection with their other medical problems. An increased appreciation of sleep disorders by both patients and clinicians alike has great potential to mitigate the untoward impact of medical illness beyond the realm of sleep disorders. This opportunity to improve patient quality of life must not be missed.

SLEEP MEDICINE AS A DISCIPLINE

Individuals with sleep disorders are seen by every discipline in medicine, as these illnesses tend to cut across the lines of traditional medical specialties. For instance, sleep apnea has pathophysiological connections to airway, brain, muscle, and heart diseases, and is a disorder seen by pulmonologists, neurologists, psychiatrists, pediatricians, and otolaryngologists. Thus, sleep medicine, by its very nature, is a multidisciplinary specialty. This diversity of illness makes the practice of sleep medicine challenging as the specialty attempts to gain independence within the framework of medicine.

Multidisciplinary sleep practices are leading the way by demonstrating how interdisciplinary collaboration can produce symbiotic benefits for both patients and practitioners. A major challenge to sleep medicine in the future is to expand upon this model, making multidisciplinary practice the rule and not the exception. This is particularly important within the framework of academic medicine where interspecialty collaborative innovation has great potential to move sleep knowledge forward. Achievement of this collaborative atmosphere could be facilitated by the development of separate divisions or departments of sleep medicine. This would require academic medical centers to look beyond short-term issues to appreciate the benefits of this arrangement. The development of these new academic divisions or departments will serve to bring academic recognition to sleep medicine. Ideally, these departments will contain specialists from diverse backgrounds including neurology, pulmonology, otolaryngology, psychiatry, pediatrics, internal medicine, and dentistry. Housing these diverse specialties under one academic "roof" will foster the development of collaborative, multidisciplinary approaches to the diagnosis and management of sleep disorders. These departments will remove boundaries that currently inhibit innovation and progress and allow the discipline to maintain a broad purview of its practice, thereby preventing the specialty from fragmenting into groups of specialists focused on individual illnesses.

Sleep medicine departments in academic medical centers will strengthen the specialty by ensuring that sleep is well represented on the medical school curriculum. This will allow young physicians to discover an interest in sleep medicine early in their careers and increase the profile of sleep and sleep disorders within the general medical community. This education will

stimulate these budding physicians to consider the impact of sleep on the illnesses seen in their future specialties. Thus, cardiologists will be more apt to consider the impact of obstructive and central sleep apnea on their congestive heart failure patients and psychiatrists will be more cognizant of the impact of sleep disorders on anxiety and depression. The end result will serve to improve the health and lives of the patients they treat.

Currently, there are very few sleep medicine departments or divisions. This will undoubtedly change due to the growing appreciation of the importance of sleep medicine and the frequent occurrence of sleep disorders in society. By bringing together the intellect, infrastructure, and enthusiasm of multiple specialties under one roof, sleep medicine will be poised to assume a greater role in academic medical centers in the future.

CONCLUSION

Sleep medicine is an exciting and vibrant field with many challenges in coming years. The sleep community must lead public health efforts educating the populace as to the importance of a healthy night's sleep. The general public must consider a healthy night's sleep as important to overall well-being as diet and exercise. Similarly, the perils of sleep deprivation must be recognized by society, hopefully providing the spark to change the economic and social pressures that limit sleep. In the future, sleep medicine must coalesce as an independent discipline within academic medical centers to ensure active cross-specialty collaboration and research. This will foster breakthroughs into the etiology and pathophysiology of sleep disorders and drive the development of simplified diagnostics and targeted therapies. In this manner, sleep medicine in the future will ensure a happier, healthier, better-rested society with all the associated benefits.

