Sleep Disorders and Neurologic Diseases
SLEEP DISORDERS

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To my wife, Susan, and my daughters, Katerina and Andrea, who felt the absences and enjoyed the successes with the same intensity that I did.
Sleep is the least understood third of our lives. From its prenatal inception to its ultimate demise, basic questions persist at all stages. We know that sleep represents an important phase in brain function, but we know much less about possible circadian variability in the activity of pathophysiological processes affecting the brain. For example, we have some idea about how sleep apnea may impact brain function, but we have no clue, yet, whether so-called silent brain infarcts occur predominantly in sleep and, if so, why and how.

Fortunately, interest, research, and overall activity in somnology is surging. As this comprehensive book illustrates, a number of specialties are converging to deal with the increasingly recognized problems associated with sleep disorders. Neurosomnology emerges as a distinct subspecialty of neurology, with its attendant professional organizations, certifications, and, eventually, formal training programs.

A number of distinguished investigators and practitioners of sleep medicine contributed to this volume. Although the basics of normal sleep development, function, and dysfunction receive their due, the emphasis remains decidedly clinical. Not only neurologists, but pediatricians, internists, pulmonologists, endocrinologists, psychiatrists, and all those dealing with sleep disorders will find parts intrinsically interesting and applicable in practice. This book deserves a wide readership. The readers and their patients will benefit.

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Sleep is a function of the brain. However, the ultimate physiological function of sleep remains enigmatic and unknown despite recent extensive research of this ubiquitous and important brain activity. Sleep intervenes in functions of somatic growth, regeneration, and memory. Sleep is important in medicine because it modulates quality of life, while its disorders provoke family pathology, disturb work routines, alter social activities, and, in general, affect the health of the individual (1).

Sleep medicine is a unique specialty with input from diverse areas of the medical sciences. Neurology, pulmonary, cardiology, pediatrics, psychiatry, otorhinolaryngology, and even dental medicine have important contributions to make. This diversity is the backbone of sleep medicine. But sleep medicine is branching out and it is clear that sleep, being a function of the brain, suffers dysfunctions that are distinctly neurological. Conditions such as epilepsy with expression only in sleep, neuromuscular disorders masquerading as sleep apnea, parasomnias mimicking seizure disorders, intrinsic hypersomnias with definite brain pathophysiology, sleep alterations in Parkinson’s disease, the risk of stroke in sleep, the organic insomnias, the emerging autonomic dysfunctions of sleep, and so many other unique neurological disturbances can only be evaluated, studied, diagnosed, and managed with comfort by neurologists with special expertise in sleep disorders. Non-neurological physicians with a title of “sleep specialist” may not have sufficient training to tackle the above conditions, despite a sleep diploma or certificate, and will value having immediate access to this important segment of sleep medicine in the form of a book.

The subspecialty of neurosomnology will eventually emerge with strength comparable to that of other subspecialties in neurology. The consequence is that sleep centers may be compelled to add specialized neurosomnology, for which they will need a neurosomnologist on staff. Eventually, clinical neurosomnology will become a subspecialty of sleep medicine and neurology to incorporate all that is new, unique, and only available in the neurology of sleep.

This book serves as a reference for those who practice sleep medicine and encounter neurological pathology. The non-neurologist will value the special information contained herein, and the neurologist will find updated clinical science in their area of expertise. The chapters have a clinical orientation; procedural aspects and laboratory tests are not addressed, except where important to enhance the understanding of clinical manifestations. Some topics are covered in more than one chapter, not by accident but by design. This should not be viewed as duplication but rather a way of presenting diverse views of the same topic.

The authors are prestigious clinical neuroscientists with an international name in the field of sleep medicine. They were invited to update work presented in the first edition (2) or to collaborate with new information developed since
this book was initially published only a few years ago. All collaborators have diligently compiled their chapters despite multiple other obligations and should be commended for their excellent work.

Antonio Culebras, MD

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Part I: Introduction

Concept of Sleep Medicine and of Neurosomnology

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Sleep medicine has experienced an exponential growth in the last 30 years. In the new international classification of sleep disorders (1), more than 80 clinical sleep disorders are codified. Neurosomnology or the neurology of sleep has grown in parallel with the expansion of sleep medicine and the demand for the neurology of sleep is growing fast. General neurologists agonize over the differential diagnosis between a seizure disorder and any of the parasomnias and fret mistaking an epileptic absence for cataplexy. Stroke physicians are seriously concerned about sleep apnea as a risk factor for stroke. Movement disorders’ specialists are increasingly battling the multiple sleep-related problems associated with Parkinson’s disease and allied dysfunctions. Neuromuscular experts dread nocturnal respiratory muscle insufficiency, whereas epileptologists think of sleep as an unknown zone of pathological activity. Increasingly, neurologists are considering sleep a trigger, a risk, and a modulator of neurological disorders. In consequence, they are using more and more the sleep laboratory as a standard testing unit for their patients.

Sleep medicine has so far served well the medical community. However, clinical queries are becoming increasingly complex and an in-depth expertise in the neurology of sleep is becoming a requisite. Unfortunately, not all sleep centers, including those accredited by the American Academy of Sleep Medicine (AASM), incorporate sleep-neurologists or neurosomnologists, who can genuinely understand the technical questions posed and deliver specialized answers to the referring neurologist and the sophisticated internist. Did the electroencephalogram (EEG) channel show epileptiform activity? Should the patient with Parkinson’s disease and insomnia receive more dopamine agonist medication or be treated with a hypnotic? Is the dose of bedtime anticonvulsant medication correct? How should the parasomnia be managed, with anticonvulsants, benzodiazepines, or tricyclics?

Many accredited sleep centers are manned by board-certified sleep specialists originally trained in a non-neurological discipline. They know and understand superbly sleep apnea disorders and may have a profound knowledge of its peripheral cardiopulmonary complications, but only a working superficial understanding of neurologically related sleep problems. It is no secret that in sleep centers where non-neurologists reign, EEG channels are limited to the bare minimum. Is it fair to ask a pulmonary physician and sleep specialist to evaluate a neurological patient with a sleep problem? Would the referring neurologist feel confident and satisfied with the diagnosis and recommendation for management dispensed by a non-neurologist sleep medicine specialist in the case of a complicated seizure problem or in rapid eye movement (REM) sleep behavior disorder secondary to some obscure neurological disease?
Neurosomnology is an active subspecialty of neurology and of sleep medicine that will acquire increasing notoriety among neuroscientists and clinical neurologists as basic and clinical research continue to unravel the neurological intricacies of sleep and its disorders. To advance the subject of sleep, the doors to the brain need to be opened and those who can open them are neuroscientists by training or by adoption. Neurosomnologists should have supra-specialized knowledge of the links between sleep and stroke, epilepsy, neuromuscular disorders, movement disorders, multiple sclerosis, neurodegenerative disorders, headaches, and traumatic brain injury. They should also possess in-depth knowledge of intrinsic brain sleep disorders such as narcolepsy, idiopathic hypersomnia, REM sleep behavior disorder, parasomnias, circadian dysrhythmias, and fatal familial insomnia.

Worthy sleep centers need subspecialists in neurosomnology. Encouraging a sleep center to have a neurologist on board is not sufficient. There should be a guarantee that a neurologist with expertise in sleep disorders is in the staff. The day will come when that expertise is documented with a certificate in neurosomnology, verifying that the professional is an expert in neurological sleep disorders.

To achieve such lofty goal, I have suggested exploring the acquisition of a certificate in the subspecialty of neurosomnology through the American Academy of Neurology (AAN)-sponsored United Council for Neurologic Subspecialties (http://www.ucns.org/certification/applications) mechanism. My vision is that certified neurologists who are American Board of Sleep Medicine (ABSM) diplomates or American Board of Internal Medicine (ABIM)-certified in sleep medicine would be eligible to reach this very specialized branch of neurology. The certificate would become an addition to the current title of specialist in sleep medicine, not a substitute. It should have no effect in the feared split of sleep medicine into sleep apnea disorders (80% of current sleep medicine) and everything else, as only sleep specialists would be eligible. The new title would empower the presence of neurologists in all sleep centers, improving the evaluation and management of patients and conferring rationality to the process, as sleep is, after all, a function of the brain.

CORPORATE ORGANIZATION OF SLEEP MEDICINE

The AASM (http://www.aasmnet.org) is the core sleep organization in the United States. Its mission is to enhance the quality and effectiveness of health care by fostering excellence and professionalism in the field of Sleep Medicine. It strives to assure quality care for patients with sleep disorders, the advancement of sleep research, and public and professional education. In 2005, AASM listed 2993 diplomates in Sleep Medicine (Fig. 1) and 550 accredited sleep centers. AASM publishes the journals Sleep and the Journal of Clinical Sleep Medicine and participates in the organization of the Associated Professional Sleep Societies Annual meeting (APSS, http://www.apss.org) that celebrated its 20th anniversary at the Salt Lake City convention in June 2006.

ACCREDITATION

AASM also offers accreditation of sleep centers and sleep-related breathing laboratories. This is a voluntary process that serves to document and validate excellence in the provision of care in Sleep Medicine. It serves to guarantee that the center has met all standards set by the AASM, such as employing skilled and qualified staff,
creating a clean and comfortable environment, developing a quality assurance plan, and adhering to evidence-based practice parameters. Accreditation is given for a period of five years.

**FELLOWSHIP TRAINING AND CERTIFICATION IN SLEEP MEDICINE**

In June 2004, the American Council for Graduate Medical Education (ACGME) (http://www.acgme.org) approved the program requirements for graduate medical education in the subspecialty of Sleep Medicine. Sleep Medicine is defined as “a discipline of medical practice in which sleep disorders are assessed, monitored, treated, and prevented by using a combination of techniques and medication.” Fellowship education must be undertaken following ACGME-approved training programs in any of the following specialties: neurology (four years), internal medicine (three years), pediatrics (three years), psychiatry (four years), and otolaryngology (five years). Fellowship training in Sleep Medicine should be separate from all other specialties, but should provide exposure to neurology, cardiology, otolaryngology, oral maxillofacial surgery, pediatrics, pulmonary medicine, psychiatry, psychology, and neuropsychology. Fellowship programs can only be accredited in institutions where the sponsoring specialty has an ACGME-accredited residency program.

One or more institutions may participate in the training program, but there must be assurance of continuity of the educational experience. There should be only one sleep center per facility. Resources must include sufficient inpatient and outpatient populations of all ages encompassing the major categories of sleep disorders that include: sleep apnea, narcolepsy, parasomnias, circadian rhythm
disorders, insomnia, and sleep problems related to internal medicine, neurology, and psychiatry. The facility should have a minimum of two fully equipped polysomnography bedrooms and support space; it should also contain meeting rooms, office space, educational aids, library materials, and diagnostic, therapeutic, and research facilities. Sleep laboratories should be accredited by the AASM or an equivalent body.

The program director is accountable for the operation of the program and should be fully committed to the fellowship program and its fellows. The program director must be a diplomate of the ABSM or be certified in Sleep Medicine by the ABIM and possess qualifications judged to be acceptable by the residency review committee (RRC). There must also be a sufficient number of participating faculties with documented qualifications to instruct fellows in the program. There should be at least two core faculties, including the director, who are specialists in any of the recognized sponsoring specialties and who are certified in Sleep Medicine. Faculty should be available to participate in consultation and teaching in disciplines related to Sleep Medicine including cardiology, neurology, otolaryngology, oral maxillofacial surgery, pediatrics, pulmonary medicine, psychiatry, and psychology.

An atmosphere of scholarship must prevail as evidenced by peer-reviewed funding or by publication of original research in peer-reviewed journals, production of review articles and chapters in textbooks, and presentation of case reports, or clinical series at local, national, or international scientific meetings. In addition, there should be participation in journal clubs, grand rounds, and research conferences.

The program curriculum should be approved by the RRC. The program must be didactic and clinical and fellows should have the opportunity to participate in research. The didactic program should cover all areas of sleep medicine, as well as techniques for diagnostic assessment, administration and interpretation of tests, financing and regulation of sleep medicine, medical ethics, legal aspects, and research methods. In addition, there should be seminars and conferences in all areas of sleep medicine and related specialties. The clinical skills should focus on interviewing patients, history taking, physical examination, formulating a differential diagnosis, diagnosis, treatment plans, and continuous care.

Overall, fellows must have at the completion of their training formal instruction, clinical experience and competence in all areas of Sleep Medicine. They should be able to work in outpatient and inpatient settings and effectively utilize healthcare resources. All patient care must be supervised by qualified faculty. Duty hours must be limited to 80 hours per week, averaged over a four-week period, inclusive of all in-hours call activities. One in seven days should be free from all educational and clinical responsibilities. Final evaluation of a fellow completing the program must include a review of the fellow’s performance and should verify that the fellow has demonstrated sufficient professional ability to practice competently and independently. Fellows thus trained may seek certification in Sleep Medicine by the ABIM newly recognized sleep board.

OTHER NATIONAL AND INTERNATIONAL SLEEP SOCIETIES

The Sleep Research Society (SRS) (http://www.sleepresearchsociety.org) fosters scientific investigation, professional education, and career development in sleep research and academic Sleep Medicine at both the national and international
levels. In 2005, SRS had 1090 registered members, 30% international from 32 countries. SRS is closely allied with the AASM.

The Academy of Dental Sleep Medicine (ADSM) (http://www.dentalsleep-med.org) is a professional membership organization promoting the use and research of oral appliances and oral surgery for the treatment of sleep disordered breathing. It provides training and resources for those who work directly with patients. In 2005, there were 540 members, mostly in North America. The ADSM is closely allied with the AASM.

The ABSM (http://www.absm.org) was established in 1978 to encourage the study, improve the practice, elevate the standards of Sleep Medicine, and issue certificates of special knowledge in Sleep Medicine. ABSM is closely allied with the AASM. ABSM has been a “rogue” board, not recognized by the American Board of Medical Specialties (ABMS), but accepted by most institutions in the United States as the “Sleep Board.” Specialists certified by the ABSM are called diplomates. The last ABSM exam will be given in the fall of 2006. The first board exam in the specialty of sleep recognized by the ABMS will be given in the fall of 2007 by the ABIM. Having ABMS recognition, individuals who pass the exam may claim to be certified in Sleep Medicine.

The Association of Polysomnographic Technologists (http://www.aptweb.org) is an international society of professionals dedicated to improve the quality of sleep and wakefulness in all people. In 2005, there were 1540 members mostly technologists. The Board of Registered Polysomnographic Technologists (http://www.brpt.org) certifies individuals in polysomnographic techniques while promoting national and international recognition and acceptance of the RPSGT credential as the professional standard for polysomnographic technologists. The board is active in the United States, Canada, China, Japan, and Australia. Exams are given annually.

The AAN (http://www.aan.com) supports a Sleep Section with 450 members in 2006, charged with organizing the educational and scientific presentations at AAN annual meetings.

The World Federation of Neurology (http://www.wfneurology.org) sponsors a Sleep Research Group that intervenes in the organization and structure of symposia and educational courses at the World Congress of Neurology. The next congress will take place in Bangkok in 2009.

International Congresses of Sleep Medicine are also organized at the regional and world levels. The World Association of Sleep Medicine (http://www.wasm.org) held the first Congress of Sleep Medicine in Berlin in 2005. It was attended by almost 1000 registrants, indicating the vigor of the specialty at the international level. In view of the initial success, the Second World Congress of Sleep Medicine was held in Bangkok, Thailand, in February 2007.

The World Federation of Sleep Research Societies (http://www.sleepresearch-society.org) also organizes international meetings, such as the one in Cairns, Australia in 2007.

Regional international congresses in sleep medicine have been held at various times in the recent past organized by European, Latin American, and Asian societies.

FUTURE

Sleep Medicine will grow exponentially in the foreseeable future. Much of that growth will come in the heels of the expansion of neurosomnology. Sleep is a
function localized in brain structures, which follows the dynamics of maturation, evolution, and decay of other complex functions also localized in the brain, such as motor development, cognition, and language. There is no one cerebral center where sleep lodges but a multiplicity of structures tightly linked in a network of nuclei, tracts, and neurotransmitters that respond to the orchestrating mandates of the circadian rhythm. Basic research in the neurosciences will advance the understanding of sleep as a ubiquitous function of the nervous system present in all vertebrates. The demands to comprehend and manage sleep dysfunctions, to study its pathology, and to develop treatment modalities will come from a variety of fronts, the most obvious of which has been sleep disorders as a medical discipline in which individual ailments such as narcolepsy, sleep apnea, and others are studied. Developing fronts are also emerging in the academic sector where educators are requesting increased learning efficiency, a process that requires an alert brain. Other fronts have appeared in government departments, where authorities are concerned about fatigue eroding safety on the road; in industry and labor, where leaders are asking for guidance in shift-work programs; and in aerospatial science, where jet-lag distortions of sleep and wakefulness create safety hazards. Indeed, neurosomnology is destined to develop as a subspecialty of the neurosciences with a corporate structure of its own.

REFERENCE

Disorders of Development and Maturation of Sleep

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INTRODUCTION
Disorders of the central nervous system (CNS) are often associated with sleep disturbances. Frequently, children who are neurologically challenged experience chronic sleep–wake problems related to circadian timing of sleep, sleep-related seizures, sleep-related movement disorders, and sleep-related breathing disorders. Traditional therapeutic interventions are often difficult and/or the response is quite variable. Behavioral management, chronotherapy, phototherapy, faded response programs, sedatives, hypnotics, and antidepressants are often unsuccessful in the youngster with a chronic disabling condition of the CNS. Some traditional therapeutic approaches may even exacerbate symptoms or result in only respite for a few days.

Symptoms range from profound sleep onset difficulties at desired bedtimes, inability to consolidate sleep, inability to maintain sleep, irregular sleep–wake schedules, rapidly changing sleep–wake schedules, obstructive sleep apnea syndrome, disorders of the central control of breathing, seizures during sleep, movement disorders, and arousal disorders. Presence of multiple symptoms is the rule, rather than exception. Sleep deprivation and fragmentation of sleep continuity occurs and considerable performance problems, as well as delay in the response to rehabilitative efforts, can result. Interestingly, not only do these disorders of sleep and the sleep–wake cycle deeply affect the patient and quality of life, but commonly result in sleep disturbances and decreased quality of life for the entire family.

This chapter addresses normal development of the CNS and sleep, anatomical correlates, and the effect that specific CNS abnormalities might have on sleep and the sleep–wake cycle. Finally, suggestions regarding management are entertained.

NORMAL AND ABNORMAL DEVELOPMENTAL AND ANATOMICAL CORRELATES OF THE CENTRAL NERVOUS SYSTEM AND SLEEP
The CNS is the predominant organ system governing sleep, sleep’s components, and the sleep–wake cycle. Major CNS alterations occur throughout fetal life, neonatal life, infancy, and childhood. Understanding these changes is essential in assessing the patient with CNS dysfunction during wakefulness and during sleep. Indeed, a comprehensive awareness of maturational changes during sleep may provide insight into management.

Genetic and environmental factors are important in determining morphological and electrophysiological development of the CNS. Differentiation begins very early in the evolution of the embryo as a thickening of the dorsal ectoderm into the neural plate. This single layer of cells rapidly enlarges in number, stratifies,
and develops two folds and a neural groove. This central groove fuses to become the neural tube giving rise to the substance of all neural elements whose cell bodies and supporting elements lie within the brain and spinal cord (1).

Early in the fourth postconceptional (PC) week, the prosencephalon subdivides the forebrain into the telencephalon and diencephalon. Telencephalon represents primordial development of the cerebral hemispheres and diencephalon is destined to become the area containing the optic vesicles. Rhombencephalon develops later into the cerebellum and pons. Myelencephalon is the primitive medulla oblongata and matures somewhat later in embryogenesis.

During regional differentiation, structural flexure begins. Three regions can be identified: cephalic flexure (region of the midbrain), cervical flexure (junction of the brain and spinal cord), and pontine flexure (junction of the metencephalon and myelencephalon). In addition, the lumen of the neural tube undergoes dramatic changes during this time, which corresponds to regional specialization. The lumen in the area of the telencephalon extends into the paired future cerebral hemispheres and will ultimately become the lateral ventricles. The lumen within the telencephalon and diencephalon will become the third ventricle. Cerebral aqueduct develops from the lumen in the mesencephalon. The lumen of the metencephalon and myelencephalon becomes the fourth ventricle.

Neuronal activity appears to be important in the migration of neurons to appropriate positions within the CNS, degree of dendritic branching, and strength of synaptic interconnections (2). Mitosis and migration continue throughout development, and completion of location of individual neurons occurs about one year after PC term. Two internal processes result in a high degree of neuronal activity: the waking state and active [rapid eye movement (REM)] sleep. It is possible that these two states are important during prenatal and early postnatal life for appropriate ultra-structural development of the CNS.

Centers responsible for control of sleep and the sleep–wake cycles are contained in areas, which will develop from the diencephalon. Appropriate diencephalic maturation is essential for normal sleep to occur. All neuronal activity which eventually reaches the cortex passes through the diencephalon, with the sole exception of those originating from olfaction. The third ventricle is contained within the diencephalon. During the seventh week of development, a small evagination appears from the caudal wall of the third ventricle. This eventually becomes glandular and forms the pineal body, which is responsible for secretion of melatonin.

Melatonin plays an important role in regulating the sleep–wake cycle presumably through entrainment to light–dark cycling. Secretion is highly responsive to afferent neural activity via the retino-hypothalamic tract. Secretion increases in dark environment and is decreased when the retina are exposed to light. Although data regarding the function of melatonin are conflicting, evidence exists that it affects the timing of sleep through its effect on circadian organization (3). Exogenous melatonin has been noted to be useful in regulating sleep in some sleep disorders (4) and in improving sleep in some neurologically handicapped children (5). It seems likely, therefore, that disorders of development of the diencephalon as well as acquired disorders which affect development or function of cells in the caudal wall of the third ventricle can result in significant sleep–wake disorders.

After the seventh PC week, thalamic regions undergo differentiation and neuronal fibers separate the massive gray matter of the walls of the thalamus into numerous thalamic nuclei. Similarly, the wall of the hypothalamus contains hypothalamic nuclei, the optic chiasm, suprachiasmatic nucleus, and neural lobe of the stalk of the body of the pituitary gland. Hypothalamus eventually becomes
the executive region for regulation of all autonomic activity including core body temperature, temperature regulation, and sleep. Since the suprachiasmatic nucleus becomes the governing region for circadian timing of many major physiological functions (the biological clock), it seems clear that dysfunctional development of, or injury to the ventral region of the diencephalon can result in profound symptoms related to the sleep–wake cycle.

Cerebral hemispheres become prominent during the sixth PC week. They expand rapidly until they cover the diencephalon and mesencephalon. Telencephalon becomes the most specialized and complex portion of the brain. Telencephalon can be quite sensitive to changes in intrauterine environment. In the presence of decreased neuronal electrical activity secondary to hypoxemia from any cause, abnormal concentrations of cellular elements, decreased dendritic branching, and lack of synaptic strength to develop essential and mature neural networks may result.

**DISORDERS IN DEVELOPMENTAL MATURATION: NEUROANATOMICAL CORRELATES**

Culebras (6) has comprehensively described neuroanatomical and neurological correlates of a wide variety of sleep abnormalities. Lesions of the medial mesencephalon almost invariably cause a reduction in the level of alertness. Symptomatic cataplexy, characterized by active inhibition of skeletal muscle tone has been described in patients with rostral brainstem tumors, which invade the floor of the third ventricle (7). Disorders of the lower mesencephalon and upper pons tegmentum involving the peri-locus ceruleus region are responsible for symptoms of REM sleep without atonia (8), whereas extensive pontine tegmental lesions cause a reduction in total sleep time, alterations in/or abolition of nonrapid eye movement (NREM) sleep states and REM sleep, as well as paralysis of lateral gaze (9).

Disorders involving the medullary regions of the CNS commonly affect respiratory centers. A wide variety of sleep-related breathing problems are seen in youngsters with Arnold-Chiari malformation (10,11). Central apnea, increased periodic breathing during REM and NREM sleep, central hypoventilation syndrome, and prolonged expiratory apneas can occur. If motor centers controlling pharyngeal musculature are involved, obstructive sleep apnea may also be present.

Many other correlations can be identified. Hypothalamic lesions have been associated with hypersomnia, diffuse lesions of the thalamus lead to either ipsilateral decrease or complete abolition of sleep spindles and represent a useful electrographic sign of thalamic abnormalities (12). The cerebral hemispheres, although not primordial in the generation or maintenance of NREM and REM sleep, do have a modulating influence. Patients with extensive cortical laminar necrosis fail to exhibit slow waves or spindles during NREM sleep, but can express cortical desynchronization during REM sleep (13). Finally, space-occupying lesions of the CNS may cause sleep–wake disturbances or specific sleep disorders by virtue of their location. They may also cause symptoms indirectly through the development of increased intracranial pressure, hydrocephalus, or both.

**DISORDERS IN DEVELOPMENTAL MATURATION: POLYSOMNOGRAPHIC CORRELATES**

Although still in its infancy, the clinical discipline of pediatric sleep medicine and the study of sleep disorders in infants and children are becoming increasingly
focused on dysfunctions of the brain. Concentration on the study of the sleeping brain has been termed by Culebras as “neurosomnology” (14). Physiological function of most other organ systems differs significantly from the waking state and there are clear ontogenetic changes, which occur in sleep and its structure. Studying longitudinal changes of multiple physiological variables during sleep in the laboratory might be termed “developmental polysomnography” (15). Evaluation of maturation of sleep within the context of normal and abnormal human development might provide a sensitive method of analysis.

It has been shown that the electroencephalogram (EEG) is an excellent method for measuring brain maturation (16). Each conceptional age reveals a characteristic pattern. The important features of normal EEG ontogeny, therefore, tend to reflect normal development. An apparent delay of the appearance of these EEG patterns might reflect an arrest or delay in maturation of the CNS. It has been proposed that close attention to stages of brain maturation in normal and abnormal EEGs, as well as the normal progression of state development during sleep, might allow more accurate timing of brain insult in infants with neurological sequelae.

Comprehensive polysomnography utilizing an EEG array, which provides greater detail than the standard montage recommended for adult polysomnography is recommended for the neonatal and pediatric patient. However, diagnosing ontogenetic EEG variations must be performed with caution, since abnormalities in the EEG reflect general pathophysiological processes, but show little specificity for particular disease (17).

Other polysomnographic variables can be important in the assessment of developmental maturation. Recording of eye movements and electromyogram (EMG) along with EEG might improve specificity. Recording of eye movements during sleep provides important information regarding identification of state. Eye movement density and bursts of saccades may hold special significance in the prediction of mental development and morbidity secondary to neonatal illness. Becker and Thoman evaluated the occurrence of “REM storms” in newborn infants and again at 3, 6, and 12 months of chronological age (18). The amount of REMs within each 10-second interval of active sleep was rated on a scale based on frequency and intensity of eye movements. Bayley scales of mental development were administered to the cohort of infants at 12 months of age. Interestingly, a significant negative correlation was found between the frequency of REM storms and Bayley scores. By six months of age, REM storms seemed to express dysfunction or delay in the development of central inhibitory feedback control for sleep organization and phasic sleep-related activities.

The degree of phasic EMG activity during sleep may also reflect maturity of the developing brainstem. Gross movements, localized body movements, and phasic muscle activity are controlled by the CNS at different organizational levels. Phasic motor activity is ontogenetically simpler and decreases early during development. Gross movements are quite complex and require a greater degree of central integration. The type and frequency of muscle activity during sleep might, therefore, add to information regarding integrity of the CNS. Hakamada et al. (19) studied various motor activities in full term newborns with significant illnesses. Generalized body movements, localized tonic movements, and generalized phasic movements were evaluated. Patients with minimally depressed EEG background activity showed an increase in generalized movements and localized tonic movements during quiet sleep. In contrast, patients with markedly severe EEG abnormalities showed an increase in phasic movements. It was
concluded that a significant decrease in generalized body movements, or an increase in generalized phasic muscle activity might indicate a poor prognosis for particular infants. However, the presence of even small amounts of localized tonic movements suggested preservation of cortical function. Nonetheless, diagnostic use of polysomnography and its components becomes most cost-effective when applied to specific problems.

**SPECIFIC SLEEP DISORDERS IN INFANTS AND CHILDREN**

Sleep disorders that occur in adults also occur in children. Disorders of sleep and the sleep–wake cycle differ from adult disorders in etiology, pathophysiology, morbidity, and treatment. Indeed, symptomatology can be dramatically different and childhood sleep disorders are frequently overlooked or overshadowed by clinical problems, which appear and are evaluated during the day. It must be remembered that disordered sleep can underlie meaningful daytime symptoms, and can exacerbate other medical disorders.

There is often considerable delay in diagnosis of disordered sleep in the neonate, infant, and child. Brouillette et al. (20) have described significant delays in the diagnosis of sleep-disordered breathing, and have demonstrated profound morbidity. In 22 patients with documented obstructive sleep apnea, mean delay in referral for 20 patients first evaluated after the neonatal period was $23 \pm 15$ months. Almost three-quarters of patients studied developed serious sequelae including: cor pulmonale, failure-to-thrive, permanent neurological deficits, behavioral disturbances, hypersomnolence, and developmental abnormalities.

In this section, common primary sleep-related disorders in children are discussed. These include: sleep-related breathing disorders, sleep-related seizures, partial arousal disorders, movement disorders associated with sleep, and sleep–wake schedule disorders. Focus is placed on clinical presentation, laboratory diagnosis, and management considerations.

**Sleep-Related Paroxysmal Disorders**

Sleep-related paroxysmal disorders may be differentiated into epileptiform and nonepileptiform abnormalities. Interictal EEG evaluations may or may not be helpful in diagnosis. Often, spells do not occur in the laboratory and comprehensive assessments and management must be based on clinical grounds. Continuous monitoring of EEG and other physiological functions during polysomnography in the sleep laboratory may be quite helpful in differentiating seizure disorders from nonepileptic paroxysmal disturbances.

**Sleep-Related Paroxysmal Disorders Associated with Seizures**

An abundant variety of paroxysmal motor disorders may occur during sleep. These recurring spells must be differentiated from sleep-related nonepileptic motor activity. The sleep of patients with true seizures is typically fragmented (21). Abnormal sleep patterns may, however, indicate a toxic effect of medication or CNS injury.

Interictal epileptiform activity tends to increase during light stages of NREM sleep and is inclined to be suppressed during REM sleep. This is particularly true in patients suffering from partial complex seizures (22). Sleep deprivation increases the rate of focal interictal epileptiform discharges most markedly in Stage 2-NREM sleep. Some epileptic seizures appear almost exclusively during sleep. For example,
a syndrome of continuous spike and wave activity during sleep occurs in young children and is associated with hyperkinesia, neuropsychological disturbances, and progressive aphasia, the Landau–Kleffner syndrome (23).

There is much literature confirming the observation that epileptic seizures occur in specific relation to the sleep and the sleep–wake cycle (24). Sleep deprivation has been a common mechanism to promote seizures in the laboratory, especially in patient with temporal lobe seizure disorders (25). Although absence seizures are recognized clinically only during the day, fluttering of the eyelids can be observed during sleep in conjunction with paroxysmal bursts of 3 cps spike-and-wave activity (26). Partial complex seizures originating in the frontal lobe occur most characteristically during NREM sleep. Among patients with sleep-related complex seizures studied by Cadilhac (27), almost two-thirds occurred during NREM sleep. Approximately, 16% of seizures studied were isolated to REM sleep and 20% occurred in both NREM and REM sleep states. There is also a strong correlation between seizures and sleep in patient with benign partial epilepsy with centro-temporal spikes (Rolandic epilepsy) (24).

In addition to sleep-facilitating seizure activity, seizure frequency may be affected by the presence of other sleep-related disorders. For example, in a group of patients with obstructive sleep apnea syndrome and partial epilepsy, six of seven patients studied by Devinsky et al. (28) revealed a significant reduction in the frequency of seizure activity and seizure severity after successful treatment of the sleep-related breathing abnormality.

Clinical differentiation of epileptic and nonepileptic spells that occur during sleep can often be difficult. Stores reviewed this issue and was able to divide these diagnostic dilemmas into three categories (29). A first group consisted of nonepileptic primary sleep disorders often associated with motor phenomena and with similar presentations. These include some nightmares and sleep terrors, NREM sleep partial arousal disorders, and REM-sleep motor disorders. The second group consisted of primary sleep disorders with motor components which can be incorrectly diagnosed as epilepsy and includes the partial arousal disorders, REM-sleep motor disorder, sleep-related rhythmic movement disorders (such as jactatio capitis nocturnes), some symptoms associated with obstructive sleep apnea, automatic behaviors, idiopathic CNS hypersomnia, and sleep-related enuresis. Finally, some epileptic disorders which occur during sleep and may be mistaken for sleep disorders. These consist of nocturnal complex partial seizures of the temporal lobe and, particularly of frontal lobe origin, nocturnal hypnogenic dystonia, episodic nocturnal wanderings, and nonconvulsive status epilepticus.

Hypnogenic Paroxysmal Dystonia
Hypnogenic paroxysmal dystonia was first described by Lugaresi in 1981 (30). It is a rare disorder characterized by stereotypic, choreo-athetotic movements, and dystonic posturing during NREM sleep. Symptoms may begin in childhood and be mistaken for normal (or abnormal) behavior patterns or other stereotypic, movement disorders. Episodes may be brief, lasting less than a minute, or may be prolonged, persisting for hours. Eyes are often open and vocalizations may occur. If episodes occur frequently or are recurrent during a single sleep period, significant sleep disruption may occur. There are rhythmic, sometimes violent, stereotypical movements (e.g., kicking, thrashing) of the limbs and/or trunk associated with dystonic posturing of the hands, feet, arms, legs, and/or
face. At the termination of an episode, patients may be coherent, but rapidly return to sleep.

Polysomnography usually reveals episodes arising out of Stage 2 NREM sleep (though it has been reported to occur in slow-wave sleep as well). An EEG pattern of arousal may occur a few seconds preceding an episode. Significant movement artifact is seen in the EEG. Clear epileptiform activity during a spell is somewhat controversial. Radiographic studies and magnetic resonance imaging are notably normal. It is unknown whether hypnogenic paroxysmal dystonia is associated with CNS (or other) pathology.

Symptoms generally run a chronic course and may persist for many years. Carbamazepine, in small doses, has ameliorated symptoms in some patients.

### Sleep-Related Nonepileptic Paroxysmal Disorders: The Parasomnias

Parasomnias are classified as dysfunctions associated with sleep, sleep stages, or partial arousals from sleep (31). They are a group of disorders with strikingly dissimilar presentations, but can share many clinical and physiological characteristics. Often parasomnias present clear symptomatology (e.g., sleepwalking, head banging, and bruxism). Manifestations appear early in childhood and might be considered by parents and health care practitioners as normal, benign, or behavioral in origin. As the child ages, benign characteristics can become exaggerated and dramatic. However, few pathophysiological abnormalities can be identified, despite occasionally severe paroxysmal features (32). As with all other disorders of sleep and wakefulness, evaluation begins with a comprehensive history and physical examination. Special attention must be placed on a detailed description of the events.

Neurodevelopmental landmarks must be carefully assessed. Sleep–wake schedules, habits, and patterns require delineation. Morning wake time, evening bedtime, bedtime rituals, and nap time rituals should be described. The presence of excessive daytime sleepiness, snoring, or restlessness during sleep should be ascertained. The presence (or absence) of concurrent medical illnesses and whether the patient is taking any medications or drugs should be obtained in the clinical interview.