REFERENCES

1. Rechtschaffen A, Bergmann BM, Everson CA, Kushida CA, Gilliland MA. Sleep deprivation in the rat: X. Integration and discussion of the findings. 1989. Sleep 2002; 25(1):68–87.
2. Bonnet MH, Arand DL. We are chronically sleep deprived. Sleep 1995; 18(10): 908–911.
3. Webb W, Agnew H. Are we chronically sleep deprived? Bull Psychon Soc 1975; 6:47–48.
4. National Sleep Foundation. 2002 Sleep in America Poll. Washington, D.C. www.sleepfoundation.org/_content/hottopics/2002SleepInAmericaPoll.pdf.
5. Van Dongen HP, Maislin G, Mullington JM, Dinges DF. The cumulative cost of additional wakefulness: dose–response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. Sleep 2003; 26(2):117–126.

6. Connor J, Norton R, Ameratunga S, Robinson E, Civil I, Dunn R, et al. Driver sleepiness and risk of serious injury to car occupants: population based case control study. BMJ 2002; 324(7346):1125.
7. Ayas NT, White DP, Al-Delaimy WK, Manson JE, Stampfer MJ, Speizer FE, et al. A prospective study of self-reported sleep duration and incident diabetes in women. Diabetes Care 2003; 26(2):380–384.
8. Ayas NT, White DP, Manson JE, Stampfer MJ, Speizer FE, Malhotra A, et al. A prospective study of sleep duration and coronary heart disease in women. Arch Intern Med 2003; 163(2):205–209.
9. Kripke DF, Garfinkel L, Wingard DL, Klauber MR, Marler MR. Mortality associated with sleep duration and insomnia. Arch Gen Psychiatry 2002; 59(2): 131–136.
10. Tamakoshi A, Ohno Y. Self-reported sleep duration as a predictor of all-cause mortality: results from the JACC study, Japan. Sleep 2004; 27(1):51–54.
11. Patel SR, Ayas NT, Malhotra MR, White DP, Schernhammer ES, Speizer FE, et al. A prospective study of sleep duration and mortality risk in women. Sleep 2004; 27(3):440–444.
12. Gottlieb DJ, Punjabi NM, Newman AB, Resnick HE, Redline S, Baldwin CM, et al. Association of sleep time with diabetes mellitus and impaired glucose tolerance. Arch Intern Med 2005; 165(8):863–867.
13. Taheri S, Lin L, Austin D, Young T, Mignot E. Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index. PLoS Med 2004; 1(3):e62.
14. Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisi J. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. Sleep Med 2003; 4(2):101–119.
15. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. Am J Respir Crit Care Med 2002; 165(9): 1217–1239.
16. Sateia MJ, Nowell PD. Insomnia. Lancet 2004; 364(9449):1959–1973.
17. O'Brien LM, Mervis CB, Holbrook CR, Bruner JL, Klaus CJ, Rutherford J, et al. Neurobehavioral implications of habitual snoring in children. Pediatrics 2004; 114(1):44–49.
18. Golan N, Shahar E, Ravid S, Pillar G. Sleep disorders and daytime sleepiness in children with attention-deficit/hyperactive disorder. Sleep 2004; 27(2): 261–266.
19. American Academy of Sleep Medicine. International Classification of Sleep Disorders: Diagnostic and Coding Manual. 2nd ed. Westchester, Illinois: Am Acad of Sleep Med, 2005.
20. Tafti M, Dauvilliers Y. Pharmacogenomics in the treatment of narcolepsy. Pharmacogenomics 2003; 4(1):23–33.
21. Tarasiuk A, Reuveni H. Obstructive sleep apnea syndrome: the diagnostic strategy dilemma. Isr Med Assoc J 2004; 6(11):686–690.
22. Zammit GK, McNabb LJ, Caron J, Amato DA, Roth T. Efficacy and safety of eszopiclone across 6-weeks of treatment for primary insomnia. Curr Med Res Opin 2004; 20(12):1979–1991.

23. Steidl U, Bork S, Schaub S, Selbach O, Seres J, Aivado M, et al. Primary human CD34+ hematopoietic stem and progenitor cells express functionally active receptors of neuromediators. Blood 2004; 104(1):81–88.
24. Mieda M, Willie JT, Hara J, Sinton CM, Sakurai T, Yanagisawa M. Orexin peptides prevent cataplexy and improve wakefulness in an orexin neuron-ablated model of narcolepsy in mice. Proc Natl Acad Sci USA 2004; 101(13):4649–4654.

Appendix

Appendix A Epworth Sleepiness Scale

How likely are you to doze off or fall asleep in the following situations, in contrast to just feeling tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently, try to work out how they would have affected you. Use the following scale to choose *the most appropriate number* for each situation:

0 = would never doze
1 = slight chance of dozing
2 = moderate chance of dozing
3 = high chance of dozing

Situation	Chance of dozing
Sitting and reading	_____
Watching television	_____
Sitting, inactive in a public place (e.g., theater or meeting)	_____
As a passenger in a car for an hour without a break	_____
Lying down to rest in the afternoon when circumstances permit	_____
Sitting and talking to someone	_____
Sitting quietly after lunch without alcohol	_____
In a car, while stopped for a few minutes in traffic	_____

Source: From Ref. 96.

Appendix B Stanford Sleepiness Scale

Circle one number which best describes your level of alertness or sleepiness right now.

Scale	Characteristics
1	Feeling active and vital; wide awake
2	Functioning at a high level, but not at peak; able to concentrate
3	Relaxed; awake; not a full alertness; responsive
4	A little foggy, not at peak; let down
5	Fogginess; beginning to lose interest in remaining awake; slowed down
6	Sleepiness; prefer to be lying down; fighting sleep; woozy
7	Almost in reverie; sleep onset soon; lost struggle to remain awake
8	Asleep

Source: From Ref. 97.

Appendix C Johns Hopkins Restless Legs Syndrome Severity Scale (JHRLSS)

Score	Usual time of day when RLS symptoms start (after 12 noon)
0 (never)	No symptoms
0.5 (infrequent)	Symptoms less than daily or almost daily
1 (mild)	At bedtime and/or during the sleep period (symptoms may occur within 60 min before the usual bedtime or simply at the time of going to bed or during the night after in bed)
2 (moderate)	In the evening (6 P.M. or later). Symptoms may start at anytime between 6 P.M. and the usual bedtime (the definition of evening may need to be adjusted for patients who routinely have much later bedtimes, such as those who have an afternoon siesta)
3 (severe)	Afternoon (before 6 P.M.). Symptoms start in the afternoon and persist into the evening and night
4 (very severe)	Morning (before noon). Symptoms may start in the morning or they may be present virtually all day. There is usually a "protected period" in the mid-morning (8–10 A.M.) with few if any symptoms. Even the protected period may have symptoms for the most severe RLS, often occurring with significant RLS augmentation

Sample Standard Questions:

1. How many days in a week or month do you have RLS symptoms?
   ___per week ___ per month
2. On a usual day, what is the earliest time after 12 noon that these sensations or movements are likely to occur if you were to sit down or rest?
   ___ P.M. or ___ A.M.
   (pick any time from 12 noon in the day through the night to the early morning)

Note: Since RLS symptoms (once started) tend to persist until morning, the number of hours in the day with RLS will be about 1–6 for mild, 7–12 for moderate, and 13 or more for severe RLS on this scale.

Appendix D International Restless Legs Syndrome Study Group RLS Rating Scale

Ask the patient to rate his/her symptoms for the following 10 questions. The patient and not the examiner should make the ratings; however, the examiner should be available to clarify any misunderstandings the patient may have about the questions. The examiner should mark the patient's answers on the form.

In the past week . . .
(1) *Overall*, how would you rate the *RLS discomfort in your legs or arms*?
[4]☐ Very severe
[3]☐ Severe
[2]☐ Moderate
[1]☐ Mild
[0]☐ None

In the past week . . .
(2) *Overall*, how would you rate the *need to move* around because of your RLS symptoms?
[4]☐ Very severe
[3]☐ Severe
[2]☐ Moderate
[1]☐ Mild
[0]☐ None

In the past week . . .
(3) *Overall*, how much *relief* from your RLS arm or leg discomfort did you get from moving around?
[4]☐ No relief
[3]☐ Mild relief
[2]☐ Moderate relief
[1]☐ Either complete or almost complete relief
[0]☐ No RLS symptoms to be relieved