A complete physical examination must be performed, and emphasis placed on a comprehensive neurological and developmental assessment. The existence of developmental delays or symptoms suggestive of neurological disorders might indicate an organic basis for the patient’s presenting symptoms. Evidence of other medical disorders should be assessed as possible contributing or co-existent factors.

Laboratory evaluations should be guided by the presenting signs and symptoms. A urine drug screen may be helpful if there is consideration of the symptoms being due to a side effect of medication. Polysomnography is often indicated. An expanded EEG electrode array is recommended. A more extensive EEG montage, than typically recorded during polysomnography, is often helpful in differentiating a nonepileptic parasomnia from sleep-related seizures. Concomitant video recording of the patient while sleeping is indispensable and can clearly demonstrate motor manifestations and chronic stereotypic movements. Attempts should be made to obtain at least 400 minutes of natural nocturnal sleep. It is often helpful to have the patient drink fluids and avoid urination prior to settling since bladder distention may precipitate some parasomnias. The need for all-night
EEG recordings, routine EEG, and radiographic studies depends upon the present-
ing situation, night-time manifestations, and clinical symptomatology.

Sleep–Wake Transition Disorders
These dyssomnias occur mainly during transitions from wakefulness to sleep, from
sleep to wakefulness, or from one sleep stage to another. All can occur in otherwise
healthy children and may be regarded as manifestations of altered normal
physiology. Symptomatology can vary from mild movements during sleep to
violent, alarming behavior. All have the potential to result in discomfort, pain,
injury, anxiety, embarrassment, and disturbance of sleep.

Rhythmic Movement Disorders: Nonepileptic Stereotypic Parasomnias
Although the phenomenon of stereotypic movements during sleep has been
recognized for many years, little is known of the etiology. Stereotypic nonepileptic
parasomnias are characterized by repetitive, meaningless movements or behaviors.
Large muscle groups are involved and manifestations include rhythmic, repetitive
movements such as body rocking, head banging, head rolling, and body shuttling.
They are typically associated with transition from wakefulness to sleep, may be sus-
tained into light sleep, and/or occur after arousal from sleep. Children are usually
developmentally, behaviorally, and medically normal. Movements may be alarm-
ing in appearance and parents often become concerned for the child’s physical
and mental well-being. Injury sometimes occurs.

Stereotypic movements occur in normal infants and children. Lack of rhyth-
mic activity during infancy has occasionally been associated with developmental
delays. When stereotypic movements during wakefulness persist into older
childhood and adolescence, a coexisting psychogenic component may be present.
Stereotypic movements may be a form of attention getting, or a mechanism of
self-stimulation or self-soothing, in developmentally disabled children.

Rhythmic movements can be observed in two-thirds of normal children by
nine-months of age. Incidence of head banging ranges from 3% to 6.5%; body
rocking from 19.1% to 21%; and head rolling in 6.3% of the normal population.
By 18-months of age, the prevalence decreases to less than 50%, and to approxi-
mately 8% by four-years of age. This consistent decrease and spontaneous
resolution of symptoms as the child grows and develops would be consistent
with a maturational origin of the disorder.

At times motor activity and head banging can be violent, and physical injury
can occur, although uncommon. Cutaneous ecchymosis and callous formation can
result. However, more serious injury, including subdural hematoma and retinal
petechiae have been reported. Rhythmic movements usually decrease in intensity
and often resolve spontaneously between two- and four-years of age. Rarely, symp-
toms persist into adolescence and adulthood.

Diagnosis is based on identification of characteristic symptoms in the absence
of other medical and/or psychiatric disorders. Polysomnography demonstrates
typical rhythmic movements during the immediate presleep period and may
persist into Stage 1 NREM sleep. Occasionally, activity is noted after spontaneous
arousal. It can occur during slow-wave sleep, but it is rare during REM sleep.
Focal, paroxysmal, and/or epileptiform EEG activity associated with the stereotypic
activity are absent, however, a full montage EEG may be necessary to rule out epi-
lepsy. Sleep architecture, stage progression, and stage volumes are typically normal.
Parasomnias Associated with Slow-Wave Sleep: Arousal Disorders

Arousal disorders are thought to be due to impaired or “partial” arousal from slow-wave sleep. A hierarchical model may exist since a continuum of manifestations of each of these disorders of sleep seems to be present. Symptoms most often begin in childhood and resolve spontaneously, though occasionally they may persist into adolescence and adulthood. Manifestations are quite alarming and injury can often occur.

Arousal disorders present with bizarre, dramatic symptoms, and share a number of common features. All seem to occur during Stage 3-4 sleep; confusion, disorientation, and amnesia for the events are present; and at times episodes can be precipitated by external stimuli. In contrast, forced arousal from REM sleep is more often followed by rapid awakening, clear thought processes, and vivid dream recall.

Partial arousal disorders occur more frequently during periods of stress, in the presence of fever, after sleep deprivation, and in patients with hypersomnolence syndromes. Partial arousals normally occur at the end of slow-wave sleep periods during ascent to lighter sleep stages. Because of the depth of slow-wave sleep and the high arousal threshold in children, these disorders of arousal may represent conflicting interaction between the mechanisms generating slow-wave sleep and arousal. Chronobiological triggers which control sleep stage cycling may be more likely to result in a partial arousal if the sleep schedule is chaotic. There may be internal desynchronization and the internal arousal stimulus may come at the “wrong time” resulting in incomplete arousal and manifest characteristics of both states. As the child develops, these CNS mechanisms mature, synchronization occurs, and symptoms resolve spontaneously.

Confusional Arousals and Sleep Drunkenness

Confusional arousals or sleep drunkenness consist of partial arousals from slow-wave sleep during the first half of the sleep period. Episodes are sudden, startling, and may be precipitated by forced awakenings. Children may appear to be awake during the episode, but do not respond appropriately to commands and resist being consoled. Confusion and disorientation are prominent. Attempts to abort the “attack” may, in fact, make the symptoms more severe and violent.

Factors which result in increased slow-wave sleep or those which impair arousal may precipitate or exacerbate confusional arousals. Hypersomnia secondary to rebound from sleep deprivation, narcolepsy syndrome, idiopathic hypersomnia, or obstructive sleep apnea may exacerbate symptoms. Confusional arousals/sleep drunkenness is frequently seen in patients with narcolepsy syndrome after prolonged daytime naps (those greater than 60-minutes in length which contain slow-wave sleep). Stress, anxiety, fever, and excessive exercise may precipitate attacks. Organic pathology is rarely noted, though CNS lesions of the periventricular grey matter, reticular activating system, or posterior hypothalamus have been reported in some patients. Injuries during confusional arousals are common if there is displacement of the patient from the bed.

The onset of symptoms is usually prior to five-years of age. Children gradually arouse from slow wave sleep, may moan or mumble unintelligibly. Symptoms then crescendo significantly. Patients may thrash about in bed or fall from the bed to the floor. During the episode, the child appears profoundly confused and disoriented. Combativeness and aggressiveness may occur and consolation or restraint
Somnambulism: Sleepwalking

Somnambulism may vary in presentation from simple sitting up in bed to agitated running and aggressive, violent behavior during sleep. A complex series of automatic behaviors are manifested which may appear, on the surface, purposeful. As with other partial arousal disorders, somnambulistic episodes occur out of slow-wave sleep, during the first third of the sleep period. Episodes may be quite alarming. Patients are uncoordinated and clumsy during the walking episode. Injuries are common. Because of the high incidence of trauma during events, agitated somnambulism should be considered a potentially fatal disorder and the major goal of management is to protect the child from harm.

Somnambulism has been reported to occur in 1% to 15% of the population. It occurs with greatest frequency during childhood, decreasing significantly during adolescence, and is uncommon in adults. Episodes vary in frequency, intensity, and length making parental reports quite inaccurate; the true incidence is therefore unknown. There appears to be an equal sex distribution. There also appears to be a significant familial pattern, though clear genetic transmission has not been identified.

Somnambulism usually begins in middle childhood, between four- and eight-years of age, though onset may occur at any time after the child develops the ability to walk. Symptoms range from simple sitting up in bed to extremely agitated, semi-purposeful automatisms, and frantic running. Most often the child will wander around the house and can perform complex tasks, such as unlocking doors, taking food from the refrigerator, and eating. At time, children may leave the house. Often the behaviors are meaningless and unusual. Verbalizations may occur, but are usually garbled, confused, and meaningless. Eyes are often open, the child may appear awake, but behaviors are only semi-purposeful. Choreiform movements of the arms and head may occur. Often, enuretic episodes occur and the child may urinate (or attempt to urinate) at unusual places around the house. During a somnambulistic spell, the child is extremely difficult to wake, though complete arousal is possible. If awakened, confusion and disorientation is usually present. Motor activity can cease spontaneously and the child may lay down and
return to sleep at unusual places around the home, or the child may return to bed without ever becoming alert.

A number of factors may precipitate somnambulistic events. Fever and sleep deprivation are notable. Any disorder that can produce significant disruption of slow-wave sleep, such as obstructive sleep apnea, may precipitate events. In addition, sleep walking can often be precipitated by urinary bladder distention in the susceptible patient. External noise may also trigger an event. A number of medications can exacerbate the disorder, including thioridazine, prolixin, perphenazine, desipramine, and chloral hydrate.

Polysomnography typically reveals an arousal from Stage 3 or Stage 4 sleep during the first half of the sleep period. Most of the background EEG activity is obscured by muscle artifact. Seizure activity is notably absent.

Though clinically difficult, somnambulism should be differentiated from other disorders of arousal, such as confusional arousals and night terrors. Displacement from the bed and calm nocturnal wanderings are less common with confusional arousals. Night terrors more typically are associated with the appearance of intense fear and panic and are less likely to be associated with displacement from bed (though displacement from bed is more common with night terrors than nightmares). Intense autonomic discharges and an initial scream herald a sleep terror and are not present in somnambulism. Nocturnal seizure disorders typically reveal epileptiform discharges during the events; however, the interictal EEG may be normal. REM-sleep behavior disorder has been described in children, characteristically occurs during REM sleep, and is associated with clear verbalizations and seemingly purposeful movements.

**Sleep Terrors**

Sleep terrors are third in a continuum of partial arousals from slow-wave sleep. The onset of a sleep terror (in contrast to the gradual onset of confusional arousals) is sudden, abrupt, striking, and frightening. These arousals are associated with profound autonomic discharges and behavioral manifestations of intense fear. Similar to other partial arousals, the exact prevalence of sleep terrors is unknown.

Onset of symptoms is usually between two- and four-years of age. Although most frequent during childhood, sleep terrors can occur at any age. As with other nonepileptic parasomnias, precipitating factors include fever, bladder distention, sleep deprivation, and CNS depressant medication. Symptoms tend to significantly decrease during puberty and rarely persist into adolescence and adulthood. Psychopathology is rare in children.

A sleep terror begins suddenly. The child typically sits upright in bed and emits a piercing scream. Severe autonomic discharge occurs. Eyes are usually widely open and pupils may appear dilated. Tachycardia, tachypnea, diaphoresis, and increased muscle tone are present. During the episode the child is unresponsive to efforts to console and parental efforts often exacerbate autonomic and motor activity. During a spell, the younger may run hysterically around the house. The child may run wildly into walls, furniture, or windows. Episodes of extreme agitation are commonly associated with injury. Unintelligible vocalizations and enuresis can occur. Similar to other partial arousal disorders, if the child is awakened from a spell, she may be confused, disoriented, and there is amnesia for the event. In contrast to confusional arousals, episodes of sleep terrors are usually brief, lasting only a few minutes, and subside spontaneously.
Diagnosis is based on identification of the above symptoms and exclusion of organic pathology. Polysomnography reveals sudden arousal from slow-wave sleep during the first third of the major sleep period. Sleep terrors, however, can occur out of slow-wave sleep at any time during the night. Partial arousals without motor manifestation occur more frequently in children with sleep terrors when compared to normal children. Autonomic discharges during these partial arousals are identified by the presence of tachycardia without full-blown symptoms.

Sleep terrors require differentiation from sleep-related epilepsy with automatisms. In these patients, EEG may show abnormal discharges from the temporal lobe, though nasopharyngeal leads may be required to identify the focus of abnormal activity. Epileptic events may also be distinguished from disorders of partial arousal by the presence of a combination of clinical features, stereotypic behaviors, and the fact that they may occur during any part of the sleep period as well as during wakefulness. Identification of epileptiform activity, however, does not completely rule-out the presence of a partial arousal, since they may occur concomitantly in the same patient.

Management of Parasomnias

There is no clear consensus regarding when a partial arousal parasomnia requires treatment. Symptoms are most often mild, occur less than once per month, and result in injury to neither the child nor the parents. In mild cases, explanation of partial arousal disorders and parental reassurance may be all that is necessary. Sleep hygiene also should be discussed. Parents should be encouraged to let the event run its course and to intervene minimally. Interventions should focus on preventing injury and simply guiding the child back to bed. Too vigorous intervention may prolong the episode.

Parents can be alerted of a quiet somnambulistic episode by the use of an alarm system (for example a bell placed on the door knob of the child’s room). Appropriate sleep hygiene is essential. Sleep deprivation should be avoided and regular sleep–wake schedules maintained. Brief daytime naps might be attempted and a period of quiet activity or relaxation techniques instituted prior to bedtime. Fluids after the night-time meal should be limited and the child encouraged emptying his/her bladder immediately prior to bedtime. Fevers, if present, should be appropriately treated.

Severity of partial arousals is considered moderate when symptoms occur less than once per week, and do not result in harm to the patient or to others. In these cases, reassurance and a behavioral approach (including behavior training, sleep hygiene, psychotherapy, and/or hypnosis) have been successful.

In severe cases, when episodes occur almost nightly or are associated with injury, nondon-drug approaches are considered first. Drug treatment, when used, should be prescribed for a short period of time and should be used in conjunction with sleep hygiene and behavioral management. Medication should be weaned when symptoms have been under good control for approximately three to six months.

The most commonly prescribed medication is diazepam. However, lorazepam or clonazepam in small doses are also quite effective. Dosage should be adjusted to the needs of the child. Prolonged use of medication increases the potential for side effects and complications. The young child generally responds well to both behavioral and medicinal approaches.
Parasomnias Usually Associated with Rapid Eye Movement-Sleep
Parasomnias previously discussed have been related to dysfunctions associated with sleep-state transitions and partial arousal from NREM Stage 3 and Stage 4 sleep. Parasomnias have also been reported to occur out of Stage REM sleep. In many cases, manifestations are dissimilar and can be differentiated on clinical grounds alone. Certain REM sleep parasomnias, however, may share similar symptoms to partial arousal disorders. Some frequently occur in children (e.g., nightmares), while others are extremely rare and have only recently been described in children (e.g., REM-sleep behavior disorder). Disorders rarely encountered during childhood are included because their importance to the practitioner may become clear when they are more completely understood and dysfunction associated with the sleeping state are further delineated in children.

Nightmares: Anxiety Dreams
A nightmare is a frightening dream, which may awaken the youngster from REM sleep. There usually vivid, clear recall of disturbing dream content. Anxiety and mild autonomic manifestations occur. Often an anxiety dream contains elements of danger to the individual; a sudden arousal from REM sleep occurs; and after awakening the youngster is oriented to the environment with clear sensorium. Dream content usually involves an experience of immediate and credible threat to survival, security, or self-esteem.

Dream anxiety attacks occur in REM sleep, and are often associated with the longest, most intense REM-sleep period, during the last third of the night. Major body movements are rare due to REM-sleep hypotonia, however, REM-sleep fragmentation, increased phasic activity and frequent movement arousals, and awakening from sleep with clear mentation are typical. Manifestations are generally mild and vocalizations are rare. Although autonomic activity increases during nightmares, it is generally mild, differentiating it from a sleep terror. There is good recall for the disturbing dream and the child functions well upon waking. In contrast, sleep terrors are brief and returning to sleep is rapid after cessation of the spell. A prolonged waking episode with difficulty returning to sleep is common after a nightmare. In addition, nightmares are generally unassociated with violent outbursts, there is no displacement from the bed (until the child awakens), and injuries are quite rare. Return to sleep is generally delayed, but the child often responds well to parental intervention.

Diagnosis of anxiety dreams is based on the identification of the mild manifestations of disturbing dreams occurring during the early morning hours, absence of intense autonomic activation, clear recall of the dream, appropriate functioning and alertness upon awakening, and a good response to parental interventions. Polysomnography may reveal an abrupt arousal from REM sleep. The REM-sleep period from which the child awakens is usually the longest and most intense period of the night. It occurs later in the sleep period, during early morning hours, is associated with mild tachycardia, and tachypnea. Increased REM eye movement density may be noted. Focal, paroxysmal, and epileptiform EEG activity are absent.

Nightmares must be differentiated from sleep terrors, REM-sleep behavior disorder, and epilepsy. Sleep terrors are usually more vivid, frightening to the observer, occur during the first one-third of the sleep period, and are associated with severe autonomic discharges. There is fragmented recall, the child is confused
upon waking, somnambulism and agitated sleepwalking is common, and many suffer injuries. REM-sleep behavior disorder has been recently described in childhood. Symptoms are similar to those seen in the adult patient. In the adult, there is sudden arousal from REM-sleep associated with significant purposeful motor activity. Similar symptoms may be seen in patient with post-traumatic stress disorder where there is state dissociation including, but not limited to increased chin muscle tone, increased phasic activity, increased major body movements during REM sleep, and increased periodic limb movements. Partial complex seizure disorders may occur during any stage of sleep and wake and automatisms and stereotypy are common. Seizure episodes are associated with abnormal EEG activity.

Sleep Paralysis
Sleep paralysis is characterized by absence of voluntary motor activity occurring at the beginning of a sleep period (hypnogogic) or immediately after awakening from sleep (hypnopompic). The patient is conscious, aware of their environment, but feels paralyzed. All muscle groups are involved, however, the diaphragm and extra-ocular muscles are spared. Active inhibition of alpha and gamma motor neurons is present and similar to that which is seen during REM sleep and cataplexy. Sleep paralysis typically lasts only several minutes and subsides spontaneously. Occasionally, attacks can be aborted by rapid movements of the eyes or by being touched. Hypnogogic or hypnopompic hallucinations are unusual, but can occur and add to anxiety.

Isolated, episodes of sleep paralysis can occur in normal individuals. Frequent spells are reported in patients with narcolepsy and in “familial sleep paralysis”. Onset is usually during adolescence, but symptoms may begin during childhood. Children have difficulty describing the events and may appear asleep during the episode. Parents are unaware of the sleep paralysis spell since the atonia can be aborted by touching or shaking.

The clinical course varies significantly. Most cases are isolated and may be exacerbated by sleep deprivation, excessive sleepiness, stress, irregular sleep–wake schedules, or after acute changes in sleep phase. Sleep paralysis runs a more chronic course in patients with narcolepsy and in the familial form of the disorder.

Diagnosis of sleep paralysis is based on identification of presenting symptoms. These may be quite difficult to interpret in children. Complaints of an inability to “get up” or inability to “wake up” may be more common in children. The youngster complaining to the parent of an inability to move after sleep offset is rarely encountered. Sleep paralysis associated with narcolepsy can be differentiated from the isolated form by the absence of chronic excessive daytime sleepiness, sleep attacks, hypnogogic hallucinations, and cataplexy. Atonic generalized seizures occur during wakefulness and may or may not be associated with changes in levels of consciousness. Syncope occurs during wakefulness as well and is most commonly associated with altered levels of consciousness.

Polysomnography usually reveals significant decrease in skeletal muscle tone in the presence of a normal waking EEG pattern and conjugate eye movements. Occasionally, patients may enter sleep during an episode of sleep paralysis and reveal an EEG pattern consistent with Stage 1 sleep. True sleep-onset REM periods may occur.
Rapid Eye Movement-Sleep Behavior Disorder
REM-sleep behavior disorder (RBD)/REM-sleep motor anomaly (RMA) has been described in adults (33). There is evidence that a similar syndrome also occurs during childhood (34). Nonetheless, RBD is an unusual disorder characterized by the appearance of elaborate, sometimes purposeful movement during REM-sleep. There is a paradoxical increase in muscle tone and patients seem to be acting out their dreams. Violent behavior such as punching, kicking, leaping out of bed, and running are reported and often correspond with dream mentation. Injuries to the patient and to bed partners are common.

Cases of RBD/RMA have been reported in pediatric patients (34) and further understanding of this disorder may reveal the incidence and prevalence to be higher than current descriptions suggest. The majority of cases are idiopathic, however, neurological disorders have been identified in approximately 40% of affected adults.

Polysomnography reveals increased muscle tone that persists throughout sleep. There is often a paradoxical increase in muscle tone during REM-sleep, increased phasic activity, and excessive limb or body jerking. Complex behaviors occur out of REM-sleep, but no epileptiform activity is noted on EEG during the complex movements. Interestingly, REM-sleep behavior disorder in adults respond well to benzodiazepines, especially clonazepam.

Management Considerations of Parasomnias in Childhood
Impervious in management of youngsters with nonepileptic partial arousal disorders is a stepwise approach. Education of parents and reassurance may be the only requirement. It is essential that the child be protected from injury, especially if spells are frequent, there is displacement from the bed, or are significantly agitated and violent. Behavioral management includes close attention to sleep hygiene, adequate total sleep time, and limited nocturnal fluids. Fever should be evaluated and treated appropriately. Sleep deprivation should be avoided. Sources of stress and anxiety identified and appropriately addressed. If motor manifestations are present, an alarm system should be established in order for the parents/caretakers to be forewarned of episodes. A bell on a door knob may be all that is needed. If medications are indicated, benzodiazepines are typically the drugs of first choice. Clonazepam in small doses (e.g., 0.25 mg orally at bedtime) is quite effective for both NREM and REM disorders. Unfortunately, due to the long half-life of clonazepam, “hang-over effect” can occur and the youngster may do poorly and exhibit excessive sleepiness the following day. Lorazepam in similarly small doses have been quite successful. Small doses of diazepam at bedtime may be most appropriate for partial arousal parasomnia, which occur only during one-third of the sleep period time. If RBD/RMA is suspected, appropriate psychological, neurological, and/or psychiatric evaluations should be considered. As previously stated, RBD/RMA has been associated with post-traumatic stress disorder in adults, and preliminary data may support a similar phenomenon in children.

Melatonin concentrations in blood, urine, or saliva, may become a useful marker of the circadian rhythm in disorders of biological rhythms (35). Among the latter, of particular interest to the pediatric population will be the potential application of melatonin treatment in establishing or re-establishing circadian rhythms in infants and children maintained for long periods under artificial light.
conditions, as encountered in intensive care units, and in the treatment of sleep and other rhythm disorders associated with developmental delay or blindness. Care must be taken in utilization of melatonin in youngsters with neurological deficits, especially those with intractable seizure disorders. There may be a pro-convulsant effect of exogenous melatonin in some children with cerebral palsy and seizure disorder (36). Until clear understanding of efficacy and side-effects of melatonin is obtained, it should be reserved for those youngsters with chronic neurological disabilities not associated with epilepsy, and sightless youngsters who are unresponsive to light–dark cycling.

Infants and children with myelomeningocele, hydrocephalus, and Arnold-Chiari malformation often exhibit symptomatic apnea or hypoventilation. In a study of 18 asymptomatic infants, Ward et al. (37) have shown that asymptomatic infants with myelomeningocele had longer total sleep time, longer episodes of longest apnea, greater duration of apnea greater than or equal to six seconds as percent total sleep time, and lower mean heart rate than did control infants. This suggested that asymptomatic infants with myelomeningocele have a high incidence of ventilatory pattern abnormalities during sleep. This is currently being studied in a multicenter retrospective analysis of respiratory patterns in children with this CNS abnormality.

To assess hypoxic and hypercapnic arousal response in children with myelomeningocele and apnea, Ward et al. (38) evaluated 11 infants in the presence of controlled hypoxemia and six infants with controlled hypercarbia challenges. During hypoxemia, only two infants with myelomeningocele aroused in comparison to eight of nine control infants. Similarly, during hypercarbia, arousal occurred in only three infants with myelomeningocele compared to all seven control infants. Three infants with myelomeningocele subsequently died. It was concluded that infants with myelomeningocele, Arnold-Chiari malformation, and apnea or hypoventilation have arousal deficits to normal respiratory stimuli.

Sleep–Wake Disorders Associated with Biological Rhythms
Children suffering from chronic debilitating neurological disabilities frequently experience disorders of the sleep–wake cycle related to intrinsic biological (circadian) rhythms. In addition to disordered sleep architecture and composition, many youngsters (and their families) will endure significant disorganization of the timing of sleep. Disorders of timing of sleep may result in as significant life style disarray, affect daytime functioning and performance, and contribute to resistance to therapeutic interventions during daytime hours.

**Delayed Sleep Phase Syndrome**
Sleep phase delay is common during childhood and is seen in many youngsters with and without abnormalities of neurological status. Bedtime struggles are common and sleep-onset difficulties can be profound. Once asleep, continuity and architecture may be normal, unless early morning waking is required or sleep maintenance difficulties also are present. If the child has early morning responsibilities, he/she may experience extreme difficulty arousing. Excessive daytime sleepiness will most likely occur, especially during early morning hours. This may be manifested by actual sleep attacks (unintentional sleep episodes), attention problems, behavioral abnormalities, and/or hyperactivity. Youngsters with delayed sleep phase syndrome function best in the afternoon or early evening.
hours. Spontaneous sleep offset when no responsibilities are present, tends to be quite late in the morning, often extending into the afternoon. On weekends, recovery may occur due to the ability to sleep later in the day, only to have the problem recur during weekdays. Treatment principally focuses on sleep hygiene. Firm, stable time of morning sleep offset is essential. Advancing bedtime will follow. Faded bedtimes with response cost is an appropriate behavioral intervention. If the youngster is not asleep within a reasonable period of time (e.g., 20–30 minutes after lights out), they may be removed from bed and perform quiet tasks until drowsiness is identified. They should then be placed back into bed. Slowly advancing bedtime after sleep onset occurs relatively rapidly will assist in changing and ultimately fixing timing of the major sleep period. Although there is typically a rapid response to this type of intervention, it may take somewhat longer in the youngster with developmental/neurological disability. Medication is sometimes required in those children with significant neurological abnormalities which delays sleep onset. Chloral hydrate and benzodiazepines are most commonly prescribed. If chloral hydrate is used, dosage should be adequate to assist in sleep onset.

**THERAPEUTIC CONSIDERATIONS**

Accurate diagnosis underlies any therapeutic consideration. Nonetheless, there appears to be three overwhelming concerns when managing youngsters with significant CNS challenges, particularly when there is a comorbid primary sleep disorder. First, management of the primary sleep disorder will solve the overall problem. For example, there may be complete resolution of attention problem, performance difficulties, and/or enuresis in children without CNS disability who have hypertrophic tonsils and adenoids associated with obstructive sleep apnea/hypopnea syndrome. Once the nocturnal sleep-related problem has resolved (typically by tonsillectomy and adenoidectomy), the daytime symptoms resolve. A second prime consideration especially in children with CNS challenges includes treatment of comorbidity. If the CNS abnormality is the primary disorder, it may be exacerbated by an underlying sleep-related abnormality. Treatment of the sleep disorder will not result in resolution of the principle problem. However, resolution of sleep-related pathology may result in improvement of daytime functioning to a point where the youngster can take best advantage of other intervention (e.g., physical therapy, occupational therapy, speech therapy, and other rehabilitative services). Finally, treatment of disordered sleep may not affect the youngster at all. Resolution or improvement of sleep-related abnormalities, regardless of type, will have no affect on the underlying problem; will not improve daytime performance, or ability to make the most of other therapeutic interventions. Yet, providing parents with a block of nocturnal hours where the youngster is sleeping without interruption can provide respite for the parents/family resulting in improved parental performance, better mood, and enhanced ability to deal with the child’s primary problem during daytime hours. Any therapeutic intervention should be based on one of these underlying principles when managing sleep-related abnormalities in children with CNS disorders.

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INTRODUCTION

Mental retardation is defined by the American Psychiatric Association as significantly sub-average intellectual functioning beginning before the age of 18 years; deficits or impairments in adaptive functioning must be present (1). A wide variety of sleep abnormalities have been reported in the mentally retarded. Some of these sleep disturbances are common to many of the mental retardation syndromes. Other sleep disturbances are associated with specific syndromes. For example, Prader-Willi Syndrome is associated with excessive daytime sleepiness (EDS) and rapid eye movement (REM) sleep abnormalities, both of which are thought to be due to hypothalamic dysfunction. Mentally retarded children with sleep difficulties are more likely to show behavioral disturbance compared with those who sleep well (2).

COMMON SLEEP ABNORMALITIES IN MENTAL RETARDATION

Sleep disturbances have been reported to occur in 16% to 86% of mentally retarded children (3–5). Reported sleep abnormalities include delayed settling, frequent nocturnal awakenings, limited hours of sleep, initial insomnia, early morning awakening, and EDS. Irregular sleep–wake cycles, in which the individual spends significant time awake at night and asleep during the day, are common (6). Compared to controls, total sleep time in mentally retarded subjects is decreased in some studies and increased in others (7–10). Predictors of nocturnal sleep fragmentation and increased daytime sleep include blindness, severe locomotor disability, and active epilepsy (11). It was previously thought that sleep disturbances improved with advancing age, but recent research disputes this assumption (12). Some mental retardation syndromes, including Down syndrome, are associated with an increased risk for obstructive sleep apnea (OSA).

Sleep difficulties may lead to inattention and poor daytime performance. In mentally retarded children, sleep difficulties have been associated with self-injury and aggression (13). Quine found that night-settling problems were associated with daytime hyperactivity, concentration difficulties, sexual problems with no social awareness, pica, running away, inappropriate behavior with strangers, destructive behavior, and being disruptive at school (14). Night waking problems were also associated with significant behavior problems including encopresis, temper tantrums, mood disturbances, hyperactivity, concentration difficulties, and problems with peers (14).

Sleep difficulties in mentally retarded children are associated with dysfunction of the family, including maternal irritability, maternal stress, and decreased
quality of the parents’ marriage (14). Whether sleep problems in the retarded child cause family dysfunction, or whether family dysfunction causes sleep problems, is unclear.

Polysomnographic studies of mentally retarded individuals have revealed abnormal sleep architecture (6). Stage REM sleep is significantly decreased, and there is a marked decrease, or total absence, of spindle activity during stage 2 nonREM sleep (15). Compared to normal controls, REM sleep is characterized by the infrequency of rapid ocular movements (16,17). In contrast to prior studies examining sleep architecture that involved primarily children, Espie et al. (6) performed sleep studies on 28 adults with severe to profound mental retardation plus epilepsy. Their study included both institutionalized and community-dwelling individuals. Espie et al. found decreased REM sleep, an increased REM sleep latency (172.5 minutes), and “indiscriminate” nonREM sleep (lack of K-complexes, sleep spindles, and well-formed delta-waves). The authors also found low sleep efficiencies (82.8%) with increased time spent in bed (10 hours, 40 minutes in those with profound mental retardation); mean total sleep time was relatively normal at 443.7 minutes. They suggest that sometimes caregivers rely upon bed as a “respite environment.”

Various etiologies have been proposed to account for the irregular sleep–wake cycles and nocturnal sleep fragmentation frequently seen in mentally retarded individuals. It is likely that sleep disturbances associated with mental retardation are heterogeneous, and the factors responsible for the sleep disturbance may vary from syndrome to syndrome, and individual to individual. It is thought that cerebral pathology plays a role in sleep problems associated with mental retardation. In some individuals, medication effect may play a role. For example, sodium valproate has been shown to significantly suppress nocturnal blood melatonin levels (18). Institutionalized behavioral routines may be associated with a weakening of the circadian rhythm (6). Blind individuals are at risk for developing a free-running, nonentrained circadian rhythm. Many individuals with mental retardation have coexisting epilepsy, which may itself disrupt sleep (14,19). Commonly reported sleep disturbances associated with epilepsy include a reduction in REM sleep, an increase in wakefulness after sleep onset, and an instability of sleep states (17). The presence of cerebral palsy increases the risk of having a severe sleep problem (5). A greater degree of mental retardation may increase the risk of sleep disturbance, though not all studies have found this association (5,14).

Mental Retardation Syndromes

Down Syndrome

Down syndrome is the most common genetic cause of mental retardation, with an incidence of one per 660 live births; the incidence increases with advanced maternal age (20). It is usually secondary to trisomy 21, but is occasionally caused by a translocation. Many who live beyond the age 40 develop Alzheimer’s disease. Other common associated conditions include congenital heart disease (most commonly ventriculoseptal defects or patent ductus arteriosus), hypothyroidism, duodenal obstruction, and atlanto-axial instability (21). Characteristic physical features include epicanthal folds, a small head with a flattened occiput, a broad bridge of the nose, flattened facial appearance, small mouth, and often a single transverse crease on the palm (2,21).
The association between Down syndrome and OSA is well established, with some studies estimating a greater than 50% prevalence of OSA in children with Down syndrome (22,23). Children with Down syndrome have an anatomically narrow upper airway due to midfacial and mandibular hypoplasia, macroglossia, glossoptosis, and adenotonsillar hypertrophy; other factors predisposing to OSA in this population include obesity and generalized hypotonia with upper airway muscle malfunction (24,25). Central sleep apnea has also been reported. Ferri et al. (26) hypothesize that the increase in the frequency of central apneas in individuals with Down syndrome is due to “a dysfunction of the central respiratory control at a brainstem level.”

Not all of the sleep disturbances in patients with Down syndrome can be explained by sleep apnea. Sleep fragmentation/arousals independent of respiratory events and periodic limb movements have been reported in children with Down syndrome (24). Settling and night-waking problems are common (2).

Adenotonsillectomy is the usual treatment of OSA in children with Down syndrome, though 30% to 50% develop recurrent or persistent OSA (25). If adenotonsillectomy does not cure OSA, nasal continuous positive airway pressure (CPAP) can be tried. CPAP has a high efficacy in the treatment of OSA, but may be poorly tolerated by individuals with Down syndrome. However, it is this author’s experience that many mentally retarded individuals can gradually come to tolerate CPAP if they have a well-motivated caregiver who is willing to work with the sleep specialist to improve compliance. One useful technique is to have the patient wear the mask alone for several nights before connecting it to the CPAP machine. In institutional settings, educating the night staff about the proper use of CPAP is critical. In selected cases of CPAP failure, advanced surgical treatments for the correction of skeletal and/or soft tissue causes of obstruction may be justified (2,27). Elevating the upper body during sleep usually reduces the severity of OSA.

**Fragile X Syndrome**

Fragile X syndrome is the most common form of inherited mental retardation. It is caused by a trinucleotide repeat expansion in the 5'-untranslated region of the *fragile X mental retardation 1* (FMR1) gene (28,29). Characteristic physical features include macro-orchidism, an elongated face, large ears, and a protruding jaw (28,30,31). Autism is common, and most fragile X patients have one or more autistic behaviors such as hand flapping, tactile defensiveness, and poor eye contact (28).

Little is known about the sleep of patients with fragile X syndrome. One small study suggested an increased risk of OSA (32). Short sleep durations, variation in sleep duration, and sleep fragmentation have been reported (30). Gould and colleagues found increased levels of melatonin across the circadian cycle in young fragile X individuals, possibly explaining the difficulties in maintaining consistent sleep patterns and the increased number and length of night wake episodes demonstrated in their study (30). Clonidine has been reported to have a beneficial affect on the hyperactivity and abnormal sleep patterns associated with fragile X syndrome (33).

**Angelman Syndrome**

Angelman syndrome has been called “happy puppet syndrome” due to the characteristic jerky movements, happy disposition, and inappropriate laughter. Other features of Angelman syndrome include severe motor and intellectual retardation,
ataxia, severe expressive language impairment, epilepsy, microcephaly, hyperactivity, and an open-mouthed expression with tongue protrusion (34,35). The classic EEG pattern consists of multiple generalized bursts of irregular, high-voltage 2–3 Hz activity, intermixed with spike and sharp wave activity, though other patterns have been described (36,37). Evidence of developmental delay occurs by age 6 to 12 months. The syndrome accounts for up to 6% of children presenting with the combination of epilepsy and severe mental retardation (38). Many cases are due to maternally inherited chromosome 15q11-q13 deletions.

A variety of sleep abnormalities have been reported in Angelman syndrome, including prolonged sleep latency, frequent nocturnal awakenings, hyperkinesis, enuresis, bruxism, snoring, sleep terrors, and sleep-walking (12). Nocturnal sleep time is reduced, with most children sleeping five to six hours per night (39). Some have abnormal sleep–wake cycles with short periods of sleep during both the day and night (40). Though total sleep time in Angelman syndrome has been reported to increase with advancing age (39), a recent questionnaire study did not find improvement of sleep disturbances from prepubertal to postpubertal ages (12).

Both behavioral and pharmacological treatments have been used to treat the sleep disturbances of Angelman syndrome. Melatonin, 0.3 mg administered one-hour prior to bedtime, reduces nocturnal hyperkinesis and improves the sleep pattern by promoting regularized and less interrupted sleep (41). Summers et al. (40) described the combined behavioral/pharmacological treatment of a nine-year-old boy with an irregular sleep–wake pattern (variable pattern of sleep onset and offset, with significant daytime sleep and early morning awakenings). Behavioral treatment included preventing daytime sleep and keeping the child in bed at night. Pharmacological treatment consisted of diphenhydramine, 25 mg at bedtime, initially scheduled and then on an as-needed basis. Their treatment resulted in seven to eight hours of nighttime sleep, with minimal daytime sleep.

Prader-Willi Syndrome

In contrast to Angelman syndrome, Prader-Willi syndrome is caused by loss of the paternally contributed chromosome 15q11-q13 region. Though feeding problems and/or failure to thrive occur in infancy, hyperphagia and the onset of central obesity occurs between ages one and three. Mental retardation is mild to moderate. Hypogonadism is a characteristic feature.

EDS is the most common sleep-related symptom in Prader-Willi syndrome. Though OSA may play a role in some patients, the primary etiology of the EDS seen in Prader-Willi syndrome is thought to be hypothalamic dysfunction. Hypothalamic dysfunction is also thought to be responsible for the reduced nocturnal REM sleep latencies (many patients have sleep-onset REM sleep periods) and the increased number of REM sleep periods seen in these patients (42–45). Nocturnal sleep is increased and usually of good quality, and there is an increased proportion of slow-wave sleep (42).

Patients with Prader-Willi syndrome have several risk factors for OSA, including obesity, cranio-facial dysmorphism, and muscular hypotonia (45). Many have symptoms of sleep-disordered breathing, including snoring and restless movements during sleep. The actual prevalence of OSA in Prader-Willi syndrome is unknown, with reports varying from 0% to 100% (46). The general conclusion of the studies examining the prevalence of OSA in Prader-Willi syndrome is that it is less
common than might be expected based on symptoms and the degree of obesity. Nixon and Brouillette note that obesity in Prader-Willi syndrome is usually in a central distribution rather than the truncal pattern seen in adult men with OSA, possibly explaining the lower-than-expected rates of OSA in morbidly obese patients with Prader-Willi syndrome (46). Alveolar hypoventilation can occur, particularly during REM sleep, and is positively correlated with the degree of obesity (47). The alveolar hypoventilation seen in Prader-Willi syndrome is caused by: (i) restrictive lung disease due to obesity and sometimes scoliosis; (ii) abnormal ventilatory responses to hypercapnea and hypoxia; and (iii) abnormal arousal responses to hypoxia and hypercapnea (46).

**Williams Syndrome**

Williams syndrome, also called Williams-Beuren syndrome, is a rare (approximately 1/20,000 births) disorder characterized by mental retardation or learning difficulties, “elfin” facies, hyperacusis, infantile hypercalcemia, and vascular and connective tissue abnormalities (often leading to supravalvular aortic stenosis) (48,49). The syndrome results from deletion of the elastin (ELN) gene and neighboring genes at 7q11.23 (49). Patients with Williams syndrome have a unique cognitive profile with relative strengths in language and memory skills, and deficits in visual-motor abilities (50,51). They tend to be overly friendly and anxious (49,50). Hyperactivity is common (52).

Limited information is available about sleep in Williams syndrome. In one study, caregivers reported little sleep or disturbed sleep in 31.4% of Williams syndrome subjects compared to 22% of control subjects matched for degree of mental retardation (53). An association between Williams syndrome and periodic limb movement disorder has been reported (51). Clonazepam, at a dose of 0.25 to 0.75 mg at bedtime, appears to be an effective treatment for periodic limb movements associated with Williams syndrome.

**Rett Syndrome**

Rett syndrome affects approximately 1 in 15,000 females. The disorder is characterized by progressive intellectual and neurological impairments beginning after apparently normal psychomotor development for the first five months of life (1). Early signs of Rett syndrome typically manifest between the ages of 6 to 18 months, and eventually the child progresses to a severe, multiple-disability syndrome (54,55). Females with this disorder display stereotyped hand movements (e.g., hand-wringing or washing) and severely impaired language functioning.

During wakefulness, approximately two-thirds of patients with Rett syndrome have a characteristic pattern of disordered breathing consisting of periods of hyperventilation followed by central apnea and desaturation (56). Breath holding may also occur (55). During sleep, respiration is usually normal, though obstructive and central apneas have been reported (55,57). Irregular sleep–wake rhythms have been frequently observed (57). Sleep is often fragmented; females with Rett syndrome may awaken in the middle of the night and be found playing or laughing for no apparent reason (55). Individuals with this syndrome fail to show the age-related decrease in total and daytime sleep seen in normally developing children (58). One study suggests that supplemental L-carnitine improves sleep efficiency and decreases sleep latency in women with Rett syndrome (59).
Smith-Magenis Syndrome
Smith-Magenis Syndrome (SMS) is caused by a deletion of part of the short arm of chromosome 17. Most individuals with SMS have mild to moderate mental retardation. Neurobehavioral features of this microdeletion syndrome include aggressive and self-injurious behavior and significant disturbances of sleep (60). Sleep abnormalities reported in SMS include low levels of REM sleep, difficulty falling asleep, shortened sleep cycles, snoring, nocturnal enuresis, EDS, and frequent and prolonged nocturnal and early morning awakenings (61,62). It is thought that a circadian rhythm abnormality is responsible for some of the sleep disturbances associated with SMS. Potocki et al. (60) found an inversion of the normal circadian rhythm of melatonin secretion in individuals with SMS, which may be secondary to haploinsufficiency for subunit 3 of the COP9 signalsome (COPS3) gene. Supplemental melatonin may be useful in treating the difficulty falling asleep and abnormal awakenings of SMS (63). A polysomnogram should be performed if sleep apnea is suspected.

Autism
Autism, one of the pervasive developmental disorders, is characterized by impairments in social interaction and communication; in addition, patients with autism have restricted, stereotyped, and repetitive patterns of activities, interests, and behaviors (64). The deficits begin before age three (1). The prevalence of autism is increasing and is currently about 7/10,000 persons, though estimates vary (65,66). About 80% of individuals with autism are mentally retarded (67).

Sleep difficulties have been reported in 49% to 89% of children with autistic spectrum disorders (68), though parental oversensitivity to sleep disturbances in autistic children may play a role (69). In one survey, over one-half of autistic children had difficulty falling asleep (70). Other commonly reported sleep problems include restless sleep, frequent awakenings, enuresis, EDS, disoriented waking, and bruxism (70,71). One study found REM sleep behavior disorder in five out of 11 autistic children with symptoms of disrupted sleep and nocturnal awakenings (72). In contrast to other developmental disability groups, sleep difficulties in autistic children do not correlate with the degree of intellectual deficits (70).

EVALUATION AND MANAGEMENT
Treatment of insomnia in the mentally retarded should be aimed at the underlying etiology. Insomnia should not be attributed to mental retardation until other causes of insomnia, such as OSA, pain, medications, depression, and periodic limb movements have been evaluated for. The American Academy of Sleep Medicine has published practice parameters regarding the evaluation of chronic insomnia (73).

Behavioral methods are considered to be the optimal treatment of insomnia in mentally retarded children. The use of medications for sleep problems in autistic and mentally retarded children should be in combination with behavioral treatments, and considered short-term (74). Though agents such as antihistamines, benzodiazepine agonists, clonidine, melatonin, and sedating antidepressants are sometimes used to treat sleep disturbances in mentally retarded patients, there exists an established (but limited) database only for the use of melatonin.
Melatonin
Limited evidence, predominantly case reports and small trials, suggests the efficacy of melatonin in treating sleep disturbances associated with developmental delay and specific mental retardation syndromes. Niederhofer et al. (75) found that melatonin, 0.3 mg given 30 minutes before bedtime, improved sleep efficiency in mentally retarded insomniacs. As noted above, Zhdanova et al. (41) found that melatonin increased total sleep time and decreased nocturnal motor activity in children with Angelman syndrome. In 25 mentally retarded patients, most with epilepsy, melatonin, three to nine milligrams at nocturnal bedtime, significantly decreased sleep latency (76).

The mechanism by which melatonin improves sleep in some mentally retarded individuals is unclear. In individuals with normal cognitive functioning, exogenous melatonin has both direct soporific and phase-shifting effects. Certain mental retardation syndromes (e.g., SMS syndrome) are associated with abnormalities in melatonin secretion that may be ameliorated by appropriately timed melatonin administration.

Though dosages of melatonin vary in the clinical trials, it is recommended that clinicians administering melatonin initiate treatment with a “physiological dose” of 0.3 mg. In most of the studies of the use of melatonin in the mentally retarded population, the dose was given within one-hour of bedtime. Although probably of only theoretical concern, melatonin has been reported to both increase and decrease seizure frequency (76,77). Clinicians should, however, monitor for an increase in seizure frequency if administering melatonin to individuals with epilepsy.

Behavioral Treatments
Various behavioral treatments have been reported effective in treating insomnia and altered sleep–wake cycles in the mentally retarded. A gradual approach may be more practical and acceptable than acute interventions (78). A detailed evaluation is necessary to clarify the type and extent of sleep problems. Functional analysis may identify a modifiable environmental variable that is maintaining or controlling the sleep problem (74). Behavioral treatments can be administered face-to-face or by means of illustrated booklets (79).

Distinct behavioral treatments are often combined in clinical practice. Behavioral treatments found effective for sleep disorders associated with Down’s syndrome include extinction/graduated extinction, positive bedtime routines, bedtime fading, and sleep scheduling/scheduled awakenings (80). Several reviews describe these behavioral treatments, and they therefore will only be briefly described below (4,81,82).

The technique of bedtime fading involves setting the bedtime at a late time when the individual will fall asleep quickly, and then gradually advancing the bedtime until the desired bedtime is achieved (4). Sleep outside of the prescribed sleep time is forbidden. Sometimes bedtime fading is combined with response cost (bedtime fading with response cost), in which fading is combined with removing the person from bed for a certain time period if he or she does not fall asleep within a preset time after going to bed. Positive routines involve a pleasant, winding-down routine of calm bedtime activities that the child enjoys (81,82). Another behavioral treatment is scheduled awakenings, in which the parent...
awakens and consoles the child approximately 15 minutes before a typical spontaneous awakening (81,82). The scheduled awakenings are gradually decreased. Sleep scheduling is a strategy in which the child is put into bed at night and awoken in the morning according to a fixed time schedule (4). Sleep outside of scheduled times is prohibited or minimized. Extinction involves putting the child into bed at a designated time and then systematically ignoring the child until a preset morning wake time (82). It can be difficult for parents to completely ignore a child’s tantrums, and therefore graduated extinction is a more frequently used technique than extinction. In this strategy, crying/tantrums at bedtime or in the middle of the night are ignored for a preset time period. If the behavior continues, the parent checks on the child and comforts him/her for 15 seconds or less (82). Over subsequent nights, the time period the parent waits before checking on the child is gradually lengthened.

Elements of the above-described behavioral treatments are often combined. In particular, the technique of positive routines is frequently combined with other strategies.

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INTRODUCTION

Insomnia is defined as difficulty with the initiation, maintenance, duration, or quality of sleep resulting in the impairment of daytime functioning despite adequate opportunity and circumstances for sleep (1,2). Although research studies sometimes require a specific quantitative definition, a patient’s subjective judgment that sleep is insufficient, inadequate, or nonrestorative is the most important factor in clinical practice. Insomnia is the most common sleep complaint. Transient insomnia lasts less than one week, and short-term insomnia one to four weeks. Chronic insomnia, insomnia lasting more than one month, affects between 10% and 35% of the population in the western world (3,4). The number of chronic insomniacs rises with age, and women of all ages complain of insomnia more often than men (3,5). Insomnia is frequently associated with other medical complaints and psychological symptoms, particularly anxiety, worry, and depression. Stressful life events (difficulties in interpersonal relationships, family discord, problems at work, and financial troubles) may also generate a nonrestorative sleep complaint. Insomnia is not a specific illness or disease, but rather a symptom or consequence of other primary disorders. “Poor quality of sleep” is a common complaint in the family members of chronic insomniacs. However, it is difficult to gauge the extent to which the emotional problems favouring the onset of a sleep disorder in adulthood are due to a genetic predisposition or the result of having lived in a family burdened by affective problems and/or interpersonal conflicts.

Neurological illness may affect the mechanisms regulating sleep and sleep architecture, but it should also be borne in mind that neurological disorders and diseases are almost always accompanied by major psychological distress. In addition, the medications used in the treatment of the neurological diseases may lead to sleep disorders. Hence, it is difficult to establish whether the onset of chronic insomnia in an individual patient with a neurological illness is due to the disease or to a psychosomatic disorder or an iatrogenic consequence of the neurological impairment.

Insomnia can be classified as primary or secondary. The pathogenesis of primary insomnia is unknown, but there is convincing evidence that some
patients with insomnia are physiologically in a constant state of hyperarousal (6). Positron-emission tomography studies during sleep in humans with insomnia compared with sleeping subjects without insomnia showed that when the arousal systems override the homeostatic and circadian regulation of sleep, the result might be insomnia (7). Secondary insomnia can be due to poor sleep hygiene, drug or substance use or abuse, psychiatric, medical, and neurological conditions.

The neurological diseases most commonly associated with chronic insomnia fall into three groups.

1. Neurological diseases or disorders (degenerative and other) impairing sleep mainly or exclusively because of illness-related personal discomfort (motor immobility, personal or familial life disruption, depression, and drugs).
2. Neurological diseases characterized by movement disorders hindering sleep onset and/or sleep continuity.
3. Central nervous system (CNS) lesions (dysfunction) impairing the basic mechanisms of sleep generation (agrypnia or organic insomnia).

INSOMNIA IN NEUROLOGICAL DISEASES (DEGENERATIVE AND OTHER)

Insomnia in Elderly Patients with Dementia

Aging accompanied by mental deterioration caused by a degenerative [e.g., Alzheimer dementia (AD)] or vascular disease (multi-infarct dementia) can compromise the sleep–wake rhythm more than the physiological aging process. Specifically, patients with AD have an increased number and duration of awakenings and, as a result, a higher percentage of stage 1 sleep. Sleep disturbance may be multifactorial and involve sleep-disordered breathing and disrupted chronobiology, both often characterized by excessive daytime napping. A recent 24-hour actigraphic study performed in institutionalized dementia patients showed four types of abnormal rhythms: a free-running (phase-delayed) type, an aperiodic type, an ultradian rhythm type with a cycle lasting three to four hours, and a flattened amplitude type in which patients were largely bedridden (8). Sundowning defines the tendency of demented people to present nocturnal agitation, and may be a primary factor leading to the decision to institutionalize a patient. Admission to a nursing home in turn exacerbates the behavioral disorder with mental confusion and hallucinations.

Less severe or better tolerated than nocturnal disruptive behavior are similar disorders arising during the day. Nursing facilities that routinely put patients to bed during the afternoon for naps had lower rates of agitation than facilities without this routine (9). The cause of sundowning in dementia is unknown, but there is much evidence of impaired circadian fluctuations in body temperature and secretion of melatonin and cortisol in patients with dementia compared with an age-matched normal population (10). It remains unsettled whether insomnia or sleep disruption in the elderly with dementia is due to an anatomical–functional impairment of the suprachiasmatic nucleus or to a more complex alteration of the neuronal network controlling circadian and homeostatic wake–sleep cycle regulation (10).

Keeping patients in well-lit rooms during the day and in dark and quiet resting rooms during the night may help to improve the wake–sleep cycle. Exposure to bright light may also help to optimize the sleep–wake cycle in dementia, although optimal timing of such light exposure (i.e., morning, afternoon, or evening) is uncertain. In any case, a comprehensive sleep education program...
with behavioral techniques (specifically, sleep hygiene education, daily walking, and increased light exposure) could improve sleep in dementia patients living at home with family caregivers (11). Benzodiazepine administration often makes the agitation worse. Clozapine (12.5–25 mg twice a day) and risperidone (1.0 mg a day) may be of value, and the more recently atypical antipsychotics, such as quetiapine (12.5–25 mg) and olanzapine (10–15 mg), led to improved night-time behavior (12,13).

Administration of 3 to 5 mg of melatonin two to three hours before bedtime may also be of some benefit.

INSOMNIA IN DEGENERATIVE DISEASES OF THE CENTRAL NERVOUS SYSTEM WITH MOTOR-SYSTEM INVOLVEMENT

This group of diseases includes Parkinson’s disease (PD) and parkinsonian syndromes [progressive supranuclear palsy (PSP) and multiple system atrophy (MSA)], Huntington’s chorea (HC), progressive dystonia, and Tourette’s syndrome (TS). Literature reports on insomnia in these diseases are fragmentary, controversial, and mainly anecdotal. Video-polysomnography (PSG) may be required only in special cases in which motor [rapid eye movement (REM) sleep behavior disorder (RBD)] or breathing disorders (laryngeal stridor) are suspected. Lacking appropriate therapy, treatment of the sleep disturbance is often difficult and confined to general measures to improve sleep quality (sleep hygiene, etc.).

Parkinson’s Disease

Almost 70% of PD patients report nocturnal disturbances, including insomnia, nightmares, and excessive daytime sleepiness (14). In idiopathic PD, both motor symptoms (nocturnal akinesia, early-morning dystonia, painful cramps, tremor, and turning in bed) and the depression that often accompanies the disease can give rise to insomnia, which may respond to administration of benzodiazepines or amitriptyline. A marked reduction of spindling, fragmentation of sleep, and a shorter total sleep time are common in the PSG recordings of patients with PD. Sleep in diffuse Lewy body disease, characterized by dementia associated with parkinsonism, is disrupted by hallucinatory episodes and RBD, clinical features complicating the disorder (15,16).

Progressive Supranuclear Palsy

Insomnia is a common complaint in patients with PSP (17,18). Axial rigidity, dystonia, and postural difficulties may contribute to insomnia in these patients. PSG recordings in patients with PSP show prolonged sleep latency, decreased total sleep time, decreased sleep efficiency, repeated arousals and awakenings, a decreased percentage of stage 2 with a drastic reduction in the number and amplitude of sleep spindles, and a reduced amount of REM sleep (17,19,20). REM sleep latency may be shortened in some patients. Rare cases of RBD associated with PSP have been reported (21). Another characteristic feature of PSP seems to be daytime somnolence that in some cases is the most prominent clinical symptom. However, subjective findings of sleepiness in these patients may not coincide with objective measurements (multiple sleep latency test). PSP is pathologically characterized by extensive damage to the basal ganglia, median thalamus, and pontomesencephalic reticular formation. Involvement of the subcortical neurological structures responsible for sleep–wake regulation accounts for the sleep impairment commonly encountered.
Multiple System Atrophy
Neurodegenerative diseases previously described as striatonigral degeneration, sporadic olivopontocerebellar atrophy, and Shy–Drager syndrome, and now grouped under the term MSA, are characterized by recurrent arousals caused by motor events (RBD) and periodic limb movements during sleep (PLMS) and/or by breathing difficulty (heavy snoring, central and obstructive apneas, and nocturnal stridor). PSG recordings in patients with Shy–Drager syndrome show a reduced amount of slow wave sleep (SWS), REM sleep and total sleep time, increased sleep latency, and recurrent awakenings (22,23). The circadian rhythms of temperature and melatonin secretion are also impaired in both PSP and MSA and reflect a severe disruption of the mechanisms controlling autonomic and endocrine homeostasis that could contribute to sleep impairment (24).

Huntington’s Chorea
Insomnia with impaired initiation and maintenance of sleep is a common complaint, especially in moderate to severe cases of HC. Sleep fragmentation and deterioration increase as the disease progresses (25,26). Polysomnographic recordings in these patients show reduced sleep efficiency with sleep fragmentation and decreased slow-wave and REM sleep. Anatomical lesions, involuntary movements, medication, and depression all contribute to the insomnia.

Progressive Dystonia
Sleep disturbances occur in many patients with torsion dystonia, and disease progression is flanked by deterioration of sleep. PSG studies in these patients disclosed increased sleep latency and frequent awakenings with reduced sleep efficiency (27). REM sleep may be reduced in severely affected patients.

Tourette’s Syndrome
Sleep complaints are common in patients with TS. The degree of sleep disturbance is correlated with disease severity. Around 40% of children with TS also have a history of somnambulism, night terrors or enuresis and are prone to “confusional arousal.” An increased number of awakenings and increased motor activity and body movements during sleep have been described in TS (28).

INSOMNIA LINKED WITH MOVEMENT DISORDERS
Some neurological disorders are characterized by abnormal movements that hinder sleep onset or interrupt SWS or REM sleep, leading to a complaint of chronic insomnia. These include: (i) restless legs syndrome (RLS) and PLMS, (ii) propriospinal myoclonus (PSM), (iii) nocturnal frontal lobe epilepsy (NFLE), and (iv) RBD.

1. RLS is characterized by an undefinable feeling of discomfort typically localized deep in the legs, usually between the knee and ankle. Paresthesias arise during rest, especially in the evening or in the early part of the night when the patient lies down trying to fall asleep. Any movement of the limbs, such as rubbing the legs together, making bicycling movements, and pacing across the room, transiently relieves symptoms (29). A milder form of the syndrome lengthens the time it takes to fall asleep and is not a true medical problem; however, patients
with the most severe forms suffer severe and persistent insomnia that not only
hinders falling asleep, but triggers recurrent prolonged awakenings throughout
the night. The most disturbing form of RLS affects 1% to 2% of the population,
whereas the mild forms were experienced by 5% of people interviewed (29). A
family history of the disorder is found in 90% of idiopathic cases with an autosomal
dominant pattern of inheritance in 2% to 10% of cases (30). The hereditary-familial
forms of RLS and severe sporadic cases arise in the first and second decades and
persist throughout life. In other cases, the disorder becomes clinically relevant
after the fifth to sixth decade. Recent studies show that RLS is more common
than suspected in childhood and adolescence. Older patients tend to complain of
more severe RLS symptoms, indicating that the disease is a progressive and
chronic condition. The etiology and physiopathology of RLS remain unknown.
Some symptomatic forms arise in patients with iron-deficiency anemia (31,32),
familial amyloid neuropathy (33), or uremia (34,35). RLS may transiently appear
during pregnancy, or intensify during treatment with various drugs (such as
typical and atypical neuroleptics, metoclopramide, estrogens, tri- and tetra-cyclic
antidepressants, and serotonin reuptake inhibitors) (29,36).

More than 80% of patients with RLS present PLMS generally confined to the
lower limbs (Fig. 1). In its simplest form, PLMS consists of a sudden dorsiflexion
of the big toe and/or foot, sometimes associated with flexion of the leg on the thigh
and of the thigh on the trunk. Both extremities are usually involved, but as a rule
not simultaneously or symmetrically, predominating in one leg or alternating
between legs. PLMS appear on falling asleep and continue in light sleep, recurring
every 20 to 40 seconds. K complexes, increased muscle tone, heart and breathing
rates, and raised systemic blood pressure coincide with PLMS during light sleep.
Thus, PLMS are part of a periodic arousal involving cortical, somatic, and visceral
functions (37,38). A dual mechanism consisting in an abnormal spinal cord hyperexciti-
ability modulated by circadian oscillations and superimposed phasic activation of
motor functions recurring every 20 to 40 seconds is responsible for PLMS (39).

FIGURE 1 Polygraph of restless-legs syndrome and nocturnal myoclonus (NM). While asleep, the
patient displays repetitive, quasi-rhythmic polyclonic jerks in the lower and upper limbs, intermingled
with voluntary movements. As soon as the patient falls asleep, periodic movements (NM) persist in
the lower limbs.
PLMS have been claimed to cause either insomnia or excessive daytime sleepiness, but in most cases the movements are simply a chance PSG observation and are virtually never appreciated by the patient. Although most often encountered in RLS, PLMS may also occur in healthy people and their prevalence increases markedly with age: they are almost always absent before thirty, but occur in 5% of normal subjects aged 30 to 50 years and in 30% of the population over 50 years of age (40). Most importantly, the prevalence of PLMS does not differ significantly in people with insomnia, hypersomnia, or healthy subjects (41). Except for very peculiar cases in which myoclonic jerks are so frequent and violent as to disrupt nocturnal sleep, PLMS are not the cause of insomnia (42).

2. PSM is characterized by muscle jerks, usually very intense, arising from an axial muscle (in the neck, chest, and abdomen), and then extending up and down via the multisynaptic pathways to the rostral and caudal muscles along the propriospinal pathways intrinsic to the cord (43). PSM typically arises when patients are about to fall asleep, when the alpha rhythm spreads to the anterior regions or is replaced by low-amplitude theta activity (stage 1 of non-REM (NREM) sleep) (44). This triggers an arousal followed by another attempt at falling asleep, during which another myoclonic jerk occurs. The jerks may recur quasi-periodically, every 10 to 20 seconds for minutes or hours, preventing patients from falling asleep and eventually leading to a severe insomnia that can persist for years or even decades and often disrupts the patient’s family and social life. Sensory activation (noise, lights, or other environmental stimuli) or mental tasks (speaking, thinking, and mental arithmetic) temporarily impede the muscular jerks. The appearance of sleep spindling in stage 2 NREM sleep (transition from stage 1 to 2) is immediately followed by the cessation of muscular jerks. Physiological sleep, when initiated, usually continues until the morning (Fig. 2). Once the patient is awake, PSM seldom recurs and in any case is much milder. Clonazepam (at a dose of 0.5–2 mg) can alleviate the disorder, reducing the jerks, and

FIGURE 2  Propriospinal myoclonus hypnogram. The histogram (bottom) indicates the number of jerks per minute. Jerks persist over 90 minutes, increasing sleep latency; they disappear with sleep onset and fail to return during sleep (stage 2).
making sleep more restful. Opiates may also be effective, but carry the risk of dependence (44).

3. NFLE is a recently identified clinical entity characterized by a wide spectrum of clinical manifestations arising during SWS and usually consisting of: (i) paroxysmal arousals (PAs), sudden awakenings accompanied by stereotyped abnormal movements, (ii) nocturnal paroxysmal dystonia (NPD), dystonic–dyskinetic attacks lasting one to two minutes, (iii) episodic nocturnal wandering (ENW), or agitated somnambulism (45). These three types of seizures often coexist in the same patient. The shortest seizures may recur several times every night, giving patients the feeling of having slept little and badly. Some patients with very frequent nocturnal seizures feel tired and weary on awakening in the morning and complain of daytime sleepiness. If seizures disappear or decline in frequency with antiepileptic drug treatment, this sense of tiredness and daytime somnolence may subside (45). NFLE can be inherited as an autosomal dominant disorder, and some mutations have been linked to familial cases of NFLE (46).

NFLE must be clearly differentiated from arousal disorders (sleep terrors or sleepwalking), sometimes a difficult task in the absence of video-PSG recordings (45).

4. RBD is a parasomnia characterized by episodes of motor agitation arising during REM sleep. Loss of the physiological muscular atonia during REM sleep (REM sleep without atonia) is the causal event leading to RBD. RBD usually occur in the middle of the night or during early hours of the morning and are characterized by more or less purposeful gestures enacting attack or defence reactions, sometimes associated with emotional expressions of joy, laughter, or sorrow (47). This results in repeated episodes of motor agitation of varying intensity during REM sleep. When RBD episodes are intense and prolonged, nocturnal sleep is disrupted and patients may feel tired and weary upon awakening. RBD is common in the older population with a mean age at onset of 60 years and a male/female ratio of 9/1. This sleep disorder may be idiopathic (in about 40% of cases) or associated with a neurodegenerative disorder, which in many cases may be a synucleinopathy (48). Several investigators have noted the tendency for RBD to appear as a symptom heralding MSA by years (49). A recent comparison of the clinical and video-PSG characteristics of idiopathic RBD versus the RBD in MSA and PD disclosed that RBD-related symptoms and neurophysiological features are qualitatively similar in RBD subjects with the idiopathic forms, MSA and PD (50). Polysomnographic abnormalities (a greater percentage of REM sleep without atonia, higher PLMS index, and less total sleep time) associated with RBD in the setting of MSA are greater than in PD, suggesting a more severe dysfunction in the structures that modulate REM sleep. This is supported by the finding that RBD is much more common, nearly ubiquitous, in MSA than in PD. Clonazepam (0.5–2 mg) is effective in 80% to 90% of cases. RBD causes sleep fragmentation and poor quality sleep mainly when it recurs every night at each REM episode.

Other Less Common Sleep-Related Movement Disorders that may Disrupt Sleep

Excessive fragmentary hypnic myoclonus (EFHM) consists in an abnormal intensification of the physiologic hypnic myoclonia and is characterized by sudden arrhythmic asynchronous and asymmetric brief twitches involving...
various body areas. The EFHM usually occurs in association with sleep apnea, RLS, RBD, and excessive daytime drowsiness, but is not necessarily associated with other sleep disorders. If severe, EFHM may disturb sleep onset and continuity (51).

Facio-mandibular myoclonus is a rare parasomnia and usually does not affect sleep. However, rhythmic or prolonged tonic contractions of the masticatory muscles may damage the tongue and oral mucosa, resulting in a burning pain, which disturbs sleep (52).

**ORGANIC INSOMNIA (AGRYPNIA) AND GENERALIZED OVERACTIVITY SYNDROME (AGRYPNIA EXCITATA)**

Some rare neurological disorders are characterized by virtually total loss of the inability to sleep, accompanied by episodes of confusion, agitation, and enacted dreams.

The term “agrypnia” (from the Greek “to chase sleep”) or organic insomnia defines loss of sleep due to lesions or impairment of the neuronal pool involved in sleep generation. An historical example of agrypnia was described by von Economo (53) in cases of epidemic encephalitis in which anatomical lesions prevailed in the anterior hypothalamus and basal forebrain. Organic insomnia has also been anecdotally described after pontine lesions (54), bilateral stereotaxic thalamotomy (55), and in cases of spinal cerebellar degeneration (56).

Interestingly, there are at least three neurological conditions [fatal familial insomnia (FFI), Morvan’s chorea (MC), and delirium tremens (DT)] in which the inability to sleep is typically associated with motor and sympathergic overactivation. Agrypnia excitata (AE) is the term which aptly defines this generalized overactivation syndrome (57,58).

The FFI is clinically characterized by apathy (attention deficit and indifference to surroundings) and an inability to sleep (agrypnia) accompanied by enacted dreams (gestures consistent with the context of a dream), sympathetic hyperactivity (profuse perspiration, tachycardia, hypertension, mild fever, etc.), and motor signs (ataxia, dysarthria, and myoclonus), and pathologically by selective degeneration of the anteroventral and mediodorsal thalamic nuclei (59). The FFI is an autosomal dominant prion disease linked to a point mutation at codon 178 of the prion protein gene at chromosome 20, in conjunction with methionine in the methionine/valine polymorphic position 129 on the mutant allele. Around 30 FFI kindreds have been described to date in addition to nine sporadic (nongenetic) cases [sporadic fatal insomnia (SFI)] (60).

The FFI starts at a mean age of $51 \pm 7$ years (standard deviation), and disease duration varies from eight months to seven years. The disease course is relatively short (9–10 months as a mean) in patients who are methionine–methionine homozygous at codon 129 of the prion protein gene, whereas heterozygous patients (expressing valine at codon 129 on the nonmutated allele) have a relatively long disease duration (30 months as a mean) (60).

The sleep disorder, documented by detailed polysomnographic studies, comprises an early disappearance of spindles and delta sleep which, markedly reduced from disease onset, disappear completely in the advanced stages of the disease. Sleep disintegration leads to a persistent state of subwakefulness interspersed with episodes of more or less purposeful gesturing in which the patient enact the content of a dream (Fig. 3). These episodes occur when atypical episodes of REM sleep emerge directly from subwakefulness. In addition, 24 hours serial
studies document that autonomic (blood pressure and body temperature) and hormonal (cortisol, norepinephrine, and melatonin) circadian oscillations progressively subside until they disappear almost completely. In short evolution FFI cases, PET scan discloses a brain hypometabolism confined to the thalamus. In long evolution cases, hypometabolism still predominates in the thalamus, but extends to the cerebral cortex (namely frontotemporal cortex) and basal ganglia. In short evolution cases, neuronal loss and astrogliosis are confined to the thalamus, whereas in long evolution cases, the lesions extend to the cerebral cortex where spongy degeneration is consistently found, especially throughout the limbic and paralimbic cortex.

Severe impairment of nocturnal sleep and daytime hypersomnolence characterize other disorders affecting the anteromedian thalamic nuclei, such as paramedian thalamic stroke syndrome (61).

The MC was first identified in 1890 and mainly reported by French researchers (62,63). The disorder consists of severe insomnia with subacute onset associated with anxiety and restlessness, profuse perspiration, tachycardia, cramps, muscular twitches (named by Morvan “fibrillary chorea”), and motor agitation (62). Fewer than 100 patients have been described to date. The MC arises at any age and has a benign evolution in 80% to 90% with spontaneous remissions (64). In the remaining cases, MC progressively worsens with a fatal outcome. One case with malignant evolution was recorded polygraphically by Fisher-Perroudon et al. (63) who documented a virtually total inability to sleep in the four months preceding the patient’s death. In a similar case we followed until death, the clinical features were characterized by a typical aspect of neuromyotonia (Isaacs’ syndrome) associated with an inability to sleep, mental confusion, dream enactment (behaviorally similar to those observed in FFI patients), and hallucinations (65). Our patient also presents motor agitation persisting day and night, central sympathetic overactivation accompanied by persistently high norepinephrine levels and reduced melatonin secretion. Subwake electroencephalogram (EEG) patterns

![Figure 3](image-url) Fatal familial insomnia. The hypnogram (top) is characterized by fluctuations from stage 1 to REM sleep, as shown in the polysomnogram (bottom).
(stage 1 NREM) interrupted by short recurring episodes of REM sleep without atonia are the hallmarks of day and night polygraphic recordings. As in FFI, spindles and delta sleep are markedly reduced or completely absent (Fig. 4). Plasma-exchange treatment led to a marked improvement of both central and peripheral signs, but the patient died suddenly two years later. Pathology was unremarkable in our patient and in the few other cases in which postmortem brain evaluation was performed (63,65). Serum IgG bound strongly to neurons in the hippocampus, thalamus and striatum of rat brain, whereas direct immunochemistry on frozen sections of postmortem brain tissue showed areas of antibody leakage in the thalamus (65).