In the past week . . .
(4) How severe was your *sleep disturbance* due to your RLS symptoms?
[4]☐ Very severe
[3]☐ Severe
[2]☐ Moderate
[1]☐ Mild
[0]☐ None

In the past week . . .
(5) How severe was your *tiredness* or *sleepiness during the day* due to your RLS symptoms?
[4]☐ Very severe
[3]☐ Severe
[2]☐ Moderate
[1]☐ Mild
[0]☐ None

(*Continued*)

Appendix D International Restless Legs Syndrome Study Group RLS Rating Scale (*Continued*)

In the past week . . .
(6) How severe was *your RLS on the whole*?
[4]☐ Very severe
[3]☐ Severe
[2]☐ Moderate
[1]☐ Mild
[0]☐ None

In the past week . . .
(7) How *often* did you get RLS symptoms?
[4]☐ Very often (this means 6–7 days per week)
[3]☐ Often (this means 4–5 days per week)
[2]☐ Sometimes (this means 2–3 days per week)
[1]☐ Occasionally (this means 1 day a week)
[0]☐ Never

In the past week . . .
(8) When you had RLS symptoms, how severe were they on average?
[4]☐ Very severe (this means 8 hr or more per 24-hr day)
[3]☐ Severe (this means 3–8 hr per 24-hr day)
[2]☐ Moderate (this means 1–3 hr per 24-hr day)
[1]☐ Mild (this means less than 1 hr per 24-hr day)
[0]☐ None

In the past week . . .
(9) *Overall*, how severe was the impact of your RLS symptoms on your ability to carry out your *daily activities*, for example having a satisfactory family, home, social, school, or work life?
[4]☐ Very severe
[3]☐ Severe
[2]☐ Moderate
[1]☐ Mild
[0]☐ None

In the past week . . .
(10) How severe was your *mood disturbance* due to your RLS symptoms—for example being angry, depressed, sad, anxious, or irritable?
[4]☐ Very severe
[3]☐ Severe
[2]☐ Moderate
[1]☐ Mild
[0]☐ None

Source: IRLS, Investigator Version 2.2.

Appendix E Diagnostic Criteria for Periodic Limb Movement Disorder

A. Repetitive, highly stereotyped limb movements are present, confirmed by polysomnography. Polysomnographic monitoring demonstrates muscle movements during sleep that are
   i. 0.5–5 sec in duration
   ii. Of amplitude greater than or equal to 25% of toe dorsiflexion during calibration
   iii. In a sequence of four or more movements, and
   iv. Separated by an interval of more than five seconds (from limb movement onset to limb movement onset) and less than 90 sec (typically there is an interval of 20–40 sec)

B. The periodic limb movements in sleep (PLMS) index exceeds five per hour in children and in most adult cases exceeds 15/hr

C. There is clinical sleep disturbance

D. Criteria are not met for another primary sleep disorder known to be associated with PLMS

Supportive features:

A. There is a sustained clinical response to dopaminergic therapy

B. The limb movements are not caused by a medication or substance known to induce or aggravate PLMS

Appendix F Sleep Apnea Screening Tool

Please check all that apply.

Category I: Snoring (checking any two of statements 2–6 indicates high risk)

1. You have a bed partner who can reliably observe your sleep
2. You have been told that you snore
3. You snore more than 3 times per week
4. You snore as loud as someone talking
5. Your snoring bothers other people
6. You have been told that you have pauses in your breathing while sleeping and these occur more than 3 times per week

Category II: Daytime sleepiness or fatigue (checking one indicates high risk)

1. You are still tired after sleeping for 8 hr on more than 3 days per week
2. You are tired during the wake time more than 3 days per week
3. You have fallen asleep while driving
4. You do things to keep yourself from falling asleep during the day

Category III: Body measurements (checking one or more indicates high risk)

1. You have high blood pressure
2. Your shirt collar size is greater than 16 in or
3. Your dress size is larger than 14
4. You weigh more than 220 lb