The DT is a well-known acute psychotic syndrome linked to sudden alcohol withdrawal after chronic alcohol abuse. Similar findings may occur after sudden withdrawal of meprobamates, barbiturates, and benzodiazepines (66). The DT is clinically characterized by an acute confusional state associated with visual hallucinations and dream enactment. Severe insomnia, agrypnia, motor agitation, and sympathetic overactivity (perspiration, tachycardia, hypertension, and mild fever) are common findings. Polysomnographic recording of a special case showed the disappearance of physiological sleep: spindle and delta sleep are remarkably reduced or even absent and wake or subwake EEG patterns alternate with long-lasting recurrent episodes of REM sleep (66,67) (Fig. 5).

The pathogenetic mechanisms of DT are not well understood, even though the diencephalic structures are known to be consistently implicated in alcohol abuse (67).
Agrypnia Excitata—A New Clinical and Pathophysiological Concept

The FFI, MC, and DT are three pathological conditions with a similar sleep disorder, but different etiology and clinical course. The clinical and polysomnographic similarities between them could be the result of a common underlying mechanism involving the same circuits responsible for sleep–wake regulation. These “agitated agrypnias” could be caused by a functional imbalance characterized by the prevalence of activating over deactivating systems in the CNS. In FFI, this could result from atrophy of the mediodorsal thalamic nuclei, preventing inhibitory impulses originating in the reticular nucleus, from reaching other cortical and subcortical structures involved in sleep regulation (68).

In delirium tremens, a similar outcome (inability to sleep and sympathetic overactivation) could ensue from downregulation of the gamma-aminobutyric acid (GABA) receptors caused by the chronic intake of GABAergic substances (alcohol, barbiturates, and benzodiazepines). The sudden withdrawal of alcohol or drugs stimulating the GABA receptors could lead to the same functional imbalance between activating structures (promoting wakefulness) and deactivating structures (promoting sleep) observed in FFI.

In Morvan’s syndrome, the mechanism responsible for such symptoms remains unclear, but the same circuits responsible for sleep–wake regulation could be implicated yet again as a consequence of an imbalance induced by some channel-specific antibodies, leading to the functional prevalence of activating over deactivating systems. The beneficial effect of plasma exchange observed in our case is consistent with this tentative pathogenetic explanation of our patient’s inability to generate sleep (57,58,60,68).

FIGURE 5 Delirium tremens. The hypnogram (top) is characterized by continuous fluctuations from wakefulness to REM sleep without atonia (REM*). During REM* the patient displays complex dream-like hallucinatory behavior. Wrist actigraphic recording (muscle activity) shows a motor overactivity with a loss of 24-hour circadian motor rhythmicity. Polysomnography documents an abrupt onset of REM* from wakefulness. Abbreviation: REM, rapid eye movement.
A transient imbalance between GABAergic and cholinergic systems has also been invoked to explain a case of agrypnia in a patient with multiple cranial nerve palsy who developed respiratory crises, dysautonomia, and inability to sleep, and who improved after plasma exchange and immunosuppressive treatment (69). The detection of anti-GABAergic synapse antibodies supports an autoimmune pathogenesis of the syndrome.

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INTRODUCTION

Sleep is an essential feature of human existence, which, under normal and routine circumstances, recurs periodically every day at a certain time. It is a common existential knowledge that sleep is optimal in both quality and quantity only when it occurs during a proper time frame in a 24-hour day. Similarly, wakefulness is optimal at certain hours and waxes and wanes predictably during the day (e.g., the siesta in the Mediterranean countries corresponds to the physiological decrease in alertness in the afternoon). The timing of sleep and wake is a complex output of both circadian and homeostatic processes, which will be reviewed below.

Attempts at falling asleep or staying awake at physiologically inappropriate times will result in distinct recurrent or chronic patterns of sleep–wake disturbance, that is, circadian rhythm sleep disorders (1). Several sources for this disturbance may exist, all resulting in misalignment of the intrinsic sleep–wake propensity of a person and the 24-hour physical and social environment. The intrinsic rhythm may be shifted relatively to the environmental time-cues (delayed or advanced sleep phase type), become disrupted (irregular sleep–wake type), or have different periodicity (free-running type). The physical environment may change faster than the adaptation ability of the intrinsic sleep–wake rhythm (jet-lag type), or an individual may choose to disregard the intrinsic rhythm and voluntarily choose to stay awake at an inappropriate time (shift work type). For classification and coding purposes, some circadian rhythm sleep disorders may also be coded as due to medical condition, due to drug or substance, or other circadian rhythm sleep disorders (1).

The correct approach to diagnosis and management of this unique group of sleep disorders requires a working knowledge of the principles of chronobiology, that is, the physiology of the circadian system; these principles will be reviewed first. Next, the circadian rhythm disorders will be sequentially reviewed, emphasizing their clinical features, pathophysiology, diagnosis, and management.

BASIC CIRCADIAN PHYSIOLOGY

Almost every cell in the organism has active molecular oscillators, which regulate circadian genes expression in response to various time-cues, mainly chemical changes induced by feeding and temperature changes [see (2) for a review]. In the absence of a central master clock, the myriad peripheral pacemakers would produce a cacophony of rhythms, which will make a coordinated circadian behavior impossible.

The paired suprachiasmatic nuclei (SCN) of the hypothalamus have long been established as the site of the mammalian master circadian oscillator (3). This small
cluster of anterior ventromedial hypothalamic neurons manifests a high-amplitude circadian pattern of firing both in intact, freely behaving animals and in vitro (Fig. 1). The SCN master clock is composed of multiple single-cell circadian oscillators that, when synchronized, generate coordinated circadian output that regulates peripheral “clocks” by transmission of circadian timing signals. The regulation is achieved by means of direct and indirect projections to other regulatory brain areas, modulating in turn their circadian outputs (4). This regulation coordinates other overt rhythms (e.g., arousal, hormonal secretion, temperature, feeding, etc.). Daily behavioral, vegetative, and circadian firing rhythms of other brain regulatory regions disappear if the SCN are lesioned, and some, but not all, are restored with fetal SCN tissue transplants into the anterior third ventricle (5). Therefore, diffusible SCN output signals must also reach peripheral tissues, thus adding to the orchestrating role of the SCN; these signals were recently identified as TGF-α and prokineticin 2 (PK2) (6,7).

The natural endogenous circadian period of humans is slightly more than 24 hours, generally about 24.2 hours (8,9). If all time-cues are removed, this 24.2-hour cycle induces all other rhythms to be progressively phase-delayed relative to the external clock time. Keeping the basic 24-hour cycle involves daily synchronizing of the internal clocks with the shorter solar day following external time-cues (a process known as entraining, a control of one oscillating process by another). This circadian correction is achieved by advancing the internal clocks by a fixed time period (about 0.2 hours) every day.

**FIGURE 1** The human circadian system outline. Melatonin (*upper right inset*) is produced in the pineal gland. The production and secretion of melatonin are mediated largely by postganglionic retinal nerve fibers that pass through the retinohypothalamic tract to the suprachiasmatic nucleus, then to the superior cervical ganglion, and finally to the pineal gland. This neuronal system is activated by darkness and suppressed by light (*left insets*). The activation of α₁- and β₁-adrenergic receptors in the pineal gland raises cyclic AMP and calcium concentrations and activates arylalkylamine N-acetyltransferase, initiating the synthesis and release of melatonin. The daily rhythm of melatonin secretion is controlled by the endogenous master pacemaker located in the suprachiasmatic nuclei. The lower right inset shows the temporal relationship between the activity of the suprachiasmatic nuclei and the secretion of melatonin within a period of 24 hours (not to scale). **Abbreviations:** SCN, suprachiasmatic nuclei; MEL, melatonin. **Source:** From Ref. 197.
Light is the main time-cue of endogenous clocks in humans, as it is in other animals and plants (10). The human circadian system is more sensitive to short-wave blue–green light than to long wave red spectrum (11). The major afferent light input to the SCN consists of a melanopsin-containing subset of photosensitive retinal ganglion cells whose axons depart the optic chiasm to synapse on the SCN cells (12,13). This retinohypothalamic tract (RHT) (Fig. 1) transmits non-visual, light–dark information to the SCN, which is probably mediated through glutamate (14). There is an additional light–dark information pathway from the intergeniculate leaflet (IGL) (located within the lateral geniculate body of the thalamus), the geniculate–hypothalamic tract, where neuropeptide Y seems to be the main neurotransmitter (15). The IGL projects heavily to the SCN and other brain areas associated with circadian time keeping (16). Another major input to the SCN is from the midbrain raphe nuclei, and there is evidence that serotonin is involved in the behavioral and light modulation of the circadian rhythm (17–19).

Exercise may also have an effect on entrainment (20,21), as may social stimuli (22); however, these may act through homeostatic regulation of sleep, rather than on the circadian clock itself (23).

There are three fundamental characteristics to the resetting capacity of the human circadian clock by light. First, the maximal response only occurs at certain circadian times, generally a few hours before or after the nadir of core body temperature, which occurs between 03:00 and 05:00 hours in normally entrained humans; thus, the best “window of opportunity” for phase shift normally occurs during the dark period. Stimuli applied during most of the daylight period have no effect on circadian phase timing (24), although there is some evidence that the human circadian pacemaker may be sensitive to bright light throughout the day (25). Second, the direction of resetting (advance or delay) is dependent on the circadian time at which it is attempted; light exposure early in the dark period delays the phase, whereas exposure late in the dark period advances it. Third, the amount of maximal daily resetting is limited to one to three hours (26). Plots of the magnitude and the direction of response (phase change) against the circadian time of light stimulus application [phase-response curve (PRC)] reveal increasing amounts of delay from dusk to about halfway through the dark period (which roughly coincides with the nadir in core body temperature). The direction of phase change then rapidly switches to maximal phase advances when the stimulus is applied near the beginning of the second half of the dark period, after which the advance response declines as the light stimulus moves closer to subjective dawn (27). The daily phase-advance in humans that keeps pace with the 24-hour day is a process that occurs immediately following arising in the morning and exposing the eyes to sufficient light.

The circadian clock phase (location of a certain event in the near 24-hour cycle), amplitude and period cannot be measured directly by noninvasive means. Core body temperature varies predictably under circadian influence, even without the masking effect of sleep (which lowers the body temperature regardless of the circadian phase); it may thus serve as a circadian marker, but necessitates cumbersome rectal probes. The rhythm of the pineal hormone melatonin is probably the best marker of the endogenous circadian rhythm, certainly the easiest to measure (Fig 1). Melatonin levels in fractional saliva specimens correlate well with plasma melatonin (28), and it is less markedly influenced by sleep and posture (29). The pineal is under the control of the SCN; this control is exerted through the multisynaptic sympathetic innervation. Melatonin is produced during darkness periods...
and is suppressed by light of sufficient duration and intensity. Its peak is tightly
coupled to the nadir of core body temperature. The circadian rhythm of melatonin
is highly robust, has low intra-individual but high inter-individual variability, and
is appreciably masked only by light. The dynamics of the daily duration of melato-
nin secretion is significant in seasonal and reproductive physiology in animals;
longer nights characteristic of winter photoperiod are signaled by longer melatonin
secretion duration. The phase of the circadian melatonin rhythm can be reset by
appropriately timed light pulse; a PRC describes the effect of light on the amplitude
and direction of the melatonin rhythm phase shift (30).

The role of melatonin in the human circadian cycle is modulatory. The SCN
exhibits dense melatonin receptors, probably establishing a feedback mechanism.
It is not clear whether endogenous melatonin entrains other circadian rhythms.
Exogenous melatonin, however, can shift circadian phase, exhibiting a PRC that
is roughly a mirror image of the PRC of light (31). The direction and the magnitude
of the shift depend on the circadian time at which the light or melatonin are applied.
Bright light in the evening delays the phase of the circadian clock, whereas in the
morning it advances the phase; exogenous melatonin does the opposite. Peak
responses to light in either direction are obtained around the time of core body
temperature nadir, at about 04:00 hours, wherein stimulation before this time
delays the phase, while stimulation after this time advances it. With exogenous
melatonin, peak phase advance occurs prior to the time of dim-light melatonin
secretion onset (at about 20:00 hours), and peak phase delay about 12 hours later.
Exogenous melatonin also affects other rhythms, like temperature, cortisol
secretion, and the sleep–wake cycle. Appropriately timed light exposure and
melatonin may reinforce a desired effect; indeed, it is possible that the physiological
role of the night melatonin secretion is to reinforce the daily resetting of the
endogenous clock by the morning light and to provide additional fine-tuning
(30,32). Mutually reinforcing timed application of light and exogenous melatonin
are used in treating circadian rhythm sleep disorders.

The sleep–wake cycle is a major overt manifestation of the circadian rhythm
possibly through SCN direct and indirect projections to wake- and sleep-promoting
brain regions (33,34). However, compared to other endogenous rhythms like core
body temperature or melatonin, it is more loosely associated with the circadian
pacemaker, and is also influenced by noncircadian homeostatic factors (e.g., prior
sleep deprivation). Sleep propensity is governed at any time by the interaction of
two processes: (i) an oscillating circadian process coupled to other circadian
rhythms (e.g., melatonin secretion and core body temperature rhythms), that
promote sleepiness at night and contribute to the afternoon “siesta” period; and
(ii) a monotonously increasing homeostatic process reflecting prior sleep depriva-
tion that discharges during sleep (35). The detailed description of the interaction
of these processes is beyond the scope of this review; suffice is to say that the classic
two-process interaction model is an abstraction, and the net result of sleep-alertness
is much more than the algebraic sum of the two processes.

CIRCADIAN RHYTHM SLEEP DISORDER—DELAYED SLEEP
PHASE TYPE (DELAYED SLEEP PHASE DISORDER)
Clinical Manifestations
Patients with delayed sleep phase disorder (DSPD) have their habitual sleep–wake
times delayed, usually by more than two hours, relative to conventional or socially
acceptable time, resulting in symptoms of sleep-onset insomnia or difficulty in awakening at the desired time; once established, the sleep is relatively normal (1).

The disorder frequently presents in childhood or adolescence. The presenting complaints are sleep-initiation insomnia, excessive morning sleepiness, and sleep deprivation while trying to maintain a socially acceptable schedule. When unrestricted by social or vocational constraints, the usual range of sleep time is at 02:00 to 06:00 hours and wake time at 09:00 to 14:00 hours. The sleep–wake cycle length remains usually at about 24 hours; however, occasional “normal” sleep and wake hours or a skipped sleep period may occur. When patients are free of conflicting schedules, their sleep length, quality, and composition are normal.

This disorder may result in chronically disrupted vocational or social functioning. Serious occupational, school or social dysfunction occurs in more than 90% of patients, even in the absence of major psychopathology (36). Tardiness or absenteeism at school or work, and daytime sleepiness are common precipitants for evaluation. Job loss due to failure to get to work on time in the morning, disciplinary measures in the military (37) have been described. Strained relationships with families, peers, or superiors may develop, solely on the basis of patients’ inability to get up in the morning. Demoralization and depression are common. Sleepiness due to chronic sleep deprivation may make driving dangerous for the DSPD patient.

The complaint of daytime sleepiness is partially due to sleep deprivation in an attempt to meet social obligations by getting up at conventional hours; short sleepers will tolerate the delayed phase better than long sleepers, because they are less sleep-deprived. Morning sleepiness is also attributable to the delayed position of the “sleepy” phase of the circadian sleep–wake rhythm. Those who do manage to arise on time are awakening in the middle of their endogenous “night”, regardless of their sleep needs. Falling asleep in morning classes and getting better grades in afternoon classes occurs commonly in patients who are students.

The patients often employ common-sense attempts to normalize their schedule (early bedtime, help from family in getting up in the morning, relaxation techniques); these may often prove futile. Sedatives are often prescribed, which have little or no effect on sleep onset when taken at normal bedtimes, unless used in more than conventional doses. Because of this lack of efficacy, chronic dependence on hypnotics or alcohol for sleep is infrequent in DSPD patients. It does occur, however, and a few patients become seriously dependent on high doses of alcohol or sedatives in their pursuit of advancing sleep onset. Some take stimulants in the morning as well (36,38).

Psychopathology of varying degrees is found in about half of adult DSPD patients, but no particular diagnostic category is characteristic, and psychopathology was no more frequent in DSPD patients compared to other insomnia patients. More than 75% of patient with DSPD were past or current users of antidepressants (36); however, these high numbers might be due to a referral bias (39). Personality disorders and emotional lability ranked high in adolescents with DSPD (40).

**Pathophysiology**

A significant inter-individual variability exists in the circadian rhythms, which determines, among other factors, the person’s being an evening or morning type (41,42). Originally and intuitively, the delayed phase of sleep-onset was explained by a delay shift in the circadian sleep–wake cycle, coupled with a weak ability to
advance the circadian rhythms in response to normal environmental time-cues (43). Also, late awakening may cause the patients miss the optimal time for phase advancement in the early morning (44). Hypersensitivity to the phase-delaying effect of artificial light at night may also be a factor (45). However, since a fairly regular, although delayed, sleep schedule is typically present in free-running conditions, the phase advance capacity in DSPD must be near normal. It is rather the complex relationships of various rhythms and the phase position of the sleep–wake cycle that may be responsible for the DSPD (46,47). Patients with DSPD may also compensate poorly for sleep loss; this may underlie their inability to advance their sleep time to unfavorable circadian time, even when sleep-deprived (48). If so, DSPD may result from a combination of delayed phase of the circadian pacemaker, its altered relationships with the sleep–wake cycle, and relatively weak homeostatic drive for sleep, the latter being unable to “overcome” the arousing effect of the delayed circadian phase. Although head trauma was reported to cause DSPD (49,50), the etiology in the majority of cases is unknown.

The genetic basis for the DSPD susceptibility may involve a length polymorphism at the circadian gene Per3, whereas the shorter alleles correlated with evening preference. Most patients with DSPD were homozygous for shorter alleles (51). Young people tend to have slightly longer circadian rhythms; this may in part be the reason for over-representation of the DSPD in this age group (52). Teenagers tend to stay up late as part of their cultural way of life, so psychosocial factors may be the primary source of the change in their sleep timing. Staying awake late, they also significantly delay their circadian rhythms (and vice versa), thus setting the stage for the development of DSPD (53). This syndrome is perhaps best viewed as the pathological extreme of a continuum of sleep-timing changes that affect the majority of adolescents.

Epidemiology
DSPD is common. Large population surveys yielded a prevalence of 0.17% to 0.7% (54,55). In adolescents, in community, the prevalence of DSPD was over 7% (56), whereas in adolescent psychiatric in-patients it soared to about 16% (40). DSPD patients comprise 7% to 10% of the patients with insomnia referred to sleep clinics (36,38). In some patients, there may be a familial tendency to DSPD (57,58). The duration of DSPD symptoms preceding diagnosis varies from months to decades. The syndrome onset has been reported as early as prepubertal childhood and as late as the sixth decade (38). Adolescence, however, appears to be a particularly vulnerable life stage for the development of the syndrome. Some DSPD patients report that the problems began abruptly after staying up late one night, after which they found it impossible to resume sleeping on a normal schedule. In most, however, the onset is gradual and progressive over two to three years.

Diagnosis
In most patients, the diagnosis of DSPD only requires obtaining the characteristic history and confirming it with a two-week sleep log detailing bed and arising times, sleep latency, total sleep time, and a tally of any awakenings during sleep. Wrist activity monitoring (actigraphy) may be useful in supplementing the subjective data of the sleep log with objective data. These studies need be performed when the patient’s schedule is not restricted (“free-running”). Polysomnography performed at the patient’s usual hours for sleep is sometimes necessary in atypical
cases, if sleep maintenance problems are also present. Sleep pathologies, for example, apnea and periodic limb movements in sleep, either of which could potentially account for the clinical complaints, are typically absent.

Differential Diagnosis
Many individuals without DSPD, particularly adolescents, adopt late bed and awakening hours. They adjust promptly to temporary periods of sleep-onset delay due to late-night studying, work or leisure activities followed by oversleeping to recover (e.g., on weekends), and do not develop chronically delayed sleep pattern when they resume a more conventional schedule. An externally imposed schedule tests one’s ability to respond to regular environmental cues and should entrain a normal individual to the new schedule fairly rapidly. The patient who reports having adapted to a strictly imposed conventional schedule and slept normally on it within 7 to 10 days probably does not have true DSPD. It is the chronic inability to advance the schedule that is a hallmark of DSPD. If sleep onset difficulties continue through the regimenting experience, DSPD is the likely diagnosis.

Late sleep onset may occur at the onset of a major psychiatric illness, particularly the manic phase of bipolar disorder and in schizophrenic decompensation. Manic patients, however, have no particular difficulty arising at a conventional hour, despite little sleep. The psychosis of the schizophrenic patient is usually readily apparent, and frightening nocturnal hallucinations contribute to the delayed sleep onset. The sleep disturbance usually parallels the course of the psychotic episode, and abates when the psychiatric symptoms do. If the delayed sleep pattern persists after psychiatric remission, it may be that DSPD was simply unmasked by the psychiatric illness. A chronic pattern of sleep phase delay is sometimes seen in individuals avoiding social interaction (e.g., some personality disorders); a response to rigidly imposed schedule may help the differential diagnosis.

Several sleep disorders, all of transient nature, such as behavioral insomnias of childhood (limit-setting sleep disorder, sleep-onset association disorder) and insomnia due to mental condition (anxiety, somatoform disorder, etc.), may present with sleep-initiation insomnia. Also, to be considered are other sleep disorders causing insomnia, for example, obstructive sleep apnea, restless legs syndrome, and others.

Treatment
Treatments for DSPD use chronobiological principles to achieve sustained phase shift to the desired sleep–wake schedule. This may be attempted by rescheduling sleep hours. Another approach is to amplify environmental time-cues using timed melatonin or light exposure. Finally, general measures to improve sleep hygiene, exercise, and relaxation, and the avoidance of caffeine late in the day, may all help to consolidate the new schedule.

The straightforward frontal assault on the DSPD by one-time advancement of sleep period is usually futile. The most effective rescheduling treatment for DSPD, known as chronotherapy, consists of progressive, daily, three-hour delays of bedtime and arising time until the patient’s sleep schedule matches the desired social schedule (59). The entire shift to a conventional sleep schedule can be completed over five to seven days in most cases. The initial resetting phase of chronotherapy must be followed by strict adherence to the new schedule, and the patient must avoid both staying up and sleeping late on all days of the week,
or risk a re-delay of the sleep phase; this indeed is the major obstacle to the treat-
ment success for most patients. A slow crawling towards the desired wake hour
may be attempted by advancing the awakening by a few minutes each day or by 15- to 30-minute increments each week. This approach may be tried in individuals
who must be awake during the daytime hours during the phase-shifting process.
Another method consists of total sleep deprivation on Friday night (or the first
night of the patient’s weekend), followed by a 90-minute earlier bedtime and awa-
kening from Saturday night onward. The same process is then repeated on succes-
sive weekends until the desired schedule is achieved.

A physiological dose of exogenous melatonin (less than 1 mg) was found to
shift circadian phase (32). A modest phase advancing effect of 5 mg of melatonin
given early in the evening was shown in DSPD patients (60,61). Melatonin
reduced sleep latency and daytime sleepiness and fatigue (62). Theoretically, indi-
vidualizing the timing of melatonin administration according to each patient’s
endogenous melatonin secretion pattern may optimize the gained phase advance.
A study utilizing this individualized approach by administering melatonin five
hours before a patient’s melatonin secretion onset achieved a similar modest
phase advance; interestingly, core body temperature nadir was not advanced
(63). In the largest group reported to date (61 patients), evening melatonin
was effective in 96.7%; however, the vast majority relapsed after melatonin was
discontinued (64). It was interesting that many patients relapsed a long time after
melatonin wash out (two months or more), and these patients tended to have
milder DSPD than patients with immediate relapse (up to one week after discontin-
uing melatonin). It could be hypothesized that the former subgroup was afflicted
mildly enough to advance to an hour early enough for the morning light exposure
to be effective, thus maintaining the achieved phase advance, at least temporarily.
Melatonin also improved the quality of life in patients with DSPD (65). Overall,
melatonin seems promising in the treatment of DSPD, although its effect seems
to last only as long as it is administered. Major issues, such as the optimal timing
and dose, remain to be evaluated. Long-term safety of melatonin needs also to be
determined. This hormone is not currently approved in the United States, except
as an investigational agent; it is available, however, as a nonprescription dietary
supplement, raising questions as to the standardization and purity of various
preparations.

Light is the most important environmental time-cue to the circadian oscillator.
Bright light exposure was found to have phase-shifting effects with phase delay or
advance following early morning or late evening exposure, respectively (66). In a
first controlled human study, enhancement of the morning time cue with bright
light (2500 lux full spectrum light between 07:00 and 09:00 hours) was helpful in
20 DSPD patients (67). More studies followed which employed different protocols
of light intensity (2500–10,000 lux at eye level), duration (0.25–4 hours), and
timing. Daily light exposure sessions are probably needed to maintain phase
shift. Since PRCs for melatonin and light are at nearly 180° phase angle difference
to each other, it may be possible to use combined light-melatonin treatment with
proper timing of each in order to increase the success rate of the treatment of circa-
dian rhythm disorders (68). Although light therapy is still a largely empirical
endeavor, Practice Parameters of the American Academy of Sleep Medicine
suggest it is a useful and effective component in the complex treatment of DSPD
patients (69). Many commercial light boxes are available, varying in design and
light intensity. Since many patients find it difficult to wake up early enough for
light therapy to be effective, an illuminating mask may provide timed light exposure through closed eyelids during morning sleep (70).

Long-term success in the treatment of DSPD is probably difficult to achieve, since it is unclear whether chronobiological interventions change the inherent tendency to relapse. To maintain a “normal” sleep–wake pattern, improving the sleep hygiene and adhering to a strict schedule are no less important than various interventions; these may prove difficult in the long run.

CIRCADIAN RHYTHM SLEEP DISORDER—ADVANCED SLEEP PHASE TYPE (ADVANCED SLEEP PHASE DISORDER)

Clinical Manifestations
Patients with advanced sleep phase disorder (ASPD) have their habitual sleep–wake times advanced, usually by several hours, relative to conventional or socially acceptable time, resulting in symptoms of late-afternoon or early-evening sleepiness or difficulty early morning insomnia; once established, the sleep is relatively normal for age (1).

Despite efforts to delay sleep to later hours, sleep onset routinely occurs between 18:00 and 21:00 hours. An ASPD patient may fall asleep at a social event or while driving in the evening. Patients frequently miss or avoid evening activities due to the need to go to bed earlier than the social norm. Final awakening is much earlier in the morning than is necessary to meet the daily schedule, typically well before dawn (71–73). Delaying evening sleep onset and morning awakening are very difficult for these patients. Unlike other sleep disorders with prominent early morning awakening, for example, sleep disorder that accompanies major depression, the awakening in ASPD occurs after a normal amount of relatively sound sleep, and there need not be major mood disturbance during waking hours.

PATHOPHYSIOLOGY

The basic pattern of ASPD is presumably phase-advance of the circadian pacemaker, coupled with a similar phase-advance of the sleep–wake cycle. Advanced sleep phase syndrome is described mainly in the elderly. Healthy older people tend to retire to bed and wake-up earlier. Age-related changes in the circadian rhythms, the nature of which in humans is still debated, may be responsible for these behavioral changes. Healthy elderly have a tendency for circadian phase advancement, sleep phase advancement, and less consolidated sleep (46,74,75). Opinions vary, however, as to whether there is a reduction in the circadian pacemaker output (e.g., the amplitude of core body temperature changes) with increasing age, which may be responsible for lesser sleep consolidation in the elderly (76–79). In addition to the possible reduction in the output, the elderly may exhibit changes in the inter-relationships (phase-angle difference) between the master circadian rhythm (manifest as melatonin and core body temperature rhythms) and sleep–wake cycle, particularly shortening of the time between core body temperature nadir and the habitual waking time (46,75), but this was also not a universal finding (74). The changes in the sleep consolidation and in sleep timing in the healthy elderly may also be due to reduction in the homeostatic drive for sleep and in the circadian drive that promotes sleep in the early morning (75,80). Psychosocial factors (isolation, reduced exposure to light, paucity in scheduled activities) may also play a role in the elderly [reviewed in...
emphasizing loose coupling between the sleep–wake rhythm and other circadian cycles. Interestingly, patients with early-morning insomnia and normal bedtime also exhibited significant advancement of their circadian rhythm; it is possible that, although suffering from mild ASPD, social considerations prevented them from adopting an earlier bedtime, contrary to what the expected coupling between the circadian and the sleep cycles would suggest (82).

From the above discussion, it becomes obvious that sometimes it is difficult to draw clear lines between the normal sleep–wake cycle changes in healthy elderly, early-morning insomnia, and ASPD. They may all represent different angles of the same spectrum of age-related changes influenced by psychosocial factors.

Recently, three large Caucasian kindreds with familial ASPD were described (73). There were, overall, 37 affected individuals (29 affected in one kindred in five generations); the youngest affected patient was eight-years old. The disorder segregated as autosomal dominant with high penetrance. They had phase advance of about four hours in sleep–wake cycle and in melatonin and temperature circadian rhythms. One of the subjects was studied in a time-isolation facility; her circadian cycle (both sleep–wake and temperature) was 23.3 hours. A missense mutation in one of the circadian genes in these kindreds was subsequently described (83). This was the first hereditary circadian rhythm variant described in humans. Later, another two pedigrees from Japan totaling nine individuals with familial ASPD were described (84). These pedigrees had no previously described missense mutation, suggesting a genetic heterogeneity in the familial ASPD.

Diagnosis
A clinical history of chronic daily sleep onsets earlier than 21:00 and offsets before 03:00, preferably confirmed by sleep logs and wrist-motion monitoring (actigraphy) for two to four weeks, should suffice to establish the diagnosis. A careful psychiatric history should be obtained to rule out an affective disorder. Sleep recorded at the patient’s usual sleeping hours should show normal sleep onset latency, staging, and duration for age. No other cause of pathologic sleepiness (sleep apnea, severe periodic limb movements in sleep) should be present.

Differential Diagnosis
ASPD is a rare disorder. Major depression with early-morning insomnia may produce a sleep pattern similar to ASPD. Early morning awakening is one of the hallmarks of major depression. The biological inter-relationships between advanced circadian rhythms and major depression have been suggested, but no clear etiologic ties have been established (85).

Treatment
Because of the rarity of this syndrome, therapeutic trials typically involved only a few patients each. In a process analogous to chronotherapy for DSPD, two patients reported in the literature were treated by daily, three-hour phase advances of their sleep schedule until the desired sleep timing schedule was reached (71,72).

Similar to DSPD, light therapy has theoretical merits in the treatment of ASPD. Evening exposure to bright light (2500 lux for two hours) was found to delay both the sleep–wake and the melatonin rhythms in an ASPD patient (86). In early-morning insomniacs, late-evening light exposure (2500 lux, between
Delayed Sleep Phase Disorder and Other Circadian Rhythm Sleep Disorders

20:00 and midnight) delayed awakening time (87); however, the late bedtime induced by therapy, rather than the light itself, could have been responsible for the later awakening time. Light therapy may be a useful component in the complex treatment of ASPD patients (69). Bright light may also improve other age-related sleep disturbances, such as low-sleep efficiency (88).

Melatonin has not been systematically studied in advanced sleep phase syndrome. On theoretical grounds and following its success in other circadian rhythm disorders, early morning melatonin, either alone or combined with evening bright light exposure, may be beneficial in advanced sleep phase syndrome.

Hypnotics to manage early-morning insomnia are best avoided.

CIRCADIAN RHYTHM SLEEP DISORDER—IRREGULAR SLEEP–WAKE TYPE (IRREGULAR SLEEP–WAKE RHYTHM)

Clinical Manifestations

Irregular sleep–wake rhythm (ISWR) consists of temporally disorganized and irregular sleep and waking behavior (1). The sleep is broken into several short blocks in the period of 24 hours, with marked day-to-day variability of sleep and wake periods and with no consistent circadian or ultradian pattern. The total daily amounts of sleep may be low, normal, or high. Few sleep episodes are of normal duration, and the patient is not consistently asleep or awake at any particular time of day. The chief complaint may be various combinations of sleep-onset insomnia, poor sleep maintenance at night, or excessive daytime sleepiness with frequent napping.

The ISWR is most common in cognitively impaired persons, particularly in those institutionalized. Formally, according to the current International Classification of Sleep Disorders, these patients should be classified as circadian rhythm sleep disorder due to medical condition, rather than “just” ISWR (1), but in clinical practice these are the patients one sees with this sleep pattern. The most common neurodegenerative disorders associated with ISWR are Alzheimer’s disease, dementia with Lewy bodies, vascular dementia, Parkinson’s disease, multisystem atrophy, Huntington’s disease; it may also be seen in children with neurodevelopmental disorders suffering from mental retardation. In patients with particularly severe cognitive impairment, skeletal circadian sleep–wake pattern may be present, comprised of short (two- to three-hour) periods of interrupted sleep alternating with quiet wakefulness, but punctuated once a day by a period of agitated wakefulness occurring at nearly the same time every evening. This clinical phenomenon of “sundowning” can be viewed as the daily expression of the intrinsic circadian rhythm of alertness and arousal impacting on a degenerated, dysfunctioning cerebral cortex. Such patients may need be physically restrained or sedated in an attempt to control evening and nocturnal wandering and agitation that may accompany the irregular sleep pattern. On the other hand, the families may complain that the patients are seldom awake during daytime visits.

The rare, cognitively intact patients with “true” ISWR frequently complain about nocturnal insomnia and regard the extremely long periods they spend in bed and daytime naps as a necessary result of it. They also may exhibit chronic depression, social isolation, and irregular patterns of other daily activities, for example, eating. Subjective cognitive impairment with no objective
findings on mental status examination often accompanies nocturnal insomnia in such patients.

**Pathophysiology**
Endogenous circadian timing system in the hypothalamus, or its connections, or neural networks mediating sleep and arousal are all vulnerable to developmental and degenerative disorders of the brain. Other medical, neurological, or psychiatric disorders and medication side-effects, on the background of age-related changes in the circadian and homeostatic sleep mechanisms, may contribute to the sleep–wake cycle disruption in patients with ISWR. In patients who are reportedly cognitively intact, extreme cases of inadequate sleep hygiene, such as those seen in chronic depression or residual schizophrenia, may be the cause of ISWR.

Indeed, degenerative changes have been shown to affect the SCN in many neurodegenerative disorders (89–91). In addition, the overt output of the SCN may become affected by degenerative changes in its input sources or outflow target systems. This may cause disorganized circadian rhythm, reflected in part by a disorganized sleep–wake schedule. The data regarding the circadian rhythm changes in neurodegenerative disorders are vast, and frequently inconsistent. The most frequent findings were reduction of amplitude and changes in phase or desynchronization of various rhythms, like core body temperature, melatonin secretion, rest-activity, and so on. (81,92–98). The chronobiological data in many studies are tainted by masking effects of activity, food intake, and other variables that are difficult to control for, in cognitively impaired subjects. It is still more complicated by the need to differentiate between normal age-related changes and those caused by neurodegenerative disorders.

However, the changes in circadian rhythms are probably not the only cause of ISWR. Social isolation, reduced light exposure, multiple medications, reduced activity and mobility, associated medical, neurological, and psychiatric disorders, and age-related changes in sleep may all contribute to the observed phenomenon of sleep–wake rhythm disintegration. As a group, demented patients tended to go to bed earlier (caregivers’ bias?), spend more time in bed, have more fragmented sleep, and sleep more than age-matched nondemented controls (99). Longer total daily sleep time was associated with more disruptive behavior and more severe dementia in both home-residing and institutionalized subjects.

**Treatment**
Patients suffering from ISWR are exceedingly difficult to treat. Because of psychiatric comorbidity, cognitively intact patients with ISWR may be highly resistant to changing their long-standing poor sleep habits. Gradual introduction of a sleep–wake schedule and regular meals, combined with a “prescription” for some kind of daily social interaction, should be helpful in such patients if they can be persuaded to be compliant.

Cognitively impaired patients may benefit from creating an “enriched environment” that includes scheduled social contacts, regular daytime physical activity, and increased indirect light exposure (100). Restriction of naps and of time in bed, if the patient’s condition permits, may also be helpful in consolidating the night sleep. Making the periods of sleep and wakefulness more predictable will make it easier for the staff to deal with such patients. However, attempts to force sleep to occur only at night in such patients by means of sedative administration
complicates the problem, and may produce significant adverse side effects including increased confusion, paradoxical agitation, and ataxia. If pharmacological means are to be used, they should be of minimal dose and selected to minimize side effects on cognition and mobility.

Melatonin may be promising in improving ISWR in both cognitively intact and impaired patients (101–104), but in placebo-controlled studies, the data are conflicting (105–107).

Bright light therapy may help consolidate the sleep–wake cycle and improve the behavioral disturbances (mostly sundowning) in demented patients (108,109). There is no consensus as to the intensity, frequency, duration, and timing of bright light exposure (69). Exposure to 3000–8000 lux every morning for 45 minutes to two hours (110,111), and 1500–2000 lux two-hour exposure (112) every evening were reported effective. Beneficial effects of light therapy may be difficult to detect in a patient with ISWR because of highly disorganized rest-activity schedule (113). Since homeostatic, not only circadian, aspects of sleep may be impaired in neurodegenerative disorders, light therapy need not be expected to improve all aspects of disordered sleep in these patients.

CIRCADIAN RHYTHM SLEEP DISORDER—FREE-RUNNING TYPE (NONENTRAINED TYPE)
Clinical Manifestations
The free-running type (FRT) is characterized by sleep symptoms that occur because the intrinsic circadian pacemaker is not entrained to a 24-hour period or is free-running with a non-24-hour period, usually slightly longer (1). The majority of patients are blind. These patients resemble normal individuals, free-running in a time-isolation facility with no external time-cues. The average sleep–wake cycle duration of these patients is approximately 25 hours, in most cases noncircadian (greater than 27 hours) sleep–wake cycles occur from time to time. In general, over every few weeks, the sleep period travels in and out of phase with the socially acceptable time frame. When in phase with local nighttime hours, there may be no sleep complaints and daytime alertness is normal. Thus, symptomatic and asymptomatic periods may alternate, depending on the degree of synchrony between patients’ endogenous sleep–wake rhythm and the solar 24-hour day. The patients may temporarily adhere to a strict, socially mediated 24-hour schedule, but the phase delay of their sleep usually resumes within a few weeks.

Such patients are usually unable to schedule ordinary social activities except when their sleep phase falls during conventional nocturnal hours. Maintaining most jobs is difficult or impossible. In most, however, socioeconomic disability is not entirely due to a constantly shifting sleep–wake pattern, but to the fact that most of the patients are blind. The syndrome has been described in congenitally blind infants and children as well as in adult patients of all ages with congenital or acquired blindness. Some of the few reported sighted individuals with FRT had avoidant or schizoid personality features (114).

Pathophysiology
Congenital or acquired chiasmal or prechiasmal blindness presumably prevents the master circadian rhythm from synchronizing with the 24-hour day by preventing light entrainment. Thus, the endogenous non-24-hour rhythm becomes unmasked and governs the sleep–wake cycle. In most blind subjects, nonphotic (social, etc.)
cues seem to be insufficient to synchronize the endogenous rhythm with the environmental one. The etiology of FRT in sighted individuals is unknown.

Failure of entrainment of the circadian oscillator in the blind is no surprise, given the overwhelming importance of light in the entrainment process. Two questions to consider are: (i) Why can some blind persons entrain to the 24-hour day, and why sighted people with FRT cannot?; and (ii) What are the mechanisms of FRT in each subpopulation?

When normal subjects in time-isolation experiments are asked to decide their own bed and meal schedules (free run), the great majority manifest sleep–wake cycles averaging slightly above 24 hours. In many such experiments, long sleep–wake cycles (30–52 hours) also occur, a phenomenon called internal desynchronization because other rhythms (e.g., core body temperature, cortisol) continue at a circadian periodicity. The phenomenological difference between free-running normal subjects and FRT patients is in the inability of the latter to entrain to the 24-hour day.

An exhaustive study addressed the hypotheses on the pathogenesis of the FRT in a sighted man and reviewed the literature available at the time (114). It seems that the main abnormality in FRT is reduced sensitivity to phase-resetting effects of light. In addition, reduced exposure to light, especially during the phase-advancing arm of the light PRC, and robust but prolonged melatonin secretion may contribute to impairment of the ability to phase-advance.

The majority of the blind suffer from the FRT. Some have abnormally entrained 24-hour rhythms and suffer from either DSPD or ASPD (115); some adhere to 24-hour sleep–wake and work schedules, despite the fact that they have free-running rhythms (116,117). In still others, photic entrainment may be possible even with no subjective light perception and negative electroretinography; this fact raised the possibility of the existence of a circadian photoreceptive system that is different from the visual and light-perception systems (118). Recently, this photoreceptive system, which is independent from the “conventional” rods and cones photoreceptors, has been localized and described; it consists of a subpopulation of photosensitive retinal ganglion cells that utilize melanopsin as their light-sensitive pigment, and their axons comprise the RHT (12,13). The opposite case of selective “circadian blindness” with intact light perception in humans may be postulated, but has not been described, although it has been seen in a strain of mutant mice. Social time-cues may play some role in the entrainment process in humans (119). They were once considered to be the major time-cue in humans (22), and it may be that sometimes they are, an example being a person entraining her normal 24-hour sleep–wake cycle to her bed-partner with FRT (120). Obviously, social stimuli are not strong enough to entrain the majority of blind individuals in whom light entrainment fails, especially if cognitive impairment confounds blindness and makes interpretation of social cues virtually impossible. Social cues are of little help to cognitively intact sighted individuals with FRT. Avoidant, socially withdrawn personalities characterize many of these sighted patients. It is possible that they are less sensitive to social cues than normal; alternatively, these personality traits might be secondary to the social isolation imposed by the circadian disorder.

**Epidemiology**

Both children and adults with FRT have been described. Although the exact prevalence of the syndrome in the blind population is unknown, surveys of completely
blind subjects show a greater than 70% incidence of chronic sleep–wake complaints, almost five times the rate in the general population (121). Chronic sleep–wake complaints are also more frequent in blind children compared to their sighted peers (122). Many patients had recognized a long-term, cyclic pattern to their sleep symptoms. Twenty-three of 30 blind patients with no light perception had an abnormal circadian melatonin rhythm (123). In sighted individuals the syndrome is rare.

**Diagnosis**

FRT should be suspected in any blind individual with sleep schedule or daytime somnolence complaints. The diagnosis is usually made from sleep logs or actigraphy of many weeks or months duration, in order to demonstrate the waxing and waning nature of sleep schedule disturbance. Sighted individuals with the syndrome and patients with acquired blindness of unknown cause should undergo a neurologic evaluation, including imaging of the suprasellar region by CT or MRI. Only one long-term polysomnographic study of an FRT patient has been reported to date (124). In this study, not only sleep latency but also sleep duration and fragmentation as well as REM latency were clearly modulated by the patient’s intrinsic circadian pacemaker that free-ran at a period of 25.25 hours, despite the strict imposition of a 24-hour sleep–wake schedule. The report is, therefore, a convincing demonstration that the cyclic sleep disturbance in the FRT in blind patients is due to free running of the circadian system, which is due to the lack of entraining to 24-hour light cues (124).

**Differential Diagnosis**

Some patients with DSPD have occasional long, noncircadian sleep–wake cycles similar to those seen in the FRT. However, these patients characteristically do not shift their major sleeping episode “around the clock,” but instead show a fairly steady, although late, sleep and arising time when not in school or work. In other words, such patients can entrain but only at a delayed phase relative to 24-hour clock time. Occasionally, the two syndromes coexist (125). Patients with ISWR also need to be distinguished from FRT, by the absence of one consolidated sleep episode and a total lack of pattern to their sleep–wake cycle.

**Treatment**

As for other circadian rhythm sleep disorders, treatments for FRT use chronobiological principles to achieve sustained phase-shift to the desired sleep–wake schedule. This can be attempted by amplifying environmental time-cues by using timed light exposure (in light-sensitive subjects) or administering melatonin. General measures to improve sleep hygiene, exercise, relaxation, as well as the avoidance of caffeine late in the day, may all help consolidating the new schedule. Oral melatonin 0.5–7.5 mg daily in the evening has been reported to be highly effective in the FRT in both blind and sighted individuals (114,123,126–131). Melatonin seems promising in the treatment of this circadian rhythm disorder, although its effect seems to last only as long as it is administered. As mentioned before, this hormone is not currently approved in the United States, except as an investigational agent.
Light therapy was sporadically reported to be effective in a few sighted patients with FRT (132–134). Light therapy may be tried even in blind patients (69), especially since their circadian photoreceptive system may be at least partially intact. Daily light exposure sessions are probably needed to maintain phase shift. It may be possible to use combined light-melatonin treatment with proper timing of each in order to increase the success rate of the treatment of circadian rhythm disorders (68).

If the long-term cycling of the sleep symptoms is not recognized by the evaluating physician, standard sedative or stimulant medications may be tried; the FRT is refractory to treatment with both. Some blind individuals living in institutions apparently respond to strict 24-hour scheduling with social time-cues. Occupational and social disability, not all of which is directly due to the sleep disorder, as well as abuse, dependence, or side effects related to sedatives and stimulants can seriously complicate the clinical picture.

CIRCADIAN RHYTHM SLEEP DISORDER—JET-LAG TYPE
(JET-LAG DISORDER)
Clinical Manifestations
Jet-lag disorder is a syndrome involving temporary mismatch between the timing of the intrinsic sleep–wake cycle and the sleep and wake pattern required by a change in time zone. The symptoms include various combinations of difficulties in initiating and maintaining sleep, excessive sleepiness, decrease in subjective alertness and performance, and somatic complaints (malaise, gastrointestinal function disturbances, frequent urination), occurring after rapid travel across multiple time zones (1).

The severity and duration of jet-lag symptoms vary depending on a number of factors including: (i) the number of time zones crossed; (ii) the direction of travel (east or west); (iii) departure and arrival times; (iv) the amount and quality of in-flight sleep; (v) the age of the traveler; and (vi) other variables that underlie individual susceptibility. Most individuals who cross three or four time zones experience at least some sleep–wake disturbance, generally lasting two to four days; symptoms may persist for 7 to 10 days after time-zone shifts of six or more hours. As a rule, jet-lag is more severe and prolonged after eastward flights, as compared to westward flights (135). The local departure and arrival times determine, to a certain extent, the amount and timing of in-flight sleep and the circadian phase of the individual on arrival. Age correlates with the severity of jet-lag (136,137). In individuals with pre-existing sleep disorders, sleep may worsen after transmeridian travel.

Frequent travelers across time zones often develop chronic sleep disturbances that are similar to shift-work sleep disorder (138); even structural brain changes were reported after prolonged exposure to chronic jet-lag (139).

Pathophysiology
Jet-lag symptoms are caused by the enforced sudden dissociation of the intrinsic circadian sleep–wake cycle from local environmental time-cues at the destination point. The intrinsic circadian system remains aligned with the home time zone and only slowly resets to new environmental time schedules after sudden changes in the environmental cues produced by jet travel. Since performance,
memory, coordination, and other work-related variables also exhibit circadian variability (140), they too may be misplaced relative to the new day–night cycle.

In transmeridian travelers, the homeostatic sleep process remains essentially unchanged (although it may be influenced by in-transit sleep deprivation), whereas the circadian sleep process is initially aligned with the external time of origin and undergoes gradual realignment with time-cues of the place of destination. This change of the relationships between the homeostatic and the circadian sleep processes adds to the temporary disruption of sleep periodicity.

The adjustment process of the circadian timing system to a new external time schedule is slow and asymmetrical, provided the traveler stays at his destination long enough. The adjustment is faster for westbound flights (141). The longer than 24-hour intrinsic circadian period, which favors phase delay (equivalent to westward travel) over advance (eastward travel), produces this directional asymmetry. However, after crossing eight or more time zones in the eastward direction, re-entrainment is frequently achieved by antidromic phase response (i.e., further phase delay, rather than advance) (142,143). This is analogous to chronotherapy in DSPD, where the circadian phase is intentionally delayed further in order to reach an advanced circadian position, metaphorically similar to the need to drive around the block in order to reach the beginning of a one-way street.

**Prevention**

It may be possible to pre-adjust for destination schedule by changing the origin sleep time in the proper direction a few days prior to travel. This change may reduce the adaptation period at the destination (144). In-transit sleep may be beneficial if it coincides with the home schedule, provided circadian readjustment is not needed. If circadian adjustment is required, sleep should be avoided unless it coincides with the destination schedule. For short stays (two to three days) in the new time zone, retaining the home sleep–wake schedule may be beneficial in preventing jet-lag symptoms during the layover (145). Long naps should be avoided at the destination for they might anchor the circadian rhythms to the home time. Brief naps in anticipation of an important event at an inconvenient circadian time may and improve alertness and performance.

**Treatment**

As a general guideline, retaining the home schedule for short stays, and adopting the new time zone schedule as quickly as possible for longer stays, are the best strategies to minimize the symptoms. Efforts should be made to promote sleep and alertness at appropriate times. Sleep promotion using short-acting hypnotics may be helpful in the short-term treatment of sleep-initiation insomnia after an eastward flight, or to improve in-transit sleep and minimize sleep deprivation (146–148). Rebound insomnia may occur after discontinuation of hypnotics, which may also be due to the continuing circadian readjustment. Promotion of alertness in jet-lag by pharmacological means has been less extensively studied (149,150). Caffeine may improve alertness in jet-lag (151). Modafinil is promising by virtue of its pharmacokinetics, pharmacodynamics, low potential of abuse and minor cognitive side effects; however, this agent has not been investigated for this specific use in field studies. Amphetamines should not be used because of their well-known side effects.
Natural or artificial light and melatonin may assist the readjustment of the circadian rhythm (152). Artificial bright light has been used to promote readjustment of the circadian system in a small number of subjects in simulated jet-lag laboratory studies and in field studies (153–156). It showed some promise in assisting resynchronization of the circadian rhythms in jet-lag. However, many important variables are unknown, such as the optimal sliding schedule of the exposures, whether the light exposure should be individualized using a practical and readily accessible phase marker, or some universal criteria may be applied, and so on (69).

Exposure to the natural ambient light may assist circadian readjustment or impede it, depending on the individual’s PRC to light and the circadian phase in which the light exposure occurs. Accordingly, exposure should be sought or avoided at certain hours. Dark sunglasses worn during unfavorable circadian time have been found to assist resynchronization independently of light exposure (157). Software has been developed to assist in planning for optimal timing and duration of natural light exposure (158); it can be found at the Circadian Technologies Inc. website www.circadian.com/midnightsun.

Repeated evening melatonin doses of 5 mg have been shown to assist re-adaptation to night sleep after simulated jet-lag even in the presence of conflicting bright light treatment; melatonin-improved sleep, mood, and memory (154). Melatonin was also shown to be effective in reducing jet-lag symptoms in field studies (143,157,159–161), and is now regarded as an effective therapy for jet-lag (162). Theoretically, due to its PRC, melatonin should be administered according to a sliding schedule based on the direction and the magnitude of time-zone change; complex tables have been developed to assist in planning (163). Simplified protocols are also available, that is, for eastward flights 5 mg in the early evening on the preflight day followed by four-day bedtime dose on arrival; for westward flights four-day late-night dose at midnight or later (164).

CIRCADIAN RHYTHM SLEEP DISORDER—SHIFT WORK TYPE
(SHIFT WORK DISORDER)
Clinical Manifestations
Shift work disorder (SWD) is characterized by insomnia or excessive sleepiness that occur in relation to work hours that are scheduled during the usual sleep period (1). Most of the medical disability occurs in night or early morning shift workers. Shift workers may develop one or more of the following: (i) shortened and interrupted sleep in the daytime after the night shift; (ii) compelling sleepiness at work; (iii) sleepiness when commuting home after the work shift; and (iv) difficulty initiating and maintaining nocturnal sleep on nights off from work.

Surveys show that permanent night workers average only six hours of sleep on work days. Their daytime sleep compared to nighttime sleep is characterized by shorter sleep latency, reduced total sleep time, reduced stage 1 and stage 2 sleep, increased stage 3 and stage 4 sleep, and variable REM latency (165). Sleep consolidation and increased slow wave sleep is consistent with chronic sleep deprivation due to repeated attempts to sleep at an unfavorable phase of the circadian rhythm.

Night shift workers differ in their strategy of obtaining daytime sleep. The majority have their major sleep period after returning from work (e.g., between 9:00 and 16:00), some sleep in the afternoon (e.g., between 14:00 and 21:00), and
still less split their sleep into two periods with the larger sleep period in the morning. The individual choice depends on family and social circumstances.

**Differential Diagnosis**

In a shift worker with sleep complaints, other sleep disorders need be excluded; for example, patients suffering from insomnia or DSPD may adopt shift work. Depression, marital problems, or job dissatisfaction are diagnostic considerations in a shift worker who has been on the same schedule for many years but has only recently developed sleep complaints.

Individual shift workers seldom consult a physician regarding their sleep problems because such patterns seem to be obvious drawbacks of the job. Nevertheless, sleepiness on the job or accidents due to falling asleep may prompt a sleep specialist's consultation, and inquiry about shift work is essential. Alternatively, a shift worker may have another sleep disorder that produces somnolence, but may erroneously attribute it to the shift work schedule.

**Pathophysiology**

Shift work involves enforced voluntary dissociation between the sleep–wake cycle and other circadian rhythms that affect sleepiness and alertness, for example, melatonin secretion, temperature rhythm, cortisol secretion, and so on. Performance, memory, coordination, and other work-related variables are also at their circadian nadir during the night shift (140). Shift workers attempt to subdue their sleep to homeostatic process only, whereas the circadian process remains mostly unchanged and frequently conflicts with sleep attempts. This results in sleep and alertness at unfavorable circadian phase positions. The circadian rhythms other than sleep–wake mostly remain synchronized with the “natural” light–dark cycle, even after years of night shift work, and do not yield easily to the shifted sleep–wake cycle; this fact is fundamental in understanding the health effects of shift work (166,167). Several mechanisms contribute to the “anchoring” of the circadian pacemaker: (i) the majority of night-shift workers are exposed to environmental light in the morning when commuting home or before going to sleep, thus entraining their circadian clock; (ii) many shift workers work rotating shifts, and the inertia of circadian entraining prevents full synchronization; and (iii) virtually all night-shift workers revert to a night-sleeping schedule on nights off work due to both social and physiological pressure to conform to a “normal” sleep–wake pattern.

The internal desynchronization of biological rhythms is probably the cause of the majority of, if not all, ill-effects of shift work.

Many variables seem to be important in a worker’s adaptation to shift work. A partial list includes: (i) Speed of shift rotation: fast rotating (e.g., three days) schedule minimizes sleep loss but prevents circadian adaptation, whereas the converse is true about slow rotating schedule (weeks). The frequent compromise of weekly rotation is probably the worst choice, since it is too short for circadian adaptation and long enough for sleep deprivation to accumulate (168). (ii) Direction of rotation: clockwise (nights to days to evenings) is biologically more sound than counterclockwise (nights to evenings to days) due to the natural tendency of the human biological rhythms to phase-delay; however, the differences may be minimal (169,170). (iii) Shift length and the time it begins. (iv) The worker’s circadian type: evening type adapts to shift work better than morning type.
Age: circadian disruption is more poorly tolerated with advancing age. Physical conditions for restful daytime sleep at home. Social factors.

Epidemiology
Except for the nursing profession, most shift workers are males between the ages of 18 and 60. In industrialized countries, about 20% are employed on jobs requiring shift work (171). Physicians-in-training experience regular and frequent night-shift work. Between 40% and 80% of night industrial workers report disturbed sleep, compared with 10% to 15% of day workers. About 10% of shift workers develop moderate to severe symptoms soon after first taking a job involving shifting work schedules, particularly if the shift rotates (172). Many leave their jobs within the first few years due to poor health.

Complications
The incidence of peptic ulcer disease in shift workers is about twice that of permanent day-workers (173). The risk of hypertension and ischemic heart disease is also higher (174,175), although shift work is not universally accepted as an independent risk factor (176,177). Metabolic syndrome and breast cancer may be linked to shift work (178,179). Other complications include gastrointestinal symptoms (dyspepsia, constipation, diarrhea), alcohol or drug abuse in attempt to improve daytime sleep, increased rates of accidents due to impaired alertness at work or during commute, depression, malaise, personality changes, and problems with interpersonal relationships. These complications may develop gradually or abruptly in a worker who has previously tolerated shift work well, as shift work tolerance seems to decrease with age.

Shift work may complicate the course and management of asthma, diabetes, epilepsy, and other disorders that have circadian rhythm components in their pathophysiology and response to treatment, and are best managed with a highly regular medication schedule that may be difficult to achieve in a patient whose work schedule is highly irregular. In addition to medical problems, psychosocial complications and maladjustment also accompany shift work (180).

Prevention
Predicting tolerance to a shifting work schedule and employing only potentially tolerant workers may prevent much of the shift work morbidity. Most potential predictors are controversial or not completely defined (181,182). In brief, factors that may predict intolerance to shift work include: age over 40, pre-existing sleep or gastrointestinal disorder, needing a rigid sleep schedule in order to sleep well, inability to resist drowsiness, being a morning type. Giving meticulous attention to sleep hygiene, minimizing light exposure in the morning, and adopting a consistent sleep schedule seven days a week may all contribute to prevention of detrimental effects on health.

The employer may contribute to prevention of shift work sleep disorder by designing shift length, shift hours, shift-rotation speed, and direction, as long as chronobiological principles are taken into consideration (183). Brightly illuminated work-space where applicable (184), and an opportunity to exercise during the night shift may improve shift work tolerance by promoting circadian adjustment (21).
Treatment
Self-initiated or hypnotics-induced naps before an occasional night mission may reduce shift work symptoms with little effect on subsequent performance and sleepiness (185,186). This is hardly a long-term solution for SWD. Caffeine may reduce sleepiness during the night shift without many detrimental effects on the subsequent daytime sleep (187). Modafinil, a novel wake-promoting agent previously indicated for treatment of excessive daytime sleepiness associated with narcolepsy, improves sleepiness associated with shift work (188). In early 2004, modafinil was approved by the FDA for this indication.

The data in the literature on whether moderate exercise during a night shift may facilitate circadian adaptation are inconsistent (21,189).

Research on the use of controlled bright light and darkness exposure to promote circadian adaptation to night shift work is abundant (142,156,167, 189–192). Several hours of high-intensity bright light in the evening, use of dark sunglasses in the morning before sleep, and sleeping in a totally dark bedroom may all independently promote circadian adaptation to the night shift (193). Bright light treatment for delaying or advancing circadian rhythms has become standard in preparing astronauts for shift work. However, these are highly selected individuals living in optimal physical conditions for phase-shifting that can be planned for maximal success (167). Circadian shifts in regular shift workers are much more difficult to achieve due to conflicting time-cues and social limitations. Many questions remain unanswered at this time; for example: (i) what timing and intensity of bright light should be used to assist return to day shift or on days-off? (ii) is repeated back-and-forth circadian shift more hazardous than sleeping at inappropriate circadian phase? (167). Bright light may affect, differently, workers of different ages (22). Although light therapy may be an optional component in the complex management of SWD, doubts still persist as to its effectiveness (69).

Repeated evening melatonin dose of 3–5 mg was shown to assist re-adaptation to night sleep after a simulated night shift, even in the presence of conflicting bright light treatment, improving sleep, mood, and memory (154,194). Thus, individuals rotating back to day shift after a period of night shift may benefit from using melatonin in the evening for a few days. Melatonin may also be used to improve daytime sleep and night alertness in night shift workers (195), but its effect may not be long-lasting (196).

Chronobiological treatments of SWD are demanding, their effects are not always predictable, and it may not be possible to administer treatments in many cases due to work and social limitations. For some patients, the best advice may be to get a daytime job, even if it entails a career change.

REFERENCES


**HISTORY**

The first description of narcolepsy with cataplexy was made by Westphal in 1877 (1). Gélineau coined the term “narcolesie” from the Greek words for seize and sleep, a name which in his words “will recall the double analogy of narcolepsy with sleepiness and catalepsy” (2). Previous reports of narcolepsy were attributed to Thomas Willis, Schindler, and Caffé, but none of these authors mentioned cataplexy (3–5).

Löwenfeld was the first author to insist on the presence of attacks of muscle weakness for the diagnosis of narcolepsy (6). The term cataplexy was coined by Henneberg from the Latin word meaning to “stroke down with fear” (7). Redlich introduced the term “affektiver Tonusverlust” (affective loss of tone) in the German literature (8,9).

The first medical descriptions of sleep paralysis came from Binns in 1842 and Mitchell in 1876 and 1890 (10). The condition had been recognized before by painters such as Heinrich Füssli (“Nightmare”) and writers such as Shakespeare (“Romeo and Juliet”), Goethe (“Wahlverwandtschaften”), Gogol (“Vij”), Maupassant (“Le Horla”), and Melville (“Moby Dick”). Wilson (11) coined the term “sleep paralysis”. Adie was the first to link sleep paralysis with narcolepsy (12). Yoss and Daly included it in the classic narcoleptic tetrad (13).

Up to 1924, only 35 cases of narcolepsy had been published (8). Many authors, including Lhermitte and Wilson, considered it a symptom rather than a single disease entity (11). The publications of Redlich, Adie, and Daniels (a series of 147 patients seen only in the Mayo Clinic) and Wilder were essential in affirming the specificity of the disorder (8,9,12,14,15). Yoss and Daly coined the term “narcoleptic tetrad,” recognizing the frequent association of sleep attacks and cataplexy with sleep paralysis and hallucinations (13).

The first treatment for narcolepsy was caffeine, suggested by Thomas Willis and favored by Gowers (3,8). Ephedrine and benzedrine were used in the 1930s and methylphenidate in the 1950s (14,16,17). The positive effect of tricyclics on cataplexy was first reported in the 1960s (18,19). Gammahydroxybutyrate (GHB) and modafinil were first used in hypersomniacs and narcoleptics in the 1970 to 1980s (20,21).

Biological markers of narcolepsy were recognized over the last five decades. Sleep onset REM (SOREM) periods and HLA-DR2 positivity were described by Vogel in 1960 and Honda in 1983, respectively (22,23). The discovery of a deficient hypocretin (orexin) transmission in human narcolepsy represents the most recent milestone in the disease’s history (24–26).
EPIDEMIOLOGY

A prevalence of narcolepsy of 0.02% to 0.07%, without obvious gender predominance, has been suggested by American, European, and multinational studies (27–31). This prevalence is possibly higher in Japan and lower in Israel (32). The percentage of familial narcolepsy, first reported by Westphal, rarely exceeds 1% to 5% (33–39). When compared to the prevalence in the normal population this corresponds to a 10- to 40-fold increase in risk. Families with more than two members affected (multiplex families) are very rare.

CLINICAL FEATURES

Excessive daytime sleepiness (EDS) is often the first and usually the most disabling symptom of narcolepsy. EDS is usually not present on awakening, but usually appears in the morning hours. During daytime hours, EDS is more or less constant but may become episodically (sometimes in periodical intervals of two to three hours) irresistible leading to involuntary naps (“sleep attacks”) (40). On rare occasions, such episodes may be mistaken for seizures or syncopes. Two or more sleep attacks per day occurred in 68% of 170 patients interviewed by Honda and coworkers (41). Gélineau’s patient reported 100 attacks per day (2). The Epworth Sleepiness Scale (ESS) score is typically >14 (42,43). Typical for narcolepsy, but not specific and always present, are reports about an overwhelming sleepiness occurring also in such unusual situations as talking, eating, standing, walking, or sexual intercourse [as reported first by Singer in 1917 (44)]. We have recently shown that a sleep propensity score during active situations more strongly discriminates narcoleptics from non-narcoleptic hypersomniacs than the ESS score (43). Some patients may develop “sleep attacks” following strong emotions, as already recognized by Gélineau. Naps last often less than 30 to 60 minutes are typically refreshing (in 95% of cases in a recent study) (43) and associated with dream experiences in one-third of occasions (28,45). Duration and time of naps influence, however, the refreshing character of naps and postnap performance (46). Some narcoleptics may better resist sleep and may report only minor subjective EDS or even deny it despite highly abnormal results on multiple sleep latency test (MSLT). These patients are more prone to develop episodes of “automatic behaviors” (15,47). Automatic behaviors are reported by up to 40% to 50% of narcoleptics and consist of recurrent “microsleep” episodes that can last from seconds to hours (43). These episodes typically occur in monotonous situations and can lead to complex, non-sensical acts (writing over the border, putting salt or dishes in the washing machine, driving to the wrong place). Patients may have a partial amnesia for these episodes and experience them as “black outs”. Resisting sleep may manifest itself also with such nonspecific symptoms as headache, ocular disturbances (blurred vision, diplopia, pressure in the eyes, twitching eyelids, micropsia), tingling/numbness of scalp or extremities, or hypoacusis.

Cataplexy refers to a sudden, bilateral loss of muscle tone that is provoked by a strong emotion, is associated with normal consciousness, and last less than a few minutes.

The most commonly involved emotions are laughing, excitement, surprise, and game playing. The most potent trigger is laughing (e.g., while telling or listening to a joke, during plantar stimulation), which is reported in more than 80% of cases (43,48,49). A triumphant or aggressive character of the involved emotion
favors cataplexy and may explain its frequency during sports, while hunting or playing games. Anticipation of an emotion may block or, in other cases, conversely trigger cataplexy. The most commonly involved negative emotions are anger, fear, and embarrassment. Pain, sorrow, or a sudden noise rarely trigger cataplexy (42). Cataplexy can appear also during sexual intercourse (orgasmoipsia). The presence of other (particularly known) people favor the occurrence of cataplexy (43). No specific correlation seems to exist between emotions triggering cataplexy and emotions experienced in dreams (43). Some patients have attacks without triggering emotions or during sudden/unexpected movements. Up to 50% of patients experience cataplexy while being tickled (43).

The loss of muscle tone in cataplexy is usually partial, may be unnoticeable to others, and most commonly involves the antigravity muscles. The lower extremities are more often involved than the upper limbs or face/neck muscles. Patients may report buckling or unlocking of the knees, zig-zag walking, closing of the eyelids, dropping of the head, and slurred speech. Some patients experience cataplexy as the inability to move [so-called affective adynamia (50)]. Only one-third of the patients experience falls. Generalized weakness may force the patient to sit down or make it impossible to rise from the sitting position. Respiratory and extraocular muscles are typically spared in severe cataplexy. The speed of fall is rarely abrupt and can occasionally be broken by the patients with their arms. Bruises are, therefore, rare, though more common in children than adults (51). Unilateral dominance of single attacks is not uncommon [19% in one series (52)], whereas cataplectic attacks involving only single muscles are exceptional (11,13).

Minor positive motor phenomena often accompany the sudden loss of muscle tone [up to 50% of cases in our experience (43,53)]. Muscle twitches or tic-like movements of the perioral/facial/tongue/head muscles, tremor or quivering of the limbs, sagging of the jaw, or stuttering are not uncommon. Irregular clonic movements of the limbs may be seen and be mistaken for a seizure. Tonic motor phenomena during cataplexy (so-called cataplectic hypertonia) have been described in facial (e.g., tongue protrusion) and limb muscles (8,9,28,54). Cataplectic hypertonia and possibly also the enhanced phasic muscle activity share some clinical characteristics with the tonic falls occasionally triggered by emotions described in children with cerebral palsy, in adults with multiple sclerosis, as well as in the context of other cataplexy-like episodes (discussed later) (55–57).

During cataplexy state of consciousness, ocular motility and breathing are usually preserved. Some patients, however, report blurring of vision and a feeling of suffocation. In severe/prolonged cataplexy, patients report also to fall asleep and/or dream after the cataplectic attack. Autonomic/vegetative symptoms including blood pressure and pulse changes, sweating, penile erection, and involuntary urination have been observed (8,58). Episodes of cataplexy with overlapping features with EDS, sleep paralysis, or rapid eye movement (REM) sleep behavior can occur (59). After cataplexy, some patients experience a persistent numbness or weakness of their limbs.

The appearance of cataplexy is favored by EDS. Patients may describe exacerbation of cataplexy by resisting a sleep attack. Some patients may prevent cataplexy by clenching of fists or forced jaw closure. Cataplectic attacks usually last less than one minute and exceed two minutes in only 10% to 20% of cases (48). Prolonged episodes >30 minutes (“status cataplecticus”) can be observed after abrupt discontinuation of different anticyclopelplectic drugs (60,61). Over short periods of time (weeks to months), the frequency of cataplexy remains, often stable (52). Within
the first few years after its appearance, two-thirds of the patients experience at least one attack per day.

Sleep paralysis refers to the inability and struggle to move and speak while in the process of falling asleep or awakening. Rarely, sleep paralysis may be experienced during the day, at times of relaxed wakefulness. Sleep paralysis is present in 50% to 75% of narcoleptics, but can be seen also in isolation or in association with other sleep disorders. Sleep paralysis (also called since the 1920–1930s by the French “cataplexie du reveil”) has similarities with cataplexy, but always involves the entire body. Anxiety (e.g., of dying) is often experienced by patients during sleep paralysis and may remain uncontrollable even in those with frequent attacks. It is noteworthy that associated features in patients with sporadic sleep paralysis include the use of anxiolytics and the presence of bipolar disorder (62). Eye-fluttering, moaning, tingling, or numbness of the involved limbs and autonomic symptoms (sweating, palpitations, shortness of breath) may accompany sleep paralysis. Some sensation of limb weakness or numbness can persist for a few minutes after an episode (63). Some patients develop insomnia, anxiety, or depression as a consequence of the frightening character of sleep paralysis.

Sleep paralysis usually last less than 10 minutes, although episodes of up to 30 minutes have been reported (64). Struggling against sleep paralysis may prolong its duration, whereas being touched by another person may abruptly end it.

The frequency of sleep paralysis can vary from a few life events to daily episodes. Stress, excessive sleepiness, irregular sleep–wake cycle, jet lag, and sleeping in an uncomfortable (e.g., semi-sitting) or supine position may increase the frequency of sleep paralysis (65).

Sleep paralysis is commonly associated with hallucinations, a combination that is remarkably constant across cultures and recognized from old times. Different terms have been used in different languages for the same phenomenon including “old hag”, “Albrucken/Hexendrucken” (Germany), “Toggeli” (Switzerland), “Kanashibari” (Japan), or “Yan/E-Meng” (Chinese). Rosenthal named it the “halluzinatorisch–kataplektisches Angstsyndrom” (hallucinatory–cataplectic fear syndrome) (50). Recent systematic studies recognized three basic forms of hallucinatory experiences accompanying sleep paralysis (66,67). The first one corresponds to a sensed presence (numen presens), the second to the sensation of a pressure on the chest with shortness of breath/sensation of suffocation (incubus), and the third one to a sensation of floating/flying (out-of-body experience).