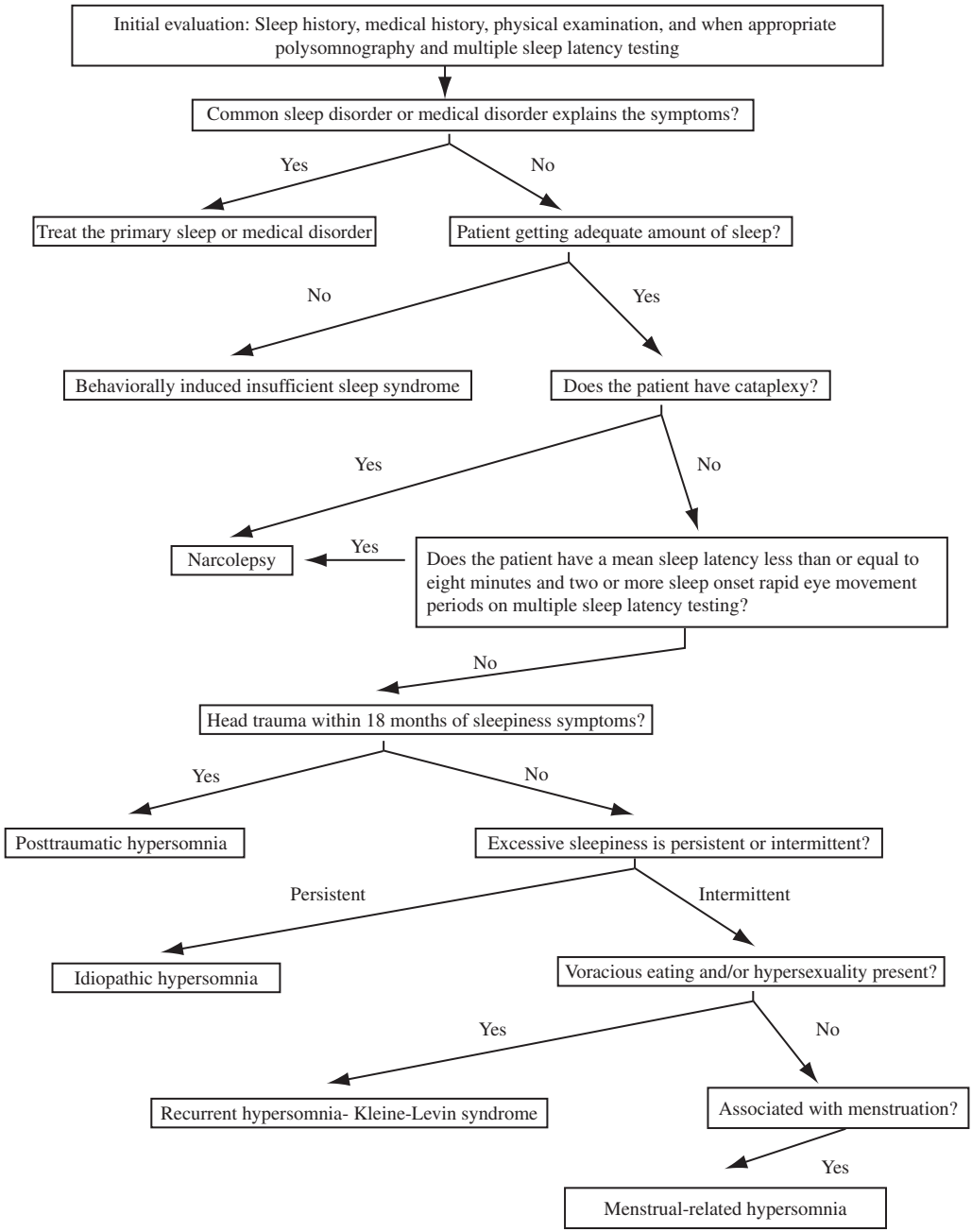
DO NOT WRITE BELOW THIS LINE. FOR CLINIC PROVIDER USE ONLY.