Hallucinations are dream-like experiences occurring at sleep onset (hypnagogic hallucinations), on waking up (hypnopompic hallucinations), or at other times during the waking state. They are reported by 50% to 75% of narcoleptics, but also by 10% to 40% of the normal population (43,68–70). Some patients report hallucinations during sleep paralysis or in association with cataplexy. Hypnopompic hallucinations are more suggestive of narcolepsy than hypnagogic hallucinations.

Most commonly, hallucinations are visual (Fig. 1). Simple sensations (e.g., geometric figures) as well as complex ones (faces, animals, landscapes), occasionally with absurd/bizarre contents, are reported. Images may be black and white or colored (68). Kinetic and acoustic hallucinations are also relatively common (70). The hallucinations of a “sensed presence” [psychic hallucination, numen presens of a person or animal nearby, standing over the bed, or lying underneath as well as out-of-body experiences (occasionally with heautoscopy, that is, with a reduplicative hallucination of one’s self)] are also possible. Sometimes, the presence is sensed as approaching, watching, or monitoring the subject. It can be
sensed as malevolent, frightening or less commonly benevolent (“guardian angel”). Fantastic, mysterious, or religious contents are also common. Acoustic hallucinations (human voices, animal sounds) may accompany visual hallucinations. Less commonly, tactile (the sensations of being grabbed), gustative/olfactory, or vestibular hallucinations are reported. Assault scenarios (by intruders, animals, or monsters) are less common.

Psychosis-like hallucinations are also possible [e.g., feeling snakes running along the back, worms beneath the skin or inside the head, blood dripping from the heart (14,50)] and may lead to the wrong diagnosis of schizophrenia (71,72). Typically, these hallucinations are not improved by antipsychotics, but can be controlled by stimulants (73).
Some patients are so distressed by their hallucinations to develop rites, sleep-preventing measures (e.g., biting their own hands), or even delusional constructs. Other patients may recognize the unreal character of these hallucinations.

Disturbed nocturnal sleep with frequent awakenings and excessive motor activities may be the first symptom of narcolepsy. Sleep onset insomnia and difficulties awakening (sleep drunkenness) are conversely rare. A weak correlation between nocturnal sleep disturbances and EDS was repeatedly found in narcolepsy (74,75). Patients with severe narcoleptic EDS may have a subjectively and objectively (polysomnographically) normal or only mildly disturbed nocturnal sleep. Motor dyscontrol in sleep, which may be present from childhood (76), can present with bruxism, periodic limb movements in sleep (PLMS, 25–50% of patients), sleepwalking, sleeptalking, sleep shouting, and REM sleep behavior disorder [10–30% (43,77,78)]. Horror dreams and vivid dreams/lucid dreams are particularly common in narcolepsy (43,79).

Memory and concentration problems are reported by up to 50% of patients and are multifactorial in origin (EDS, automatic behaviors, depression, etc.). Sexual dysfunction including impotence and diminished libido are present particularly in males in up to 25% of cases and may be in parts related to treatment (80,81). Nonspecific autonomic disturbances such as Raynaud-like phenomena, fainting spells, cold extremities, or migraine are seen in narcoleptics as well as other functional hypersomnias (82).

Psychiatric Disturbances

Several papers in the 1920 to 1950s hypothesized a psychiatric origin of narcolepsy (83–86). There are indeed multiple observations that link narcolepsy with psychiatry. First, psychogenic stress may trigger the onset of narcolepsy (87). Second, psychiatric symptoms are not uncommon in narcolepsy. In up to one-third of patients, a psychiatric diagnosis is considered first (88). Depression, anxiety, reduced self-esteem have been found in up to 20% to 50% of patients and were in most studies (but not all) more frequent than in controls (89–91). This relatively high frequency is in parts related to the high psychosocial burden of narcolepsy (92). In addition, psychiatric disorders may reflect a primary brain dysfunction in narcolepsy. Third, psychosis-like hallucinations are also possible and may lead to the wrong diagnosis of schizophrenia (discussed earlier). Less commonly, psychosis is secondary to stimulant treatment (1–3% of patients on long-term treatment). The co-occurrence of narcolepsy and schizophrenia is also possible although rare [0.5–9 cases in a population of 1 million (72)]. Fourth, narcolepsy-like symptoms have been reported in patients with psychiatric symptoms and disorders (see differential diagnosis).

Psychosocial problems are frequent in narcoleptics, possibly even more than in patients with epilepsy (93). Problems include increased incidence of accidents, poor school performances, occupational problems, and interpersonal problems (81,92). Anxiety, depression, social withdrawal, and reduced self-esteem are present in at least 30% of patients and arise from a complex interaction between basic mechanisms of the disorder and psychoreactive mechanisms (90). Rarely, narcoleptics may present with a hallucinatory syndrome that can mimic schizophrenia and may improve with stimulant treatment (50,71,72). A recent study has also shown that narcolepsy causes elevated direct and particularly indirect costs (e.g., unemployment) (94).
Obesity/Neuroendocrine Disturbances
Narcoleptics are occasionally obese, as recognized already by Daniels (14), particularly in childhood and around disease onset, and on average, their body mass index is 10% to 20% higher than that of the general population (95,96). A reduced metabolic rate, a decreased motor activity, or abnormal eating behavior (very little is known about appetite in narcoleptics) have been suggested as possible explanations for this finding. An association of EDS with (in variable combination) increased BMI, hypo-hypersexuality, psychiatric symptoms, DR2 positivity, and diabetes has been noted in narcolepsy and disorders that fall into the borderland of narcolepsy (idiopathic hypersomnia, Kleine–Levin syndrome, hypersomnia with mood disorder) (95,97–99). These observations suggest the possibility of an underlying hypothalamo-pituitary dysfunction, as postulated already by Redlich (8), which may be related to but not necessarily determined by low levels of hypocretin-1 and altered levels of leptin in cerebrospinal fluid (CSF) (elevated) and serum (reduced) (100–102). Noteworthy in this context is the existence of pediatric obesity syndromes such as the Prader–Willi and Cohen syndromes, which may present with a narcoleptic or Kleine–Levin phenotype (103,104).

Evolution
Narcolepsy starts before the age of 25 years in 70% to 80% of patients. In about 10% to 15% of patients, narcolepsy starts before the age of 10 years (43,51,105). Onset after the age of 40 years is uncommon (less than 10% of patients) (43,106).

The first symptom is usually EDS, occasionally sleep paralysis/hallucinations. Cataplexy appears mostly within one to four years after the onset of EDS, in rare cases, however, only after a latency of as long as 40 to 60 years (43,107). The onset of EDS may be difficult to recognize and assess retrospectively. First, the onset of EDS is usually gradual. Second, EDS may present in childhood with irritability, hyperactivity, and attention deficits symptoms. Third, hallucinations and cataplexy-like symptoms can be physiological in infants and children. Less commonly, EDS may develop rapidly in association with such events as infection, surgery, psychosocial stress, minor head injury, pregnancy/childbirth, menarche, abrupt change of sleep–wake schedule, overexertion, or anesthesia (64,87,108).

Cataplexy represents the first symptom of the disorder in 5% to 10% of patients. EDS usually appears within a few years. In rare occasions, cataplexy may, however, remain isolated for up to 30 to 50 years (88,107,109,110). The intensity and frequency of cataplexy tend to decline with age and may disappear in one-third of patients (108). Only about 10% to 20% of narcoleptics exhibits the full clinical tetrad (88). Exceptional familial cases of isolated cataplexy have been reported (111,112).

PATHOPHYSIOLOGY AND ETIOLOGY
Neurochemistry
Several observations, including studies in animal models/equivalents of human narcolepsy, suggest that a reduced monoaminergic (and particularly dopaminergic) transmission in forebrain and brainstem areas together with a reduced hypocretin transmission in the hypothalamus represent the neurochemical core-features of both EDS and cataplexy (113–115).
The involvement of the newly discovered hypocretin (orexin) neuronal system in the pathophysiology of narcolepsy has been recognized only recently. Hypocretins (also known as orexins) are peptides that are synthesized by a few thousands of neurons in the lateral hypothalamus (perifornical area). These were initially thought to be implicated in the control of food intake (116,117). More recently, the hypocretin system has been linked more with the regulation of arousal, sleep–wake cycle, motor functions as well as emotional and motivated behaviors (118–120).

In 1999, it was shown that the genetic alterations in the hypocretin receptor-2 or the hypocretin ligands cause narcolepsy-like conditions in dogs and rodents (121,122). The involvement of the hypocretin system in human narcolepsy was subsequently proven by the demonstration of (i) reduced/absent CSF levels of hypocretin-1 in about 90% of narcoleptics, (ii) a loss of hypocretin neurons in narcoleptic brains, and (iii) identification of a mutation in the preprohypocretin gene in one child with severe narcolepsy (24–26,100,123–126).

The exact contribution of ascending (brainstem–forebrain) and descending (forebrain–brainstem) aminergic and nonaminergic pathways to the neurochemistry of narcolepsy and the interaction of these systems with the hypocretin system remain unclear at this point (127,128).

It is possible that the amygdala plays a role in the pathophysiology of narcolepsy. The amygdala is involved in REM sleep processes and links hypothalamus and brainstem in the regulation of arousal, motor, and emotional processes (129–131). Animal data have demonstrated the existence of cataplexy related neurons in the amygdala (132). Furthermore, dopamine D2 receptor density is elevated in the amygdala of cataplectic dogs (113). Finally, we have recently observed the absence of an aversive startle reflex potentiation in human narcolepsy, an observation which favors the hypothesis of an amygdala dysfunction in this disorder.

EDS hypocretin-deficiency predicts severe objective daytime sleepiness in human narcolepsy (133). One mechanism by which a decreased hypocretin transmission may lead to EDS is an insufficient stimulation (physiologically mediated by type 2 hypocretin receptors) on arousal-stimulating histaminergic neurons in the posterior hypothalamus (127).

Hypocretin deficiency is probably only one of the neurochemical explanations of EDS in narcolepsy, which probably involves also an insufficient activation of other (monoaminergic) alerting neuronal pathways and possibly also other systems (134,135). Several studies have in fact shown that severe EDS may be seen in narcoleptic patients even in the absence of a detectable hypocretin deficiency [for review, see (136)]. Furthermore, animal data suggest that stimulants exert their alerting effects by facilitating dopaminergic and histaminergic transmission independent from the hypocretin system (113,137,138). Finally, hypocretin deficiency in non-narcoleptic patients is not always associated with EDS (136).

We have recently suggested that narcoleptic (and other forms of) EDS is associated with abnormalities in the CSF activity of the lipocalin-type prostaglandin D synthase (L-PGDS) a brain enzyme, which produces prostaglandin D(2), a substance with endogenous somnogenic effects (139).

Cataplexy hypocretin-deficiency predicts the presence of “true”/definite cataplexy in human narcolepsy (43,136,140). On the other hand, human and particularly animal data have suggested that cataplexy is linked to a disruption of other neurotransmitter systems in both brainstem and supratentorial areas. The net
result of this disruption is an imbalance between a (M2 muscarinic) cholinergic hypersensitivity and an altered monoaminergic (noradrenergic, dopaminergic, histaminergic) transmission (113,114,127).

Sites and mechanisms of interaction between hypocretin, monoaminergic, and cholinergic systems in cataplexy are still a matter of debate. One mechanism by which a decreased hypocretin transmission may lead to the above-described cholinergic–aminergic dysbalance (and cataplexy) is an insufficient stimulation (physiologically mediated by type 1 hypocretin receptors) of noradrenergic neurons in the locus coeruleus. These neurons are implicated in maintaining a sufficient muscle tone during wakefulness and particularly during sudden emotions (127). This insufficient stimulation may, on the other hand, lead to the activation of cholinergic neurons in the pedunculopontine nucleus, which in turn excite inhibitory neurons in the magnocellular nucleus of the medial medulla leading to muscle atonia. Such a recruitment of REM sleep atonia mechanisms may be mediated also by a decreased activation, secondary again to hypocretin deficiency, of dopaminergic neurons at midbrain and diencephalic sites (114). An interaction between hypocretin and dopamine transmission has been shown to exist in the regulation of motor and emotional functions (128,141).

The association of cataplexy with preserved consciousness has been linked to the persistence, during the atonic episodes, of an alerting effect of histaminergic neurons (127). The combination of an insufficient dopaminergic activation of motor pathways together with a persistent histaminergic activation of arousal is indeed characteristic of cataplexy and differentiate it neurochemically from REM sleep atonia (114,127). Similarities and differences between the two phenomena have been recently discussed also at the clinical and neurophysiological level (142,143).

**Neurophysiology and Neuropathology**

The neurophysiological hallmark of narcolepsy is the occurrence of REM sleep within 15 to 20 minutes from sleep onset (SOREMs, Fig. 2). Narcolepsy is, however, associated also with abnormalities of wakefulness and nonrapid eye movement (NREM) sleep in the presence of normal sleep amounts over 24 hours (144). Furthermore, dissociated states in which elements of wakefulness, NREM, and REM sleep intermingle are frequent in narcolepsy and lead to such symptoms as cataplexy, sleep paralysis, and REM sleep behavior disorder. Narcolepsy may, therefore, result from a “state boundary dyscontrol”, in which homeostatic, circa- and ultradian sleep–wake regulatory mechanisms appear to be essentially preserved (145–147). Two recent studies of our group have indeed shown that homeostatic NREM- and REM-sleep regulation is functional in narcolepsy (148).
EDS is characterized neurophysiologically by an often-persistent (although waxing and waning in intensity) drowsiness (stage 1a sleep) during the day. Compared to controls, the wake EEG of narcoleptic patients is characterized by lower alpha and higher (and over the course of the day further increasing) delta, theta, and beta powers (149). Drowsiness can evolve into episodes of “microsleep” (stage 1b sleep) lasting 3 to 15 seconds (150). Longer episodes of sleep often also occur voluntarily or involuntarily (“sleep attacks”). When patients resist sleep or start treatment with stimulants prolonged sleep episodes may be replaced by “microsleep episodes” and drowsiness, which can lead clinically to so-called automatic behaviors (discussed earlier). The severity of EDS, as estimated by the MSLT, appears to correlate with the appearance of SOREMs. Furthermore, naps associated with REM sleep appear to be linked to a more imperative sleepiness and a greater restorative effect (151).

EDS may theoretically arise from an increased pressure for NREM sleep or REM sleep, from a decreased arousal, or from all three. During wakefulness, episodes of sleep occur at intervals of 90 to 120 minutes. On the other hand, arousals and episodes of wakefulness are frequently observed during NREM sleep. Considering the observation in narcoleptics of (i) a lack of correlation between nocturnal sleep disruption and EDS (74,75) and (ii) normal amounts/24 hours of NREM and REM sleep (144,152), it is reasonable to assume that a deficient arousal is essential in the above postulated “state boundary dyscontrol” and may eventually represent the primary mechanism of narcoleptic EDS.

Cataplexy is accompanied neurophysiologically by areflexia, reduction of EMG tone (Fig. 3), disappearance of the H-reflex, and awake EEG (48,153–157). Noteworthy, a depression of the H-reflex can be observed also in normal subjects.
when laughing loudly and cannot be explained alone by changes in respiration (57,158,159).

In cataplexy, the reduction of muscle tone can be occasionally only mild, the H-reflex can present a waxing and waning character correlating with bursts of EMG activity, and the EEG and electro-oculographic features may be indistinguishable from those of REM sleep (160,161). A detailed study in a single patient has shown that during cataplectic attacks muscle atonia is associated (and in fact preceded) by a phasic and tonic increase in the EMG activity (53). A recent publication confirmed the coexistence of inhibition and excitation of distinct brainstem neuronal circuits during human cataplexy (162). Finally, narcoleptic also exhibit altered startle responses (57,163).

Studies mainly in the canine model suggest the involvement in cataplexy of a complex neuronal network in infra- and supratentorial brain areas including the medial medulla, the dorsal pons and midbrain, the hypothalamus and the amygdala (119,127,164,165) (Fig. 4). The presynaptic hyperpolarization of spinal cord motoneurons during cataplexy is due to the activation of neurons in the magnocellular nucleus of the medial medulla. This activation is related in turn to a unique dissociation between mainly activating ascending and mainly inactivating descending influences that are similar but not identical with that of REM sleep atonia including the activation of histaminergic and dorsal raphae neurons during cataplexy (127,132,164,166). The involvement of supratentorial neurons in the pathophysiology of cataplexy is further supported by the following observations: (i) canine cataplexy can be triggered by stimulation of basal forebrain (ii) cataplexy is accompanied by the activation of neurons in hypothalamus and amygdala (132,167).

The existence of cataplexy-like episodes in normal subjects (discussed later) and the recent demonstration also of a depression of the H-reflex during laughing in healthy subjects give support to the hypothesis that cataplexy may represent the

![FIGURE 4 Neuronal pathways involved in cataplexy. Abbreviations: REM, rapid eye movement; LC, locus coeruleus; LDT/PPT, laterodorsal tegmentum, pedunculopontine tegmentum. Source: From Ref. 165.](image-url)
exaggeration of a physiologic motor reaction/reflex. The recent observation in rats of an increased firing of hypocretin neurons during exploratory and motivated behaviors suggest a specific role of the hypocretin/orexin system in regulating (preserving) muscle tone during sudden emotions (119). Whether this postulated exaggeration of a physiologic reflex arises from an alteration of emotional perception, their motor accompaniments, or both (as most probable) remains, however, to be determined (159).

Sleep paralysis is considered along with cataplexy and hallucinations to represent a dissociated manifestation of REM sleep. This hypothesis was suggested by the observation of muscle atonia and suppressed H-reflex in association with SOREM or a wake EEG during episodes of sleep paralysis in narcoleptics (157,168). The existence of sleep paralysis without cataplexy in patients with and without narcolepsy and reports of sleep paralysis without SOREM suggests that the pathophysiology of the two phenomena (sleep paralysis and SOREM) is distinct although related.

Hallucinations are often considered to represent intrusion of REM sleep dreaming/mentation into a half-awake state. Indeed, hallucinations are accompanied by SOREM and/or sleep paralysis. Contents of narcoleptic hallucinations and children dreams in children can be similar and raise the possibility of a common generator (archaic form of mental activity?).

Hallucinations also occur, however, during the transition from wakefulness to NREM sleep in both normal subjects and narcoleptics (68).

**Etiology**

Human narcolepsy can be viewed as a multifactorial (multistep) disorder arising from the contribution of (HLA-dependent and HLA-independent) genetic predisposition and environmental factors that often, but not invariably, lead to a detectable hypocretin deficiency. In patients with detectable hypocretin deficiency, this finding is typically already present as symptom onset (169,170).

The spectrum of human narcolepsy (narcolepsy with and without cataplexy, sporadic narcolepsy, familial narcolepsy, symptomatic narcolepsy) is probably best explained by the variable contribution of these single factors in a given patient. HLA positivity and hypocretin deficiency are strongly but not invariably linked in narcolepsy (140,171,172).

**Genetic Factors**

Only about 1% of narcolepsy cases are familial. Genetic factors play, however, a role not only in familial but also in sporadic narcolepsy. The risk for first-degree relative of a narcoleptic is about 1% to 2% and represents a 30 to 40 times higher risk than in the normal population (39).

The most important genetic predisposing factors are related to the HLA haplotypes DR2 and particularly DQB1*0602. Narcolepsy is associated with a 85% to 100% HLA-DQB1*0602 positivity across various cultural and ethnic groups compared to a 12% to 38% positivity in the normal population (39). The interaction between different HLA-DR and -DQ alleles influences the overall risk of narcolepsy. Significant higher risk is observed for heterozygote combinations of six alleles (DQB1*0301, DQA1*06, DRB1*04, DRB1*08, DRB1*11, DRB1*12) whereas three alleles (DQB1*0601, DQB1*0501, DQA1*01) were found to be protective (173).

The presence of typical cataplexy is associated with a 90% DQB1*0602 positivity, a percentage that is much lower (30–45%) in narcoleptics with atypical or no
cataplexy (174). Nevertheless, rare cases of sporadic and familial cases of narcolepsy with typical cataplexy that were negative for both DR2 and DQB1*0602 have been reported (39,140,172,174).

Other genetic factors are probably involved in familial and sporadic narcolepsy. About a third of narcoleptics in families with multiple-affected individuals are in negative for HLA-DQB1*0602 (39,174). Significant evidence for a linkage to specific loci was reported recently in eight Japanese families (on chromosome 4) and in one French family (on chromosome 21), respectively (175,176). A mutation in the hypocretin gene was found in only one of 74 narcoleptics so-far tested (25).

In sporadic narcolepsy, a polymorphism in the catechol-O-methyltransferase gene was found to affect the severity of EDS and a polymorphism in the preproorexin gene was found to be associated with the disorder (177,178). Other non-HLA genes such as tumor necrosis factor alpha (TNF-A), TNFR2 (in Japanese), and monoamine oxidase-A (MAO-A) may also increase the susceptibility to sporadic narcolepsy (179–181).

Finally, an autosomal dominant DR2-negative syndrome with familial narcolepsy with cataplexy, cerebellar ataxia, sensorineural deafness, optic neuropathy, and hypocretin deficiency was reported in a Swedish family (171,182,183).

Nongenetic Factors
The importance of (still unknown) nongenetic factors in narcolepsy is stressed by (i) the low (25–31%) concordance for narcolepsy–cataplexy in monozygotic twins (39,172,174,184) and (ii) the existence of symptomatic forms of narcolepsy even in genetically nonpredisposed subjects (185). Environmental factors at birth or later in life (and particularly in the months preceding the onset of narcolepsy) have been discussed. Such factors include mild head trauma, psychosocial or physical stress, nonspecific infections, abrupt change in sleep–wake habits, and pregnancy (8). Specific agents/mechanisms could, however, not (yet) be identified (87).

Autoimmunity and Sporadic Narcolepsy
Considering the strong association with HLA together with the recent demonstration of a hypocretin deficiency and neuronal loss in human narcolepsy (discussed earlier), the possibility of an autoimmune-mediated cell damage has been raised (124,125). The hypothesis of an underlying, autoimmune process is further suggested by the bimodal distribution of age at onset, the presence of gliosis in the posterior hypothalamus, the detection of functional (cholinergic) autoantibodies in the serum, and the potential benefit of immunomodulative treatments (discussed later) (26,169,186,187). However, final proof of an autoimmune etiology of narcolepsy is still lacking. It is noteworthy, that a systematic search for neuron-specific, non-neuron-specific, and hypocretin antibodies (in serum and liquor) in narcoleptic patients was negative, with the exception of the recent detection of antibodies reacting with rat hypothalamic epitopes (188–190).

Symptomatic Narcolepsy
Narcolepsy-like syndromes have been reported in association with stroke, encephalitis, hypothalamic disorders, brain tumor, multiple sclerosis (and other autoimmune diseases), endocrine disorders, neurodegenerative disorders (e.g., Norrie’s disease, Möbius syndrome, Niemann-Pick disease type C, Coffy–Lowry syndrome), and head trauma.
Many of these reports, particularly the oldest ones (191), are questionable or uncertain. In some cases of narcolepsy following mild traumatic brain injury, it is likely that head trauma triggered an underlying condition rather than being per se the cause of narcolepsy (8,192). On the other hand, cataplexy-like episodes appearing in association with neurodegenerative disorders or brainstem lesions often appear to differ in terms of sensorimotor manifestations, triggering factors, duration, or accompanying features from definite (“clear cut”, typical) cataplexy of patients with idiopathic narcolepsy.

Symptomatic narcolepsy appears to arise from brain lesions of different topography, although posterior hypothalamic (193,194) and brainstem (99,195,196) are more often involved (185). An HLA-DQB1*0602 positivity is not always present and narcolepsy (as well as cataplexy) may resolve with specific treatment (197).

**DIAGNOSIS**

The diagnosis of narcolepsy is mainly a clinical one and is usually straightforward in patients with typical and frequent (“clear-cut”) cataplexy.

The international classification of sleep disorders has recently four diagnostic criteria for narcolepsy with cataplexy (“classical narcolepsy”) (198).

1. Complaint of EDS occurring almost daily for at least three months.
2. A definite history of cataplexy.
3. Confirmation, whenever possible, by nocturnal polysomnography followed by an MSLT (mean sleep latency less or equal to eight minutes, two or more SOREMPs) or hypocretin-1 levels in the CSF (less than or equal to 110 pg/ml or one third of mean normal control values).
4. Hypersomnia not better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.

Video-polysomnographic recordings of cataplectic attacks are rarely possible, although viewing humorous videotapes has been reported to sometimes help elicit attacks (199).

An estimated 85% of patients with narcolepsy remain undiagnosed (200). Lack of awareness about narcolepsy in the general population and among general practitioners, mild courses of the disease, and late-life-onset of cataplexy may contribute to the often delayed recognition of narcolepsy (106).

**Narcolepsy Questionnaires**

Patients with narcolepsy have typically values on the ESS score >14 (43,201). In a study of 522 narcoleptics free of drugs, the mean ESS score was 18 ± 4 (201). In a personal series of 41 narcoleptics with definite cataplexy, we similarly found mean ESS score of 17 ± 5 (43).

\[\text{to be labeled as cataplexy, episodes must be triggered by strong emotions (most reliably laughing or joking) and must be generally bilateral and brief (less than two minutes). Consciousness is preserved, at least at the beginning of the episode. Observed cataplexy with transient loss of deep tendon reflexes is a very strong, but rare diagnostic finding.}\]

\[\text{ancillary tests would be most needed clinically in patients with suspected narcolepsy but a negative history of definite cataplexy. Unfortunately, the most accurate ancillary finding of classical narcolepsy (low/absent CSF hypocretin-1) is usually not found in “narcolepsy without cataplexy” (discussed later) (136).}\]
The Ullannlinna Narcolepsy Score (UNS) and the Swiss Narcolepsy Score (SNS) consisting of four and five questions respectively have been shown to have a sensitivity and specificity of 80% to 90% for the diagnosis of narcolepsy with cataplexy (43,200). In a personal series of 41 narcoleptics with definite cataplexy, we found mean values of $27 \pm 7$ (UNS) and $49 \pm 24$ (SNS), respectively (43).

**Polysomnography/Sleep Studies**

Typical findings in the nocturnal study are a sleep latency <10 minutes and a REM sleep latency < 20 (Fig. 2, in 40–50% of cases). Other typical polysomnographic findings include frequent arousals, reduced total sleep time, and an excessive motor activity in both NREM and REM sleep. Fragmentation of sleep (and wakefulness) can be documented also actigraphically (Fig. 5). Amounts of REM and NREM sleep are usually normal. Slow wave activity is normal in the first NREM sleep episodes of the night in narcoleptics, but decreases more rapidly than in normal subjects across subsequent NREM sleep episodes (147,202). PLMS are found in up to 40% to 60% of patients (75,77). Sleep disordered breathing, depending on definition, is found in 10% to 20% of patients (75). REM sleep behavior was found polysomnographically in 12% of narcoleptics (77). Questionnaire-based studies suggest a frequency around 30% to 40% (43,78).

The amounts of sleep over 24 hours are normal in narcolepsy (144). Circadian and homeostatic regulations of sleep are essentially preserved in narcolepsy (146–148). Narcolepsy may be associated, however, with an ultradian rhythm that entrains slow wave activity in four hourly distribution (147).

scores of <14 of the UNS and <0 of the SNS are suggestive of narcolepsy with cataplexy.
Multiple Sleep Latency Test/Maintenance of Wakefulness Test

Typical findings on MSLT are a mean sleep latency \(<5\) minutes \([87\% \text{ of patients in a series of 106 narcoleptics with cataplexy (203)}\) and the presence of two or more SOREMPs \((91\% \text{ in the same series)}\). In a personal series of 41 narcoleptics with definite cataplexy, the mean sleep latency on MST was \(2.4 \pm 1.8\) minutes (43). Patients with narcolepsy without cataplexy and/or normal CSF hypocretin-1 levels have generally longer mean sleep latencies (43,133,140).

About \(70\%\) of patients with narcolepsy with cataplexy have both a mean sleep latency \(<5\) minutes and two or more SOREMPs (203). In other words, up to \(30\%\) of patients presenting with EDS and both of these MSLT findings have a condition other than narcolepsy (203).

A recent paper has shown that with increasing age the number of SOREMPs decreases and the mean sleep latency increases (204). These findings suggest that age should be taken into account in interpreting MSLT results.

Typical findings on MWT are a mean sleep latency \(<12\) minutes \([85\% \text{ of patients in a series of 530 narcoleptics (205)}]\) and the presence of one or more SOREMPs. In a series of 530 narcoleptics free of drugs, the mean sleep latency on MWT was \(6.0 \pm 4.8\) minutes (as compared to a value of \(18.7 \pm 2.6\) minutes of 64 controls) (205). The correlation between MSLT and MWT results is not very good (206).

Data of patients with narcolepsy without cataplexy are scarce and inhomogeneous. In a first personal (United States) series of 28 narcoleptics without cataplexy, the mean sleep latency on MSLT was \(2.8 \pm 1.1\) minutes (98). In a second, distinct (Swiss) series of 16 patients the mean sleep latency on MSLT was \(3.7 \pm 2.1\) minutes (43).

HLA-Typing

A DQB1*0602 positivity is found in \(90\%\) of patients with narcolepsy with definite cataplexy, but only in \(40\%\) to \(50\%\) of those with narcolepsy without cataplexy (discussed earlier). Considering the high frequency of DQB1*0602 positivity in the normal population, \(>99\%\) of subjects with either of these two haplotypes do not have narcolepsy.

Normal adults with DQB1*0602 positivity have been found to have reduced REM sleep latency (207).

Hypocretin-1 Levels in the Cerebrospinal Fluid

Low/absent CSF hypocretin-1 levels are the most accurate ancillary test for the diagnosis of narcolepsy with cataplexy. In a review of the 150 patients with HLA-positive, sporadic narcolepsy with cataplexy reported in the literature low/absent CSF hypocretin-1 levels were found in \(93\%\) of patients (136). On the other hand, in patients without an overt neurological/brain disorder (e.g., acute head trauma, Guillain–Barré syndrome) and in normal controls low/absent CSF hypocretin-1 levels are extremely rare and never been found, respectively (123,136,140).

Nevertheless, patients with definite cataplexy and normal CSF hypocretin-1 levels also exist. A significant percentage of these patients are HLA-negative and have a positive family history for EDS or narcolepsy. In a series of 65 patients with narcolepsy and normal hypocretin-1 levels, Mignot et al. found that 25 \((38\%\) had a typical cataplexy, 17 \((26\%\) a positive family history, and 41 \((66\%\) a negative HLA-DQB1*0602 typing (140). Conversely, in the same series, \(92\%\) out of 106 narcoleptics with low CSF hypocretin-1 levels had a definite (typical) cataplexy.
Low/absent CSF hypocretin-1 levels were found in 17% of the 113 patients with narcolepsy without cataplexy reported in the literature [for review, see (136)]. In a series of nine narcoleptics without cataplexy, we found normal levels in eight patients and low (but detectable) levels in one patient (123). In a series of nine patients with narcolepsy without cataplexy, Krahn et al. reported normal CSF hypocretin-1 levels in all patients (208).

Assessments of hypocretin-1 levels are not free of methodological pitfalls (209). They may, however, be particularly helpful in situations in which the clinical diagnosis of narcolepsy is uncertain and neurophysiological tests are inconclusive (a single MSLT test may be “negative” in up to 30% of patients with narcolepsy with definite cataplexy). These situations include patients with unclear history, children, patients under anticonvulsant/stimulant treatments, patients with associated brain or sleep disorders (severe sleep apnea), important legal implications, psychiatric patients and drug-seeking subjects reporting narcolepsy-like symptoms.

**Neuroimaging Studies**

Brain magnetic resonance imaging is typically normal in idiopathic narcolepsy (210). Data of voxel based brain morphometry studies are contradictory/inconclusive [for review of the five published studies, see (211)], probably related to inhomogeneous populations, small series, and methodological differences. One spectroscopy study reported normal NAA/creatine–phosphocreatine content in the ventral pons of 12 narcoleptic patients compared with control subjects (212). A second spectroscopy study reported reduced hypothalamic NAA/creatine–phosphocreatine content in 10 narcoleptic patients compared with control subjects (213). The results of a few PET and SPECT studies (using different methodologies) performed during wakefulness and sleep of patients with narcolepsy are somewhat contradictory and inconclusive (214–217).

**DIFFERENTIAL DIAGNOSIS**

The two main challenges in the diagnosis of narcolepsy are (i) the identification of patients with “clear-cut” cataplexy and (ii) the differentiation of “narcolepsy without cataplexy” from other conditions causing EDS.

**Cataplexy Vs. “Cataplexy-like Episodes”/Pseudocataplexy**

The main difficulty is the differentiation of definite (“clear-cut”, typical) cataplexy from cataplexy-like episodes (pseudocataplexy) following strong emotions in non-narcoleptics normal subjects (8,158,218,219). Such episodes, that are reflected by such popular expression as “weak with laughter”, dropping of the jaw with surprise, buckling of the knees with fear, and loss of speech with anger may occur in 3% to 30% of healthy adults (43,200,218,220). Healthy subjects (most often women) may report a urine loss with laughing, a symptom than can accompany also cataplexy in narcoleptics (6,8). Cataplexy-like episodes tend to be more common in subjects complaining of EDS, usually involve only the lower limbs, and are more commonly triggered by negative emotions (e.g., stress, anxiety, sorrow) than “clear-cut” (true) cataplexy (43). Cataplexy-like episodes in normal subjects probably correspond to an abolition of the H-reflex that is similar (but less pronounced) to that observed in definite cataplexy and may
imply a presynaptic mechanism (57,158,159). This effect may be due to a descending supraspinal inhibition suppressing afferent inputs of the H-reflex, but leaving unaltered alpha-motoneuron excitability (so-called presynaptic inhibition) (221). Interestingly, enough voluntary jaw clenching, which can help narcoleptics to prevent definite cataplexy (discussed earlier), is known also to facilitate the H-reflex response (222). On the other hand, abrupt discontinuation of aminergic reuptake inhibitors can lead transiently to cataplexy-like episodes in non-narcoleptic subjects (223).

Cataplexy-like episodes can be observed also in association with brain disorders that are often obvious already on clinical grounds based on associated neurological disorders (mental state changes, motor symptoms/signs, general medicine findings). Such episodes can be seen in association with Niemann-Pick disease type C, Norrie’s disease, diencephalic and brainstem lesions, encephalitis lethargica, and the Prader–Willi syndrome (182,224–229).

Cataplexy and cataplexy-like episodes are usually easily differentiated on clinical grounds from startle-syndromes, atonic/astatic seizures, gelastic (laughing) seizures, sudden falls (secondary to periodic hypokalemic paralysis and myasthenia gravis), and drop of vascular origin because emotional triggers are not features of these disorders (230). Laughing syncope (Oppenheimer’s geloplegia) consists of a short loss of consciousness during bouts of laughing, probably related to similar mechanisms implicated in cough syncope (231).

**Narcolepsy Without Cataplexy**

The conditions to be considered in the differential diagnosis include sleep disorders breathing syndromes, chronic sleep deprivation, restless legs syndrome/PLMs disorder, idiopathic hypersomnia, circadian rhythm disorders, periodic hypersomnias (e.g., Kleine–Levin syndrome), neurological disorders (sleep–wake dysfunction associated with such central nervous system (CNS) disorders as stroke, head trauma, or Parkinson’s disease), mood disorders, drug intoxication/withdrawal, postviral/infectious conditions, obesity (without sleep apnea), and hypothyroidism (98,232–238).

Intriguing (and unclear) is the association among abnormal MSLT results, increased body mass index/obesity, depression, DR2/DQB1*0602 positivity, decreased motor activity (as assessed for example by actigraphy), and normal CSF hypocretin-1 levels occasionally observed in young adults with non-narcoleptic EDS of unknown origin (99).

In children, narcoleptic symptoms may lead to the misdiagnosis of hyperkinetic disorder or epilepsy.

**Sleep Paralysis Vs. Sleep-Paralysis-Like Episodes/Pseudosleep Paralysis**

The main difficulty represents the differentiation between “true sleep paralysis” from pseudosleep paralysis associated with hysterical states and depression. In the general population, hypnagogic/hypnopompic hallucinations and sleep paralysis are associated in fact with anxiety, depressive, psychotic symptoms (62,69). In these conditions, however, muscle weakness is only partial and patients usually can raise a finger or roll over.

Hyperkalemic paralysis occurs usually at rest, occasionally on awakening, and can be associated with SOREMPs (239). Symptomatic sleep paralysis was
described in the course of postencephalitic parkinsonism, but is uncommon in idio-
pathic Parkinson’s disease with EDS (50,233).

“Psychiatric” and “Psychogenic” Narcolepsy

The association of cataplexy-like and sleep-paralysis-like episodes have been
observed, with and without EDS, also in patients with psychiatric disorders
(219,240). Rosenthal reported hallucinations and cataplexy-like episodes in patients
with schizophrenia (50). In the general population, hypnagogic/hypnopompic hal-
lucinations and sleep paralysis are associated with anxiety, depressive, psychotic
symptoms (discussed earlier). Some of these patients present SOREM episodes
but typically have normal hypocretin-1 levels.

However, we have observed the occurrence of both “true” cataplexy and
psychogenic cataplexy-like spells in a hypocretin-deficient narcoleptic patient, in
analogy to the existence of “true” seizures and pseudoseizures in epileptic
patients (unpublished personal observation). A similar observation was made
by Krahn et al. in a patient with diagnosis of definite narcolepsy but no assess-
ment of hypocretin-1 levels (240). The existence of such a psychogenic modulation
is further supported by the observation of a placebo effect in a recent trial, in
which cataplexy was treated with sodium oxybate (241). Finally, transient
cataplexy-like episodes have been recently reported after discontinuation of
venlafaxine in two HLA-negative depressive/bipolar patients with normal CSF
hypocretin-1 levels (223).

On the basis of these observations, we hypothesize that “REM-sleep symp-
toms” (sleep paralysis, hallucinations, cataplexy), together with SOREM episodes
and increased REM density, may occur in both narcolepsy and psychiatric disorders
through the recruitment of same “final common pathways.”

Patients seeking stimulants may give also a typical history of narcolepsy.
Ancillary tests are often essential in the recognition of such patients.

TREATMENT
Nonpharmacological Treatments

Narcolepsy is a life-long disease that is associated with and increased risk for acci-
dents. Furthermore, complete control of symptoms even with optimal treatment is
rare. Individualized treatment programs including information and counseling
(e.g., timing and type of work, driving, pregnancy, expectations from treatment),
support, and regular follow-up are needed and suggested (242). Regular follow-
ups (e.g., every six months) are helpful in assessing effects/side effects of
drugs, development of new sleep disorders and mood changes, and to assist
patients in coping with occupational and social problems.

Alcohol and certain foods (carbohydrate-rich meals) may enhance EDS (243).
Scheduled naps (1–3/day, duration of 10–60 minutes) may increase alertness and
decrease the need for stimulants (244). The combination of regular naps in the mid-
afternoon and regularly scheduled nocturnal sleep may be particular helpful in
mild cases (245,246). In moderate/severe cases, naps are, however, usually insuffi-
cient. Treatment of associated conditions (in up to 20–30% of cases) such as PLMs
disorder, sleep-disordered breathing, or depression may improve EDS. Patients
may profit from joining patients’ organizations.
Pharmacological Treatment of Excessive Daytime Sleepiness

On the basis of four class I evidence studies, the drug of first choice in the treatment of EDS is modafinil (start with 100 mg/day, maximal dose: 400 mg/day, in 1–2 dosages) (242,247–250). Animal data suggest that modafinil may exert their alerting effects by facilitating dopaminergic and possibly also histaminergic transmission independent from the hypocretin system (115,137,138). Its half-life is 10 to 12 hours. The drug was approved for treatment of narcolepsy first in Europe (France 1992, U.K. 1998) and later in the United States (1998) and its arousing effects are probably similar to that of methylphenidate and inferior to that of amphetamines. Compared to these compounds, modafinil has, however, the advantage of lower side-effect profile, absent effect on nocturnal sleep, and lower abuse-potential. Modafinil achieves a good effect in about 70% to 80% of patients with an improvement of MSLT/MWT of about 30%. Tolerance has only rarely been observed. A few open-label studies have shown that modafinil (most commonly at a dose of 400 mg/day) maintains its efficacy for up to 16 to 40 weeks (251,252).

Headache (in up to 50% of patients), gastrointestinal symptoms, nervousness, and rhinitis are the most frequently reported side effects. Modafinil is contraindicated in pregnancy and increases the metabolism of oral contraceptives (250).

In countries in which modafinil is not available, methylphenidate (start 5 mg/day, maximal dose: 100 mg/day, in 2–3 dosages, less with the slow release form) should be tried next. The effect of methylphenidate is probably related to a direct and indirect activation of dopaminergic transmission. Its half-life is two to seven hours. There have been five treatment trials, one of which provided a class II evidence for treatment of narcolepsy (17,250,254,255). Sympathomimetic side effects are more common than with modafinil but less than with amphetamines. Tolerance can develop and the abuse potential is low in narcoleptics. Sympathomimetic side effects are the most frequently reported side effects. Methylphenidate is contraindicated in pregnancy (250). Use in children between the ages of 6 and 15 appears relatively safe (242). The costs of methylphenidate therapy (usual dose) have been estimated to be about 50 to 100 USD per month (242,253).

In milder cases of narcolepsy, mazindol (not available in the United States) (start 1–2 mg/day, maximal dose: 6 mg/day, in 1–2 dosages) may be tried before methylphenidate. Its half-life is about 10 hours. There have been five treatment trials, one of which provided a class II evidence for treatment of narcolepsy (250,256). Nervousness, headache, gastrointestinal symptoms, tachycardia, insomnia, dry mouth are the most frequently reported side effects. Mazindol is contraindicated in pregnancy.

In patients nonresponding to modafinil and/or methylphenidate metamphetamine and dextroamphetamine (start 5 mg/day, maximal dose: 60 mg/day, in 1–2 dosages) should be considered (in countries in which their use is accepted).

The effect of amphetamines is related to an activation of dopaminergic, noradrenergic, and serotonergic transmission. Their half-life is 10 to 30 hours. Three class II evidence studies have shown efficacy of amphetamines in the short-term treatment of narcolepsy (250). The benefit-to-risk ratio for long-term amphetamine treatment is instead unclear (242). Nervousness, headache, gastrointestinal symptoms, tachycardia, sweating, tremor, mood changes, irritability, and insomnia are the most frequently reported side effects. Headache sides effects, tolerance (in up to one-third of patients), abuse are in fact of concern. Hypertension,
myocardial ischemia, ischemic stroke, and cerebral hemorrhage are rare in patients without associated cardiovascular risk factors (257,258). A neuronal toxicity has been described for amphetamines only at very high dosages of 500 to 3000 mg/day (259). Psychosis is rare in narcoleptic patients treated with amphetamines (not more than 1–3% of cases) (257,260,261). Amphetamines are contraindicated in pregnancy. Amphetamines are controlled drugs that are allowed only in a few countries.

Sodium oxybate (GHB) was approved in the United States and other countries first for the treatment of cataplexy and more recently also (only in the United States, April 2006) for the treatment of EDS in narcoleptics.

Other stimulants for the treatment of narcoleptic EDS include selegiline (an irreversible MAO-inhibitor, 10–40 mg/day), pemoline (start with 20 mg/day, maximal dose: 200 mg/day, in 1 dosage), and levodopa. The positive effect of selegiline on EDS has been shown in one Class I evidence study (262). Clinical experience with this compound has confirmed only in parts these good results. The use of selegiline is limited by its sympathicomimetic side effects and the risk of interaction with other drugs (250). Pemoline was withdrawn in some countries because of (rare) reports of hepatotoxicity (263,264). It is the only stimulant drug that is considered relatively safe in pregnancy. The effect of levodopa (250–500 mg/day) seems to be either limited to single patients or short-lived (265). Drugs with anticitaplectic effect such as venlafaxine, rebotexine, viloxazine, and fluoxetine can show a favorable effect also on EDS.

Co-administration of stimulants (e.g., modafinil with methylphenidate, modafinil with venlafaxine, modafinil with sodium oxybate) is used in clinical practice, but scientific evidence to support this approach is poor.

The effect of stimulants is best assessed clinically (e.g., ESS), although some patients may underestimate the degree of residual EDS (266). In selected cases, MSLT/MWT may be used to monitor treatment response. Drug holidays of 1 to 2 days/week (lower dosages or no medication) may be of benefit. Data on improvement of life quality in narcoleptics treated with stimulants are scarce (251).

**Pharmacological Treatment of Cataplexy**

Improvement of EDS may have a beneficial effect on cataplexy, which may be sufficient in patients with only rare or mild cataplectic episodes. Modafinil may, however, potentiate cataplexy in single patients (personal observation).

Clinical experience suggests that in patients with frequent/severe cataplexy treatment can be started with tricyclic agents, although only class III and IV evidence studies support this approach (242,250). The most effective/used drugs are clomipramine (10–200 mg/day), imipramine (25–200 mg/day), and (particularly in the United States) protryptilin (5–30 mg/day) (18,19,242,250,267). The absence of any response to these anticitaplectic drugs, which is usually apparent within days (268), should prompt to reconsider the diagnosis of (definite) cataplexy: Sedation, dry mouth, orthostatic hypotension, urinary retention, impotence, sweating, blurred vision, and weight gain are the most important side effects. These agents can also worsen or trigger de novo REM sleep behavior disorder in narcoleptics and non-narcoleptic subjects (77). Contraindications to these compounds include glaucoma, prostatic hyperplasia, severe cardiac arrhythmias, acute myocardial infarction, or concomitant treatment with MAO-inhibitors (e.g., selegiline). Tolerance to these drugs may develop (occasionally within a few weeks). Their abrupt
discontinuation may cause rebound cataplexy and status cataplecticus in narcoleptics patients and cataplexy-like episodes in depressed patients (60). Tricyclic agents are generally contraindicated in pregnancy, although severe/frequent cataplexy may harm the child more than the drug (250). The costs of therapy with tricyclic agents (usual dose) have been estimated to be about 50 to 100 USD per month (242,253).

In the United States (2002) and later other countries (Germany 2005, U.K. 2006), sodium oxybate (GHB, start 3 g/day, maximal dose: 9 g/day, in 2 dosages given at bedtime and two to three hours later), an endogenous short chain fatty acid, has been approved for the treatment of cataplexy on the base of class I evidence studies (241,269). The effect of sodium oxybate is related to the activation of putative specific GHB receptors leading to an activation of GABA\(_{B}\) receptors which in turn inhibits arousal-promoting neurons (including the hypocretin ones) (165,270,271). Neuromodulatory effects of GHB (e.g., on dopaminergic and opioid systems, as well as growth hormone) are also known (165,270). The half-life of GHB is 30 to 60 minutes and the compound is available only in liquid form. Because of the rapid onset of sedation GHB should ingested while in bed. Sodium oxybate achieves, usually only after a couple weeks, a 85% to 90% reduction in median cataplexy attacks weekly (272). One study has shown that sodium oxybate maintains its efficacy for up to 12 months (270). Several studies have proven a favorable effect of GHB, alone or as add-on treatment with modafinil, also on narcoleptic EDS and led to the approval of the compound in the United States (November 2005) also for the treatment of EDS (241,269,273). Tolerance has only rarely been observed. Headache, gastrointestinal symptoms, dizziness, nocturnal confusion and amnesia are the most common side effects. Sleepwalking and enuresis are also possible. Of concern is the abuse potential GHB and withdrawal syndrome. Illicit forms of the drugs have been used as a recreational drug and by bodybuilders (270). However, abuse has not been reported in narcoleptics and withdrawal syndromes only for daily doses of GHB of 18 g or more (270). Sodium oxybate is contraindicated in pregnancy. Patients should be also warned against the use of alcohol or sedative/hypnotic drugs with GHB because of the risk of a dangerous CNS-depression (the therapeutic window of GHB is relatively narrow). A severe encephalopathy with coma, myoclonus, and respiratory depression is seen with doses exceeding 40 to 60 mg/kg of body weight (270). The monthly costs of GHB therapy (usual dose) are between 400 to 800 USD in the United States (274). Sodium oxybate is a controlled drug.

Other drugs in the treatment of cataplexy include selective serotonin reuptake inhibitor such as fluoxetine (20–60 mg/day) and citalopram (20 mg/day) (275,276), noradrenergic reuptake inhibitors such as reboxetine (10 mg/day) (277), and other aminergic reuptake inhibitors such as venlafaxine (50–300 mg/day) and femoxetine (200–600 mg/day) (278). These drugs are usually tried in patients with untolerable anticholinergic side effects of the tricyclic agents. Their efficacy is known from clinical experience but supported only by case reports or small series (165,250). Occasionally, improvement of EDS is also observed with these agents. Rebound cataplexy and status cataplecticus have been observed with these agents (61).

Selegiline (discussed earlier), mazindol (discussed earlier), carbamazepine, clonidin, or anticholinergic drugs can be tried in patients without response to other anticataplectic drugs (279,280).
Prazosine should be avoided in narcoleptics because of its well-known aggravating effect of cataplexy (281).

**Pharmacological Treatment of Other Narcoleptic Symptoms**

Hallucinations and sleep paralysis can be improved by tricyclic antidepressants and GHB (282).

For management of insomnia triazolam (0.25–0.50 mg at bedtime) can be tried (250). Probably today, the best treatment of insomnia in narcoleptics is GHB (discussed earlier), which has been shown to increase sleep continuity and amounts of slow wave sleep (241,269,273).

PLMs can be reduced in narcoleptic patients with dopamine agonists and bromocriptine and GHB (265,283,284).

REM sleep behavior disorders in narcoleptics improve with clonazepam (0.5–1.0 mg at bedtime) or melatonin (3–12 mg at bedtime) and worsens by the use of anticitaplectic agents (285–287).

**FUTURE (POTENTIAL) APPROACHES TO TREATMENT OF NARCOLEPSY**

Future treatment approaches may include the use of immunomodulatory interventions near the onset of disease and the use of hypocretin-agonists, selective (H3) histamine antagonists and possibly cell transplantation (250).

A positive response to immunoglobulines particularly on cataplexy has been observed in five children and four adults, usually (but not invariably) near the onset of the disease (169,288,289). In two additional, personal cases (unpublished) and in a case reported in the literature no effect could be observed (290). A placebo-component of these responses is not excluded (discussed earlier). In one case resistant to immunoglobulines, plasmapheresis was transiently effective (290). Steroids were ineffective in one eight-year old boy with acute onset of the disorder (291).

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Secondary Narcolepsy

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INTRODUCTION

In 1930, von Economo hypothesized that narcolepsy might be caused by “a yet unknown” disease of the posterior hypothalamus (1). This prediction was remarkably accurate as it is now clear that idiopathic narcolepsy is caused by a loss of the hypocretin/orexin neurons in the lateral and posterior hypothalamus. Furthermore, strokes, tumors, or other lesions of these areas sometimes produce all the symptoms of narcolepsy, most likely, from injury to the hypocretin neurons and their projections.

This chapter focuses on narcolepsy caused by an identified pathologic process. This heterogeneous disorder is often termed secondary narcolepsy, symptomatic narcolepsy, or narcolepsy due to a medical condition.

Secondary narcolepsy is rare, probably accounting for only about 1% of all patients with narcolepsy. Still, familiarity with the clinical presentations of secondary narcolepsy is important, because good clinical management requires identification and treatment of the underlying disorder. In addition, these lesions shed light on the neurobiology of narcolepsy and state control.

Because secondary narcolepsy is so uncommon, most reports describe single patients, and descriptions of large clinical series are practically nonexistent. Many of these case reports lack important details, and one needs to examine this literature cautiously to determine whether the narcolepsy is authentic. In the first half of the last century, many sleepy patients were diagnosed with narcolepsy when in fact they had sleep apnea or another sleep disorder. As a further complication, the term narcolepsy was often used interchangeably with sleepiness or lethargy. Bonduelle and Degos (2) reviewed the early literature on secondary narcolepsy and appropriately dismissed most as incorrect diagnoses. Autret et al. (3) reviewed some of the older polysomnographically confirmed cases of secondary narcolepsy, and Nishino and Kanbayashi (4) have presented a comprehensive and semiquantitative review of the topic.

Sometimes, it is difficult to establish whether the symptoms of narcolepsy are a direct consequence of a brain lesion. Many reports describe individuals with narcolepsy that developed months or years after the lesion; other patients carry human leukocyte antigens (HLA) that may have fostered the development of coincidental, idiopathic narcolepsy. Thus, the most informative cases are those in which the narcolepsy developed around the same time as the brain lesion, in a HLA-negative individual.

To provide the most robust evidence, this chapter generally highlights cases that fulfill the definition of “narcolepsy due to a medical condition” described in the International Classification of Sleep Disorders (5): excessive daytime sleepiness (EDS) plus definite cataplexy or a positive multiple sleep latency test (MSLT) [mean sleep latency...
less than eight minutes and two or more sleep onset rapid eye movement sleep periods (SOREMs)]. A very low cerebrospinal fluid (CSF) hypocretin level (<110 pg/mL) also provides strong supportive evidence. Using these criteria, it is clear that secondary narcolepsy can occur with a wide variety of bilateral injuries to the hypothalamus, is always accompanied by focal neurologic deficits, and is often associated with hypersomnia. (The author and others define hypersomnia as an increase in the daily amount of sleep, but note that some writers loosely use this term to mean sleepiness.) Secondary narcolepsy is always accompanied by other neurologic deficits including obesity, hypopituitarism, and autonomic dysfunction (Table 1).

STROKES

Clinical case 1: An 18-year-old, male college student initially presented with short stature, gonadal hypoplasia, and delayed puberty. A large craniopharyngioma was identified below his posterior hypothalamus and was surgically removed. Soon after surgery, he became comatose because of bilateral infarcts of nearly the entire hypothalamus, most likely caused by vasospasm of the circle of Willis. This lesion included all of the caudal two-third of the hypothalamus except for the most lateral component on the right, and also extended into the mediodorsal thalamus bilaterally, the left amygdala, and parts of the basal forebrain and the rostral midbrain (Fig. 1). His postoperative course was complicated by severe sleepiness, hypersomnia, panhypopituitarism, and hydrocephalus requiring a shunt.

His neurologic deficits slowly improved, and at age 23, his height had increased to 187 cm, and he weighed 111 kg [body mass index (BMI) = 31.7]. He was moderately inattentive, with poor recent memory, pseudobulbar affect, a partial right
third nerve palsy, mild dysarthria, and slow fine finger movements bilaterally.
Several times each day, he had episodes of sleepiness, with confusion and worsen-
ing of his dysarthria and diplopia that often improved with several minutes of
sleep. He slept 10 hours each night, was difficult to rouse each morning, and
would take a one- to two-hour nap each afternoon. He often dozed off while watch-
ing television or while riding in the car. He had occasional episodes of weakness
when he laughed, sometimes falling to the ground without injury, but often these
episodes would just include weakness of the neck or right arm. He had two epi-
sodes of sleep paralysis and often had vivid visual hallucinations when drowsy.
There was no family history of narcolepsy or excessive sleepiness. Routine EEG
and several days of video/EEG monitoring demonstrated diffuse cortical slowing
but no epileptiform activity. An overnight polysomnogram showed a sleep
latency of one minute, a rapid eye movement (REM) sleep latency of only
1.5 minutes, and 15 spontaneous awakenings without significant sleep apnea.
MSLT showed a latency to stage one sleep of less than 0.5 minutes on average
across the day, with SOREMs occurring within 3.5 minutes in all four naps.
Unlike most individuals with idiopathic narcolepsy, this patient tested negative
for HLA DQB1*0602. The concentration of hypocretin in spinal fluid was
moderately low (167 pg/mL; normal is about 280–344 pg/mL) (6).

This patient’s sleepiness, cataplexy, and SOREMs are probably due to injury
to the hypocretin neurons and their projections. His hypersomnia may be a conse-
quence of injury to other wake-promoting systems (7).

Stroke is one of the more common causes of secondary narcolepsy, accounting
for about one-quarter of all reported cases. Strokes that produce sleepiness usually
injure the rostral pons, midbrain, thalamus, or much of the cortex, but strokes
that produce narcolepsy generally involve the hypothalamus and rostral midbrain.

Compared to most other brain regions, the hypothalamus is a rare site of
ischemic injury. Most likely, this is because the hypothalamus is supplied by numer-
ous small perforating vessels from the large arteries and the circle of Willis that
provide some redundancy in the event that one vessel is occluded (8). The anterior
hypothalamus is supplied by perforating vessels from the anterior and middle
cerebral arteries. The middle and posterior parts of the hypothalamus (including

![FIGURE 1](A, B) T1-weighted sagittal and horizontal magnetic resonance images demonstrating ex vacuo changes (between arrows) in the posterior hypothalamus and rostral midbrain of a patient with narcolepsy caused by a stroke. Source: From Ref. 7.
the lateral hypothalamus and perifornical region) are irrigated by the thalamotuberal arteries and smaller vessels that arise from the top of the basilar artery, the posterior communicating artery, and the posterior cerebral artery (8–11).

Narcolepsy has occurred with hypothalamic strokes from vertebrobasilar insufficiency (12), vascular malformations (13), hypoxic-ischemic injury (14), radiation vasculitis, or vasospasm after hypothalamic surgery (7). Though not yet linked to narcolepsy, hypothalamic strokes also can occur with other processes that disrupt the small penetrating vessels such as vasospasm after subarachnoid hemorrhage, arachnoiditis of the basal meninges (tuberculosis, cysticercosis, cryptococcus), moyamoya, and mitochondrial disorders.

Hypothalamic strokes typically present with sudden coma, though with vascular malformations or vasculitis, the onset may be more gradual (13). As the patient gradually recovers consciousness, the symptoms of narcolepsy become apparent, along with signs of hypothalamic dysfunction such as panhypopituitarism, diabetes insipidus, impaired thermoregulation, and obesity (Table 1). Hypersomnia, an increase in the total amount of sleep over 24 hours is common in all these patients. Because some of the perforating vessels that supply the hypothalamus also extend into the thalamus and medial rostral midbrain, hypothalamic strokes often produce deficits attributable to these nearby areas such as mild hemiparesis (descending corticospinal tracts or thalamus), ataxia (thalamus, superior cerebellar peduncle), and vertical gaze palsies (midbrain tectum).

Narcolepsy can occur with hypoxic-ischemic injuries. A 51-year-old man had cardiopulmonary arrest that was followed by five days of coma. After three weeks recovery, he began to notice EDS, cataplexy, hypnagogic hallucinations, and sleep paralysis (15). Another woman had sleepiness, cataplexy, and three SOREMs, five days after a hypoxic-ischemic injury (14). In general, global hypoxia and ischemia injure the hypothalamus less than other regions, and it’s possible that these two patients had critical stenoses of the posterior circulation or circle of Willis that resulted in hypothalamic strokes.

Radiation treatment of brain tumors can gradually induce hyaline thickening of vessels, producing small strokes long after treatment. In a few patients, radiation vasculitis has produced sleepiness and cataplexy months after treatments for a craniopharyngioma, pituitary adenoma, and frontal glioma (14,16). One of these patients with cataplexy had a normal hypocretin level, suggesting injury to critical hypocretin targets or pathways (16).

Patients with subarachnoid hemorrhage may have low hypocretin levels, but it is unclear whether they have any symptoms of narcolepsy. In one series of 15 patients with subarachnoid hemorrhage, the mean concentration of hypocretin in CSF from the lateral ventricles was low (72 pg/mL) and remained low over 10 days after the injury (17). The concentration of hypocretin in ventricular CSF of normal subjects is unknown, but three of these subjects had similar levels in lumbar CSF. The levels did not correlate with depth of coma and were not clearly lower in those patients with delayed ischemic injury. Whether these low levels are due to direct hypothalamic injury or are simply a consequence of coma remains to be determined (6,18).

As patients recover from their strokes, the symptoms of narcolepsy may improve. One young, HLA-negative man with an arteriovenous malformation of the diencephalon had a marked improvement in his sleepiness and cataplexy, after embolization of the malformation (13). The patient in clinical case 1 has gradually
improved over the 10 years since his stroke, and now has only mild cataplexy and sleepiness (7).

**TUMORS**

**Clinical case 2:** A 23-year-old man presented with EDS, diplopia, and ptosis. A few months later, he began to have sleep paralysis and cataplexy induced by startle. His exam showed bilateral ptosis, poor downgaze, nystagmus on upgaze, inability to converge or adduct the eyes, mild ataxia, and facial weakness on the left. He also had diabetes insipidus. Autopsy two months later showed an astrocytoma extending through the hypothalamus from the optic chiasm to the superior cerebellar peduncle in the midbrain and pons (19).

Tumors may be the most common cause of secondary narcolepsy and hypothalamic injury in general. Some, such as pituitary tumors, arise adjacent to the hypothalamus and compress it from outside, but many tumors such as astrocytomas damage the hypothalamus from within (Table 2).

Tumors in this region are often difficult to treat, and sometimes the surgery or radiation therapy produces additional injury to the hypothalamus [see Ref. (20) for a dramatic example]. For example, vasculitis caused by radiation therapy has produced narcolepsy, years after the original treatment (14).

As with strokes, sleepiness and hypersomnia are common with hypothalamic tumors. Among 14 children referred to a sleep clinic with brain tumors, nine had daytime sleepiness and five of these had two or more SOREMs on their MSLT (21). Hypersomnia was present in four out of seven children with tumors in or adjacent to the hypothalamus, but in only one of seven with tumors in other brain regions. One study of six children after surgery for hypothalamic tumors showed more sleep than baseline, elevated Epworth sleepiness scale scores (15 points on average), and short MSLT latencies (10.3 vs. 26 minutes in controls), but CSF hypocretin levels were normal (22). Another study describes hypersomnia in three children with hypothalamic tumors (23). These studies demonstrate that sleepiness and hypersomnia are common with hypothalamic tumors, even when hypocretin levels are normal.

Hypocretin levels do not always parallel the symptoms of narcolepsy. One 16-year-old girl with surgery for a hypothalamic pilocytic astrocytoma had EDS, hypersomnia, and a low hypocretin level (102 pg/mL) without cataplexy or SOREMs (24). In such patients, the low hypocretin level may result from a

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<td>Astrocytomas, gliomas&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Craniopharyngiomas&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>Germ cell tumors (germinomas, teratomas, choriocarcinoma)</td>
<td>Pituitary adenomas and carcinoma&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>Metastases (rare)</td>
<td>Colloid cyst of third ventricle&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>Hamartomas</td>
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<td>Dermoid and epidermoid cysts</td>
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<td>Chordoma</td>
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<sup>a</sup>These tumors have been reported to cause definite narcolepsy.
depressed level of conscious. Others may have EDS with cataplexy or SOREMs in the context of a normal hypocretin level (16,25). In these cases, injury to hypocretin pathways or targets may produce the cataplexy or SOREMs.

Surgery to remove hypothalamic tumors sometimes produces more dysregulation of REM sleep than typically seen in narcolepsy. One 11-year-old girl had extensive damage to her hypothalamus after removal of a craniopharyngioma (20). She developed diabetes insipidus, panhypopituitarism, poikilothermia, hyperphagia, poor memory, and bitemporal hemianopsia. She also had severe EDS but no cataplexy. Her overnight polysomnogram showed numerous episodes of REM sleep that accounted for 41% of her total sleep. Her MSLT sleep latency was only 1.4 minutes with three out of five SOREMs. She lacked HLA DQB1*0602 and had a low CSF hypocretin level (93 pg/mL). Another young woman with surgical removal of a craniopharyngioma developed EDS and probable cataplexy (26). She had emotionally triggered episodes of muscle atonia, but they were often accompanied by rapid eye movements and vivid dreams. These episodes were sometimes followed by a confusional state in which she walked and had perseverative vocalizations until being woken; it is unclear whether this was somnambulism or REM sleep behavior disorder. The apparent dysregulation of REM sleep phenomena in these young women is unusual, but highlights the sometimes vague boundaries between cataplexy and REM sleep. The severity of these symptoms suggests the existence of other REM-regulating systems in this area besides the hypocretin neurons.

For additional examples of narcolepsy caused by tumors, see Refs. (21,27,28).

INFLAMMATION

Clinical case 3: A 31-year-old man developed headache, pharyngitis, and a slight fever. A few days later, he began to have diplopia and severe sleepiness with a tendency to fall asleep while sitting or standing and even during a meal with food in his mouth. He began sleeping 18 hours each day, but when woken, he was fully alert. On exam, he was fully attentive for brief periods. He had bilateral ptosis, upgaze nystagmus, and could not adduct or converge his eyes. His CSF showed 15 lymphocytes and a slightly elevated protein. Over the next two weeks, he became comatose, and he died two months later. Autopsy in similar cases revealed perivascular infiltrates with degeneration, and phagocytosis of neurons in the hypothalamus and midbrain consistent with encephalitis lethargica (29).

Encephalitis lethargica affected about half a million people between 1916 and 1926 and then faded away. After a brief, flu-like illness, these patients developed severe sleepiness and slept most of the day, but when roused they were fully alert and oriented. On waking from sleep, they often reported vivid dreams and probably hypnagogic hallucinations. Hypotonia and reduced deep tendon reflexes were common, but only a few patients were noted to have true cataplexy (30–32). Many of these patients had clinical dysfunction of the midbrain with ptosis, weak eye adduction, absent pupillary light reflex, and corticospinal weakness. The Viennese neurologist Constantin von Economo found that nearly all these patients had inflammatory lesions involving the posterior hypothalamus and rostral midbrain. Von Economo (29) was able to transmit this disease to monkeys by inoculating them with a filtered extract from the brains of affected patients, but the causal agent has never been identified.
The classic form of encephalitis lethargica disappeared by 1930, but other forms of viral encephalitis often produce sleepiness. In fact, the sleepiness may persist for many years, even after other signs have improved (2,3). One patient with postviral encephalopathy had mild sleepiness, two SOREMs, and sleep paralysis with a hypocretin level of 140 pg/mL (33).

Several other processes can cause inflammation of the hypothalamus resulting in narcolepsy. Sarcoïdosis occasionally affects the basal meninges and perforating vessels, and one patient had sleepiness and four out of five SOREMs (14). Others have reported similar cases with or without cataplexy (27,28,34). Langerhans cell histiocytosis produced sleepiness and more than two SOREMs in a two-year-old child (21). Tertiary syphilis has been reported to cause narcolepsy but is now quite rare (35,36). Tuberculosis, Whipple’s disease, and lymphocytic hypophysitis are less common causes of hypothalamic inflammation that can produce sleepiness but have not yet been reported to cause narcolepsy-like symptoms.

A small number of paraneoplastic syndromes can affect the diencephalon, and, though rare, anti-Ma2 encephalitis frequently causes narcolepsy. This autoimmune, limbic encephalitis is usually associated with germ cell testicular tumors and can also occur with lung cancers. Magnetic resonance imaging (MRI) shows inflammation of the hypothalamus, limbic regions, and brainstem (37–40). Brain biopsies reveal neuronal loss, gliosis, and inflammatory infiltrates. About one-third of these patients have EDS, many have low CSF hypocretin levels (<100 pg/mL), and a few have cataplexy (37,38,41). Recognition of this syndrome is important, because treatment of the underlying cancer sometimes improves the neurologic symptoms.

One might hope that observations such as these would shed light on a possible autoimmune cause of idiopathic narcolepsy. However, idiopathic narcolepsy is not associated with other autoimmune disorders. Some reports have hinted at autoantibodies that alter cholinergic signaling (42), but thus far, the search for functionally significant autoantibodies has been fruitless (37,43–45).

Guillain–Barre syndrome (GBS) is an autoimmune disorder, which produces ascending paresthesias, numbness, and weakness sometimes resulting in quadriplegia. Autoantibodies directed against gangliosides destroy peripheral myelin, but some patients also have signs of central nervous system dysfunction with ophthalmoplegia, ataxia, diabetes insipidus, or the syndrome of inappropriate antidiuretic hormone secretion. Others can have hypnagogic hallucinations, sudden transitions into REM sleep, and REM without atonia reminiscent of narcolepsy (46). In part, this apparent disinhibition of REM sleep may be related to high REM sleep pressure from poor quality sleep in the intensive care unit, but many patients with GBS have hypocretin levels in the intermediate to undetectable range (6,46–49). The patients with the lowest hypocretin levels often show the greatest REM sleep dysregulation, and its possible that the autoimmune process in GBS injures the hypocretin system. Perhaps future studies will be able to determine whether GBS patients have evidence of EDS or cataplexy.

**Demyelination**

**Clinical case 4:** A 38-year-old woman was admitted with six weeks of severe daytime sleepiness and an increase in total sleep time to 16 hours each day. She reported forgetfulness and impaired vision but denied cataplexy, sleep paralysis,
or hypnagogic hallucinations. Her exam was notable for obesity, disorientation, poor visual acuity, and a reduced pupillary reaction to light. She had bilateral internuclear ophthalmoplegia with poor upgaze and convergence. CSF had slightly elevated protein (44 mg/dL) and a low hypocretin level (87 pg/mL). She was positive for HLA DQB1*0602. MRI revealed multiple areas of T2 and fluid-attenuated inversion recovery (FLAIR) hyperintensity involving the corona radiata, and deep periventricular gray matter (Fig. 2). This region of increased signal was especially intense around the third ventricle and aqueduct, involving most of the hypothalamus and extending rostrally to the basal forebrain. Scattered regions of contrast enhancement were evident throughout the hypothalamus, especially near the fornix.

She was diagnosed with acute disseminated encephalomyelitis and treated with high-dose steroids. Six months later, the CSF hypocretin-1 level had increased to the intermediate range (148 pg/mL). One year after her initial presentation, some sleepiness persisted and she slept 12 hours each day off methylphenidate. MSLT still showed an average sleep latency of 2.6 minutes and four out of five SOREMs (51).

Because both demyelinating diseases and narcolepsy may be caused by autoimmune or neurodegenerative processes, many clinicians have taken a special interest in cases of narcolepsy associated with multiple sclerosis (MS) or acute disseminated encephalomyelitis (ADEM).

Many reports describe daytime sleepiness in patients with MS, but almost none of these describe true narcolepsy or rule out causes of sleepiness other than narcolepsy. In a survey study of patients with MS, 77% reported daytime sleepiness and 56% reported episodic weakness resembling cataplexy (51). However, on closer questioning, it became clear that fatigue was often mistaken for sleepiness, and the episodes of muscle weakness were generally not triggered by strong emotions. In nine adults with MS and narcolepsy-like symptoms, the average MSLT sleep latency was 16.3 minutes, none fell asleep in less than five minutes, and no SOREMs occurred (51). Among a random sample of eight patients with MS, hypocretin levels were normal (47). Thus, although patients with MS can have symptoms suggestive of narcolepsy, a detailed history and sleep studies are necessary.
Polysomnograms are particularly important in sleepy MS patients, because their sleep can be disrupted by periodic limb movements, spasticity, and other disorders.