Category IV: Physical examination

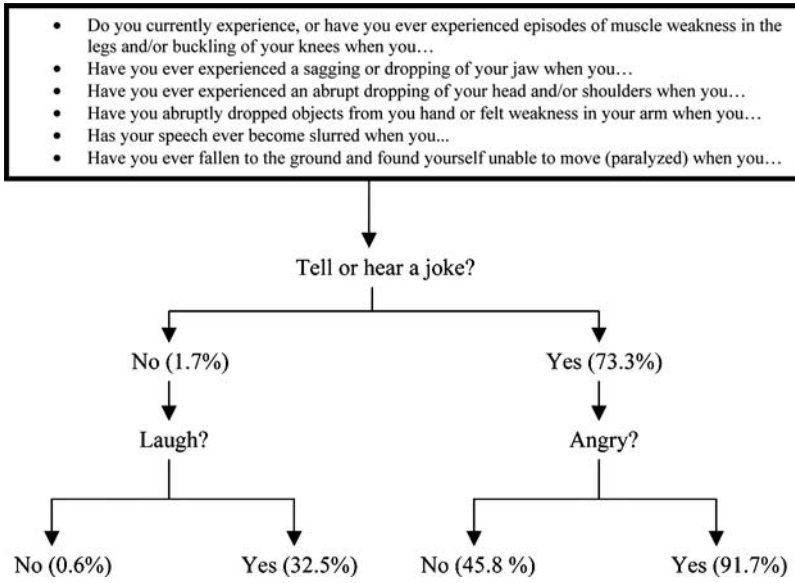
- Height: _____ in./cm Weight: _____ lb/kg
- Neck circumference: _____in./cm
- Body mass index: _____ kg./m^2

(If neck circumference is $\geq$41 cm or BMI $\geq 30\,kg/m^2$, patient is at high risk.)

Appendix G Clinical Approach to the Sleepy Patient



Appendix H A Decision Tree for the Definition of True Cataplexy (The Risk of Clearcut Cataplexy is Indicated in Parentheses.)



Source: From Ref. 8.

Appendix I The INBED Protocol

I—Individual sleep features (memory aid: FAQ)
  Sleep phase (F)
  Sleep amount (A)
  Sleep quality (Q)
If a sleep disorder is present, proceed to next step:
N—nature → Biologic factors → Behavioral interventions
N—nurture → Environmental factors → Environmental modifications
N—neither → Diagnostic studies → Diagnosis and treatment

Appendix J The Pittsburgh Sleep Quality Index

Instruction: The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all the questions.

During the past month:

1. When have you usually done to bed? _____
2. How long (in minutes) has it usually taken you to fall asleep each night? _____
3. When have you usually gotten up in the morning? _____
4. How many hours of actual sleep did you get on a usual night? _____
   (*Note*: This may be different than the number of hours you spend in bed).

5. During the past month, how often have you had trouble sleeping because you....	Not during the past month (0)	Less than once a week (1)	Once or twice a week (2)	Three or more times a week (3)
a. Cannot get to sleep within 30 min	0	1	2	3
b. Wake up in the middle of the night or early morning	0	1	2	3
c. Have to get up to use the bathroom	0	1	2	3
d. Cannot breathe comfortably	0	1	2	3
e. Cough or snore loudly	0	1	2	3
f. Feel too cold	0	1	2	3
g. Feel too hot	0	1	2	3
h. Have bad dreams	0	1	2	3
i. Have pain	0	1	2	3
j. Other reason(s) please describe: (include how often you have had trouble sleeping for each reason)	0	1	2	3
6. During the past month, how often have you taken medication (prescribed or "over the counter") to help you sleep?	0	1	2	3
7. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?	0	1	2	3
8. During the past month, how much of a problem has it been for you to keep up enthusiasm to get things done?	No problem at all (0)	Only a slight problem (1)	Somewhat of a problem (2)	A very big problem (3)
9. During the past month, how would you rate your sleep quality overall?	Very good (0)	Fairly good (1)	Fairly bad (2)	Very bad (3)

Index