Overall, the co-occurrence of narcolepsy and MS appears to be quite rare. MS with EDS and cataplexy developed over a few months in one patient (14). Another man developed sleepiness at age 23 in association with CSF pleocytosis, and eight years later, he suddenly developed cataplexy, optic neuritis, ophthalmoplegia, and ataxia (52).

Still, these individuals are quite exceptional as most MS patients with narcolepsy-like symptoms have EDS and hypersomnia without SOREMs or cataplexy. Severe sleepiness was reported in two early cases in which autopsy revealed plaques in the midbrain and periventricular region of the hypothalamus (53,54). A 22-year-old woman with a nine-month history of MS presented with sleepiness and hypersomnia without cataplexy (55). Her MRI showed a new plaque in the tuber cinereum that extended into the hypothalamus bilaterally, and her CSF hypocretin was undetectably low. Kato (56) describes a 45-year-old woman with a three-year history of MS who presented with severe sleepiness. MRI two months before had revealed an asymptomatic lesion in the right hypothalamus, but with the development of this new sleepiness, she now had an additional left hypothalamic lesion. CSF showed a mildly elevated protein and no detectable hypocretin. After treatment with high-dose steroids, her sleepiness and the left hypothalamic lesion completely resolved, and her hypocretin level increased to the intermediate range (167 pg/mL). This last case nicely demonstrates that hypothalamic demyelination can produce reversible sleepiness and low hypocretin, but the lesions need to be bilateral.

In most reports, the occurrence of narcolepsy is not clearly linked to an episode of demyelination. One 56-year-old woman developed EDS with cataplexy 25 years after the onset of MS (57). The late onset of her narcolepsy makes idiopathic narcolepsy unlikely, but no evidence suggested that her narcolepsy was caused by a new plaque. A causal connection is even less apparent in many other reports (58–61).

ADEM is severe multifocal demyelination of the brain and spinal cord that develops over several days. This disorder sometimes follows a viral illness and is generally monophasic, though some patients go on to develop MS.

Several ADEM patients have now been reported to have sleepiness and hypersomnia, but none fulfill the criteria for true narcolepsy. One 12-year-old girl presented with excessive sleepiness without cataplexy, and her MRI showed areas of increased T2 signal in the hypothalamus, midbrain, and other areas (62). She had a short mean sleep latency on MSLT (4.5 minutes) but no SOREMs. She was HLA DQB1*0602 negative. CSF hypocretin was only 102 pg/mL. Her sleepiness completely resolved after treatment with high-dose steroids. Three additional Japanese girls presented with hypersomnia, hypothalamic demyelination, and low hypocretin levels (63–65); after treatment with steroids, all improved, sometimes with an increase in the hypocretin concentration. Hypothalamic inflammation probably caused these low hypocretin levels, because other sleepy ADEM patients lacking hypothalamic lesions had normal hypocretin levels (62).

Based on these case reports, it appears that MS does not cause narcolepsy except on very rare occasions. Both MS and ADEM can cause EDS, hypersomnia, and low hypocretin levels, but true narcolepsy with cataplexy or SOREMs is quite rare.
GENETIC SYNDROMES

A variety of genetic syndromes produce symptoms that resemble narcolepsy. Prader–Willi Syndrome includes severe hyperphagia and obesity, mental retardation, hypogonadotropic hypogonadism, and short stature. These symptoms may be caused by hypothalamic dysfunction that results from deletion or functional silencing of several genes on 15q11-13. As infants, many Prader–Willi patients have hypotonia, and later on, EDS and cataplexy triggered by food or excitement can occur. In many individuals, the EDS may be caused by obstructive sleep apnea. However, patients with Prader–Willi can have EDS that is independent of sleep apnea as well as SOREMs and probable cataplexy (66–68). Preliminary studies suggest that hypocretin levels are sometimes low in Prader–Willi syndrome, particularly in those individuals with more severe sleepiness (69–72), but the number of hypocretin-producing neurons is normal (73).

Niemann–Pick disease, type C is a neurodegenerative disorder caused by the accumulation of sphingomyelin because of mutations in the NPC1 gene. It usually begins around age two to four and produces developmental regression, ataxia, myoclonic seizures, and hepatosplenomegaly. Symptoms are quite variable, but can include sleepiness, cataplexy triggered by laughter, short MSLT sleep latencies, and moderately low hypocretin levels (69,74–77).

Autosomal dominant cerebellar ataxia, deafness, and narcolepsy is a rare, probably neurodegenerative disorder described in one family from Sweden (78). Of the five reported patients, all had ataxia and deafness, and four had narcolepsy with cataplexy and two or more SOREMs. Two of them also had sleep paralysis, hypnagogic hallucinations, and REM sleep behavior disorder. The age of onset varies from childhood to the forties. Optic atrophy, tremor, and other neurologic and psychiatric symptoms tend to develop over years. Some of these patients are DR2 negative. One patient lacking DQB1*0602 had a reduced hypocretin level of only 97 pg/mL (79). Imaging studies show hypothalamic atrophy with marked dilation of the third ventricle (80). The responsible gene has not yet been identified, but this disorder is not linked to the genes typically involved in the spinocerebellar atrophies.

Moebius syndrome is associated with abnormal development of the pons and often includes congenital paresis of the sixth and seventh cranial nerves with occasional hypogonadotropic hypogonadism, axonal neuropathy, and limb deformities. Many of these individuals report poor quality sleep and parasomnias, and a few have EDS and a tendency to collapse with laughter (81,82). This syndrome is especially interesting because it suggests that abnormal development of the pons can result in poor control of sleep and atonia mechanisms.

Many patients with myotonic dystrophy have EDS (83,84), often because of central and obstructive sleep apnea. However, myotonic dystrophy can also cause hypothalamic dysfunction, and the sleepiness may be caused by degeneration of wake-promoting systems. Patients with myotonic dystrophy have mildly elevated Epworth sleepiness scale (ESS) scores and can have more than two SOREMs (85,86). One small study reported moderately low hcrt levels (85), but this was not confirmed in a subsequent investigation of 38 myotonic dystrophy patients (86). The latter study also found no differences in the splicing of hypocretin receptor mRNA. Neuropathologic studies will be helpful, but for now, deficient hypocretin signaling seems unlikely to be the basis for sleepiness and SOREMs in myotonic dystrophy.
Two other genetic disorders can produce atonia that resembles cataplexy: Norrie Disease is characterized by mental retardation, ocular atrophy, and deafness and is linked to Xp11.4, a region that includes the genes for monoamine oxidase (MAO) A and B. A few patients with Norrie disease have been reported to have episodes of atonia triggered by pain or laughter as well as atonic spells without obvious triggers (87). These individuals also had very low platelet MAO activity, and because norepinephrine and serotonin inhibit cataplexy, it is possible that these cataplexy-like events are related to abnormal monoamine signaling.

Coffin–Lowry syndrome is characterized by mental retardation, facial dysmorphism, skeletal deformities, and hypotonia. Some of these individuals have sudden drop attacks without any loss of consciousness or epileptiform activity (88–90). These attacks resemble cataplexy in that there is a sudden loss of muscle tone, but the attacks differ in several ways. The drop attacks of Coffin–Lowry syndrome are not triggered by laughter or other emotions but are triggered by sudden visual, tactile, or auditory stimuli; injury is common; and the duration of these events is only a few seconds at most (89,91). Over years, the spells may begin to resemble hyperekplexia, with stimuli inducing brief increases in muscle tone like a startle response (89,91). These stimulus-induced drop episodes may involve some of the same atonia pathways as in cataplexy, but there appears to be little resemblance to true cataplexy or narcolepsy.

OTHER DISORDERS THAT HAVE CAUSED NARCOLEPSY-LIKE SYMPTOMS

Wernicke's encephalopathy can produce symptoms suggestive of narcolepsy. One five-year-old girl presented with severe sleepiness, an increase in daily sleep to 15 to 20 hours each day, confusion, and ocular abnormalities (92). Her MRI showed edema bilaterally in the hypothalamus, periaqueductal grey, and floor of the fourth ventricle. Initially, her hypocretin level was less than 40 pg/mL but after treatment with thiamine, it increased to 158 pg/mL along with an improvement in her sleepiness.

Kleine–Levin syndrome is characterized by recurrent episodes of sleepiness and hypothalamic dysfunction. Most typically, this affects adolescent men, and during the episode they may sleep up to 18 hr/day with binge eating, hypersexuality, and aggressiveness in some cases. CSF hypocretin levels are sometimes low (71,93), but cataplexy has not been reported.

Patients with parkinsonism often have fragmented sleep and daytime sleepiness. In Parkinson’s disease, the EDS is often caused by sedation from dopamine agonists, or poor quality sleep from muscle rigidity, sleep disordered breathing, or periodic limb movements. Hypocretin levels may be slightly low or normal in Parkinson’s disease (69,94), but cataplexy has not been reported. Autret (95) described one patient with striatonigral degeneration with sudden transitions into REM sleep and cataplexy. One individual with progressive supranuclear palsy was noted to have atrophy of the midbrain and hypothalamus in association with EDS, fragmented sleep, and no detectable hypocretin in her CSF, but cataplexy and SOREMs were absent (96). These findings hint at some involvement of the hypocretin system in disorders that produce parkinsonism, but true narcolepsy seems very rare.
HEAD INJURY

Sleepiness is common after head injury, and many anecdotal reports suggest that narcolepsy may follow trauma to the head. Potentially, head injury could directly damage the hypocretin neurons or expose antigens on these cells that then serve as a target for an autoimmune attack. However, current data indicates that head injury rarely produces true narcolepsy (see chapter 22, “Traumatic Brain Injury”).

Analyzing these reports is often challenging because, in some cases, pre-existing sleepiness may have contributed to the head injury. Furthermore, in some cases, the narcolepsy appeared to develop long after the head injury and may be coincidental (97–99).

However, a couple reports show compelling connections. One patient had cataplexy and 5/5 SOREMs, 10 days after closed head injury (14). Another man had a severe head injury resulting in coma for five days that was followed by sleepiness, sleep paralysis, and cataplexy; he had four SOREMs and was HLA negative (59).

These cases are exceptional, and most head injured patients simply have sleepiness but not narcolepsy. Guilleminault (100,101) reviewed 186 patients with head injury, and found that 48 had MSLT latencies less than five minutes and ESS scores greater than 16. Only five of these patients had two or more SOREMs, and none had cataplexy. Chronic EDS seems more common in subjects that present with coma, and the duration of loss of consciousness may be proportionate to the eventual EDS. If so, this would indicate that the EDS is related to the severity of brain injury.

In support of this perspective, hypocretin levels are often low soon after traumatic brain injury, especially in patients with coma (102,103). In a prospective study of 44 patients with acute traumatic brain injury, 84% had low CSF hypocretin levels, and this was roughly correlated with the severity of injury; the lowest levels occurred in patients with more severe coma and obvious mass effect on brain computed tomography (102). Possibly, this represents injury to the hypocretin neurons or their projections, but it may also reflect depressed consciousness after head injury. With recovery, some sleepy head trauma patients continue to have intermediate hypocretin levels (33,71), suggesting permanent injury to the hypocretin system.

In summary, sleepiness is common after head injury, especially when the trauma is severe. In part, this may be caused by injury to the hypocretin neurons or other wake-promoting systems, but true post-traumatic narcolepsy is rare.

ISOLATED CATAPLEXY

Cataplexy almost always occurs along with daytime sleepiness. Isolated cataplexy from brain lesions has been reported just a few times, but these cases provide useful perspectives on the neural circuits that control motor tone.

Stahl (104) describes a 36-year-old man with bilateral internuclear opthalmoplegia caused by a glioblastoma originating near the medial longitudinal fasciculus in the midbrain. This patient had mild EDS, but severe and variable cataplexy. They report that, “When he walked he resembled a puppet on strings; his face sagged; his arms became limp; his back bowed; and his legs buckled.” They add that this status cataplecticus was accompanied by a loss of deep tendon reflexes. The authors postulate that this lesion injured a pathway that normally inhibits the descending atonia system.
Three other patients had more typical cataplexy with brainstem lesions. A 28-year-old, HIV positive man presented with headache, upgaze paresis, and cataplexy triggered by laughter (105). He also had sleep paralysis but no daytime sleepiness. MRI showed an enhancing mass in the midbrain tectum. After treatment for presumed toxoplasmosis, all symptoms resolved. A 19-year-old woman with a three-year history of MS developed cataplexy triggered by laughter (106). MRI showed extensive areas of increased T2 signal in the dorsal and ventral midbrain, central pons, and medial medulla. A six-year-old girl had persistent vomiting and cataplexy that occurred while playing (106). Her symptoms gradually improved after removal of a pilocytic astrocytoma at the dorsal ponto-medullary junction.

The manifestations in these individuals demonstrate that tumors, inflammation, or demyelination in the midbrain and dorsal pons/medulla can cause cataplexy, most likely from injury to circuits that normally inhibit descending atonia pathways. Sleepiness was not a prominent symptom in these patients, and the full narcolepsy syndrome probably requires direct injury to the hypocretin neurons or their connections to nuclei that regulate arousal and atonia.

HYPERSOMNIA

Nearly all patients with secondary narcolepsy have hypersomnia, an increase in the total amount of sleep over 24 hours. Though this can occur in occasional patients with idiopathic narcolepsy, most sleep about eight hours (107). Furthermore, mice lacking hypocretin or the hypocretin-producing neurons have normal amounts of sleep (108,109). Thus, hypersomnia is probably not caused by just a loss of hypocretin signaling.

In contrast, hypersomnia is common with lesions of the lateral hypothalamus that also injure nonhypocretin neurons. This phenomenon is well described with lateral/posterior hypothalamic lesions in rats, cats, and monkeys (110–113). Hypersomnia is also very common with the clinical lesions discussed in this chapter as well as others cases of hypothalamic injury (21,114), including several patients with normal hypocretin levels (22). Most likely, this hypersomnia results from a loss of other wake-promoting neurons in this region, such as the histaminergic neurons of the tuberomammillary nucleus or perhaps glutamatergic neurons of the lateral and posterior hypothalamus.

CLINICAL DIAGNOSIS AND MANAGEMENT

The clinical management of secondary narcolepsy often focuses on treating the underlying disorder. For example, surgery, radiation therapy, and chemotherapy may be required for a hypothalamic tumor, whereas MS should respond well to immunomodulation including high dose steroids. Measurement of hypocretin in CSF is unnecessary for many patients with definite cataplexy, but it can be helpful in patients with atypical cataplexy. If sleepiness or cataplexy persist after optimally treating the lesion, then symptoms should be treated as outlined in chapter 6.

CONCLUSIONS

Von Economo demonstrated great foresight when he predicted that narcolepsy was caused by injury to the posterior hypothalamus. It is now clear that idiopathic
narcolepsy is caused by a selective loss of the hypocretin-producing neurons, and secondary narcolepsy is often caused by lesions of the lateral and posterior hypothalamus, sometimes with extension into the midbrain. With true secondary narcolepsy, these lesions often injure the hypocretin neurons and/or their projections to key brainstem regions that control arousal and motor tone. Strokes, tumors, and inflammation of the hypothalamus are the most common causes. Secondary narcolepsy can also occur with genetic syndromes such as Prader–Willi syndrome and Niemann–Pick syndrome, but cases due to MS and head injury are quite rare. Clinically, secondary narcolepsy can be easily recognized, because these individuals always have focal neurologic deficits such as vertical gaze palsies, confusion, poor memory, impaired thermoregulation, obesity, and endocrine dysfunction. Furthermore, and in contrast to most patients with idiopathic narcolepsy, nearly all patients with secondary narcolepsy have hypersomnia.

ACKNOWLEDGMENTS

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REFERENCES

After the outbreak of the large European epidemic of encephalitis lethargica in 1916, the Austrian neurologist von Economo observed that encephalitic lesions in the posterior hypothalamus resulted in hypersomnia (1). Based on these observations, he was among the first to suggest a key role of the hypothalamus in the regulation of sleep–wake functions and hypothesized that these regions contained neurons essential for the promotion of wakefulness. At the end of the same century, in 1998, the discovery of the hypocretin neurotransmitter system confirmed the paramount role of the hypothalamus in the regulation of sleep–wake functions and its role in the pathophysiology of narcolepsy, the sleep–wake disorder “par excellence.”

Two independent U.S. research groups discovered simultaneously two new neurotransmitter peptides: hypocretin-1 (orexin A) and hypocretin-2 (orexin B). One group observed an appetite-stimulating effect of these peptides and suggested the term “orexin,” derived from the Greek word “orexis” (appetite) (2). The other group coined the name “hypocretin,” because of its hypothalamic origin and its structural similarity with the secretin family (3).

Besides sleep–wake regulation, animal and human studies suggest a wide variety of functions of the hypocretins, including neuroendocrine, locomotor, autonomic regulation, feeding behavior, and energy homeostasis.

HYPOCRETINS AND SLEEP–WAKE REGULATION

The alternation of wakefulness, nonrapid eye movement (NREM), and rapid eye movement (REM) sleep is associated with distinct firing patterns of thalamo-thalamic, thalamo-cortical, and cortico-thalamic neurons. Thalamo-cortical neurons are influenced by several brain regions (Table 1).

Activation of wakefulness-promoting brain regions projecting to the thalamus is necessary for thalamo-cortical activation, which results in the low-amplitude, high-frequency EEG characteristic of wakefulness.

Hypocretin neurons play an important role in this wake-promoting activation. These neurons are almost exclusively localized in the posterior and lateral hypothalamus (2,3). Their dendrites secrete excitatory hypocretin peptides (hypocretin-1 and hypocretin-2, also called orexin A and B), which interact with two receptors (Hcrtr1 and Hcrtr2, also called OXR1 and OXR2). The latter have different distributions and functions in the central nervous system (4–8).

Hypocretin neurons excite a multitude of central nervous system areas, including monoaminergic and cholinergic neuronal systems such as basal forebrain, laterodorsal tegmental/pedunculopontine tegmental area, tuberomammillary nucleus, locus coeruleus, dorsal raphe nucleus, ventral tegmental area, and local glutaminergic neurons, as well as spinal cord regions (Fig. 1) (4–13).
The hypocretin system is most active during wakefulness, particularly during loco-motor activity (Fig. 2, see also next paragraph) (14–18). Hypocretin can enhance the activity of hypocretin neurons through hypocretin receptors on local glutamatergic neurons. This positive feedback mechanism may help orchestrate the excitatory wakefulness-promoting output signal of this hypothalamic region (9).

During NREM sleep, hypocretin cells are significantly less active than during wakefulness (19). Inhibition of hypocretin neurons through gamma aminobutyric acid (GABA)ergic inputs from the ventrolateral preoptic area (VLPO) and basal forebrain areas is thought to be crucial for sleep initiation (Fig. 3) (20–22). The exact role of the hypocretin system in REM sleep regulation remains controversial. Decreased (23) as well as increased hypocretin activity during REM sleep has been suggested (24).

Muehlethaler et al. (25,26) interpreted the interaction between sleep-active VLPO neurons and wake-active monoaminergic and cholinergic neurons as a reciprocal mechanism, leading to either sleep or wakefulness. As hypocretin

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**TABLE 1** Synopsis on sleep–wake regulating systems

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<thead>
<tr>
<th>Wakefulness-promoting brain regions</th>
<th>Acetylcholine</th>
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<tr>
<td>Laterodorsal tegmental/pedunculopontine tegmental area (LDT/PPT)</td>
<td>Acetylcholine</td>
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<tr>
<td>Basal forebrain (BF)</td>
<td>Acetylcholine</td>
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<td>Locus coeruleus (LC)</td>
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<td>Glutamate</td>
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<td>Hypothalamus (HT) (hcrt)</td>
<td>Hypocretin</td>
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**NREM sleep-promoting brain region**

- Ventrolateral preoptic area (VLPO) - GABA

**REM sleep-promoting brain region**

- Laterodorsal tegmental/pedunculopontine tegmental area (LDT/PPT) - Acetylcholine

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**Abbreviations**: NREM, nonrapid eye movement; REM, rapid eye movement.

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The hypocretin system is most active during wakefulness, particularly during loco-motor activity (Fig. 2, see also next paragraph) (14–18). Hypocretin can enhance the activity of hypocretin neurons through hypocretin receptors on local glutamatergic neurons. This positive feedback mechanism may help orchestrate the excitatory wakefulness-promoting output signal of this hypothalamic region (9).

During NREM sleep, hypocretin cells are significantly less active than during wakefulness (19). Inhibition of hypocretin neurons through gamma aminobutyric acid (GABA)ergic inputs from the ventrolateral preoptic area (VLPO) and basal forebrain areas is thought to be crucial for sleep initiation (Fig. 3) (20–22). The exact role of the hypocretin system in REM sleep regulation remains controversial. Decreased (23) as well as increased hypocretin activity during REM sleep has been suggested (24).

Muehlethaler et al. (25,26) interpreted the interaction between sleep-active VLPO neurons and wake-active monoaminergic and cholinergic neurons as a reciprocal mechanism, leading to either sleep or wakefulness. As hypocretin

---

**FIGURE 1** Neurochemical interactions between monoaminergic, cholinergic, glutaminergic, GABAergic, and hypocretinergic systems. Red arrows indicate activation and blue arrows indicate inhibition. **Abbreviations**: HT, hypothalamus; VLPO, ventrolateral preoptic; BF, basal forebrain; TMN, tuberomammillary nucleus; VT, ventral tegmentum; DR, dorsal raphe; LDT/PPT, laterodorsal tegmentum/pedunculopontine tegmentum; LC, locus coeruleus; hcrt, hypocretin; glu, glutamate.
neurons interact with both sleep- and wake-active neurons, they hypothesized that hypocretins might act as a “stabilizer” between wakefulness-maintaining and sleep-promoting systems, preventing sudden and inappropriate transitions between sleep and wakefulness.

**HYPOCRETINS AND MOTOR FUNCTIONS**

The hypocretin projections to locus coeruleus, the trigeminal motor nucleus, and spinal cord suggest a role of the hypocretin system also in the regulation of motor functions and muscle tone (27). Several studies have provided evidence for a positive correlation between hypocretin neuron activity and motor activity (15,17). Recent in vitro studies have shown that hypocretin neurons in rodents are activated during eating, grooming, and particularly exploratory behaviors, conditions known to trigger cataplexy in narcoleptic animals (28). This anticataleptic effect may involve hypocretinergic projections to the mesencephalic locomotor region and the pedunculopontine and laterodorsal tegmental nuclei (29).
HYPOCRETINS AND OTHER FUNCTIONS

The hypothalamus is known to be involved in the control of (neuro-)endocrine, metabolic, and autonomic functions. Lesions in the lateral hypothalamus lead to hypophagia and weight loss. Pace-maker neurons in the hypothalamic arcuate nucleus, which are known to integrate satiety and hunger signals and to play a major role in maintenance of energy homeostasis, have recently been shown to be activated by hypocretin (and inhibited by leptin) (30).

Finally, recent works have demonstrated a role of hypocretin neurons in modulating drug-seeking behavior induced by the activation of dopaminergic pathways (31).

In summary, functions of hypocretin neurons are thought to include the stabilization of wakefulness (and other states of being) and the regulation of motor functions (locomotion, muscle tone) and energy homeostasis. Hypocretin
systems may play a key role in orchestrating functions that are linked with “ergotropic” and “motivated” behaviors.

**HYPOCRETINS AND HUMAN DISORDERS**

Narcolepsy is the sleep disorder par excellence characterized by excessive daytime sleepiness, sudden transitions from wakefulness into NREM and REM sleep, and disturbed night sleep. After studies in rodents and canine models of narcolepsy, in which a hypocretin (ligand/receptor) system deficiency was found (32), Nishino et al. (33) first described the association between decreased cerebrospinal fluid (CSF) hypocretin-1 levels and human narcolepsy. This result was confirmed in subsequent larger series (34–37). In line with this finding, autopsy studies of narcoleptic patients revealed a marked reduction (85%–100%) of hypocretin mRNA and peptides in the posterolateral and tuberomammillary hypothalamus (38,39). The reduction of neurons containing prodynorphin mRNA and NARP protein (which colocalizes with hypocretin) to about 5% to 10% of normal confirms that narcolepsy–cataplexy is caused by a loss of hypocretin neurons, rather than a failure of hypocretin ligand production (40,41).

The etiology of this hypothalamic neuronal loss is not known. Because of the HLA-association of narcolepsy, many authors consider the possibility of an autoimmune etiology. This hypothesis is indirectly supported by the bimodal age-of-onset of narcolepsy and by the observation of improvement of narcoleptic symptoms after high-dose intravenous immunoglobulins near the time of onset of the disorder (42,43).

Clinical data suggest a relationship between CSF hypocretin-1 levels and severity of both (definite) cataplexy and excessive daytime sleepiness, as estimated by the multiple sleep latency test (MSLT), in sporadic narcolepsy (32,34,44). Hypocretin determination is associated with methodological pitfalls. The high interassay variability of the commercially available radioimmunoassay kit necessitates the use of standardized protocols with pooled reference CSF at different concentrations, and accounts for the fact that normative values differ between laboratories (45). Hence, some uncertainty remains about the exact “cut-off” values of CSF hypocretin concentrations and the diagnostic value of borderline “low” CSF hypocretin-1 levels. Mignot et al. (34) have determined that 110 pg/mL is the cut-off value in their laboratory to diagnose narcolepsy.

The sensitivity and specificity of low/undetectable CSF hypocretin-1 levels are 87% and 99% for narcolepsy with definite cataplexy (32,34). However, in narcoleptics with no/atypical/mild cataplexy, mild excessive daytime sleepiness, positive familial history, or negative HLA-DQB1*0602 typing CSF hypocretin-1 levels are often normal (32,34–37,46). Unfortunately, CSF hypocretin-1 measurements are therefore rarely helpful in narcoleptics in whom diagnosis is uncertain on clinical grounds. Hypocretin determination can be of definite help in patients with narcolepsy-like symptoms secondary to psychiatric or sleep disorders, in small children (less than eight years) in whom MSLT criteria are not available, and in patients with atypical electrophysiological findings or under treatment.

In other sleep–wake disorders than narcolepsy, such as idiopathic hypersomnia, recurrent hypersomnia, sleep apnea syndrome, post-traumatic hypersomnia, familial fatal insomnia, and restless legs syndrome, CSF hypocretin-1 levels are typically normal (32,34–37).
In most neurological patients without sleep–wake disorders, tested CSF hypocretin-1 levels were also found to be normal (35,47). There are currently only two medical conditions in which low/undetectable hypocretin levels appear to be common: in a majority (95%) of patients with acute severe/moderate traumatic brain injury (48) and in a subset of patients with severe Guillain-Barré syndrome (49,50). The pathophysiological implications of these findings are unclear at the present time. Low hypocretin levels after traumatic brain injury may represent a phenomenon secondary to hypothalamic traumatic shearing injury. In the Guillain-Barré syndrome, deficient hypocretin levels could imply an autoimmune neuronal damage or an antigen–antibody interaction in the detection of the peptide. The existence of these (and other) non-narcoleptic, hypocretin-deficient syndromes suggests the possibility that several mechanisms may lead to a CSF hypocretin-1 deficiency, even in the absence of narcolepsy-like clinical manifestations.

The potential impact of hypocretin and hypocretin-modulating substances in the treatment of human narcolepsy remains speculative at this time.

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Idiopathic Hypersomnia and Recurrent Hypersomnia

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INTRODUCTION

Excessive daytime sleepiness is the most common complaint in sleep-disorder clinics and also one of the most common complaints in primary care practices. The vast majority of such complaints can be attributed to insufficient sleep, medical or psychiatric illness, specific causes of insomnia, sleep-disordered breathing, circadian rhythm sleep disorders, or narcolepsy. A small percentage of severely sleepy patients, however, do not meet the criteria for any of these common causes of sleepiness. The etiology in such cases is assumed to be neurologic, and may well be heterogeneous given that these rare patients are defined in part by exclusion of other diagnoses. Beyond these exclusion criteria and confirmation of excessive sleepiness, patients are classified largely along empiric, symptom-based findings: those with constant sleepiness have idiopathic hypersomnia with or without long sleep time, whereas those with only periodic sleepiness have recurrent hypersomnia. This chapter summarizes knowledge about these intriguing conditions that are among the most challenging and least-well understood causes of excessive daytime sleepiness.

IDIOPATHIC HYPERSOMNIA

Historical Introduction

The term “idiopathic hypersomnia” was used as early as 1829, but a more formal disorder definition did not emerge until Roth’s work in the 1950s and 1960s (1,2). As understanding of narcolepsy was clarified by newly discovered sleep-onset rapid eye movement (SOREM) periods, Roth determined that certain patients previously diagnosed with narcolepsy did not fit the newer criteria. Based on systematic studies of more than 600 patients with hypersomnia, Roth categorized patients without classical narcolepsy or obvious secondary reasons for sleepiness as having “functional hypersomnia.” The functional hypersomnias were divided into a short-cycle variety, in which episodes of a few hours in length occurred every day, and a long-cycle variety in which episodes lasting days to weeks occurred, separated by intervals of months to years. Among the short-cycle hypersomnias, the most common disorder was described as “idiopathic hypersomnia” and manifested as diurnal sleep, excessive by one to several hours, with onset in puberty or the
following 10 years and thereafter a stable lifetime course. Daytime sleep attacks were described as more resistible than those experienced in narcolepsy (1). These patients were then further classified as monosymptomatic (permanent drowsiness with sleep attacks) or polysymptomatic (prolonged night-time sleep with sleep attacks and “sleep drunkenness”). Roth described “sleep drunkenness” as a difficult, prolonged period of confusion and disorientation prior to full awakening. Other terms have been used to describe idiopathic hypersomnia, such as non-REM (NREM) narcolepsy (3), essential narcolepsy (4), and idiopathic central nervous system hypersomnolence (5).

**Epidemiology**
In part because the definition of idiopathic hypersomnia has evolved with time, the exact prevalence of the disorder is uncertain. Several studies in sleep-disorder clinics have found different frequencies of idiopathic hypersomnia. Roth’s 1975 series of 642 patients included 274 diagnosed with non-narcoleptic hypersomnia, among whom 174 carried a diagnosis of mono- or poly-symptomatic idiopathic hypersomnia. The number of narcoleptics in this series was 226, and the ratio of idiopathic hypersomnia to narcolepsy was 0.77 (2). In 1987, Matsunaga (6) reported idiopathic hypersomnia in only seven of 500 consecutive patients from sleep-disorder centers. Bassetti and Aldrich (7) characterized more than 4000 sleep-center patients (1997): 42 (1%) were diagnosed with idiopathic hypersomnia and 258 patients with narcolepsy, suggesting a ratio of only 0.16. The sample reported by Billiard (8) in 2001 showed a ratio of idiopathic hypersomnia to narcolepsy of about 0.10. The decrease in frequency of idiopathic hypersomnia in comparison to other sleep-related diagnoses and, more specifically, to narcolepsy during the past 30 years may reflect advances in detection of underlying causes of hypersomnolence. Table 1 lists studies of patients with hypersomnia and categorizes the patients into narcoleptics and those with idiopathic hypersomnia.

Overall, based on a prevalence of narcolepsy of 20 to 50 per 100,000 people, the estimated prevalence of idiopathic hypersomnia appears to be two to five per 100,000 people (7). Among Bassetti and Aldrich’s (7) 42 patients, the diagnosis appeared to be more common among Caucasians than African Americans, and more common in women than men (1.8:1). However, extrapolation from these findings is difficult given the size of the sample, albeit one of the largest available.

**TABLE 1** Large Case Studies of Patients with Hypersomnia

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Narcolepsy</th>
<th>Idiopathic hypersomnia</th>
<th>Ratio IH:N</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roth</td>
<td>1976</td>
<td>226</td>
<td>174</td>
<td>77%</td>
<td>(2)</td>
</tr>
<tr>
<td>Van den Hoed et al.</td>
<td>1981</td>
<td>41</td>
<td>17</td>
<td>41%</td>
<td>(65)</td>
</tr>
<tr>
<td>Coleman et al.</td>
<td>1982</td>
<td>425</td>
<td>150</td>
<td>35%</td>
<td>(66)</td>
</tr>
<tr>
<td>Baker et al.</td>
<td>1986</td>
<td>257</td>
<td>74</td>
<td>29%</td>
<td>(67)</td>
</tr>
<tr>
<td>Bassetti and Aldrich</td>
<td>1997</td>
<td>258</td>
<td>42</td>
<td>16%</td>
<td>(7)</td>
</tr>
<tr>
<td>Billiard and Dauvillers</td>
<td>2001</td>
<td>339</td>
<td>35</td>
<td>10%</td>
<td>(8)</td>
</tr>
</tbody>
</table>

Abbreviations: IH, idiopathic hypersomnia; N, narcolepsy.

Source: From Ref. 8, p. 355.
Clinical Features
The recent publication of the International Classification of Sleep Disorders (ICSD), 2nd edition, again modifies the definition of idiopathic hypersomnia, which is divided into two separate diagnoses: idiopathic hypersomnia with long sleep time and idiopathic hypersomnia without long sleep time.

Idiopathic hypersomnia with long sleep time is characterized by constant, severe excessive sleepiness, not improved after the major sleep episode (10 or more hours), and by nonrefreshing naps of up to three to four hours. Awakening from sleep is often difficult, even with an alarm clock, and some patients require an hour or more to fully arouse. Confusion upon awakening from a nap or the major sleep episode is common. This “sleep drunkenness,” also known as “Schlafrunkenheit” (German), “ivresse du sommeil” (French), or “syndrome of Elpenor,” was present in 50% to 60% of the patients studied by Roth, but in only 21% of those described by Bassetti and Aldrich (7,8). Common behaviors associated with sleep drunkenness may include slurred speech, aphasia, amnesia, and gait difficulty. Examination of a patient while symptomatic may reveal diminished performance on psychometric testing, hyporeflexia, gait ataxia, and orthostatic or vestibular signs (9).

Associated symptoms may include several related to autonomic dysfunction, such as migrainous headaches, orthostatic hypotension with syncope, and Raynaud’s phenomenon. The onset of idiopathic hypersomnia with long sleep time generally occurs prior to the age of 25 years. The condition is chronic with stable symptoms, though rare episodes of spontaneous recovery have been reported. Difficulty with performance may arise at school or work, and social impairment can occur (10). However, at least one study did not demonstrate a clear decrease in vigilance in idiopathic hypersomnia patients, in contrast to those with narcolepsy and sleep apnea (11).

In idiopathic hypersomnia without long sleep time, the major sleep episode is generally less than 10 hours, but otherwise the condition resembles idiopathic hypersomnia with long sleep time. Cataplexy should not be present in either condition (10). Psychiatric symptoms were notable in Roth’s idiopathic hypersomnia patients, occurring in approximately 50% (14–26% had depression), though these symptoms were less common in Bassetti and Aldrich’s sample (7,8). Motor vehicle accidents and near-miss collisions may arise because of the hypersomnia. More rarely described associated symptoms include problems with recent memory, food craving, and sexual dysfunction (8).

Pathophysiology
No animal model of idiopathic hypersomnia exists, and the underlying neurobiology remains poorly understood. Patients with idiopathic hypersomnia or narcolepsy, in comparison to normal controls, have lower levels of dopamine and indoleacetic acid in the cerebrospinal fluid (CSF) (12). In contrast, no difference from controls was detected for several other monoamine metabolites, including 3,4-dihydroxyphenylacetic acid, 3-methoxy-4-hydroxyphenylethylene-glycol, homovanillic acid, and 5-hydroxyindoleacetic acid (13). Subsequent reassessment of this study using multivariate statistical analysis demonstrated a relationship between these four metabolites in normal controls; however, 3,4-dihydroxyphenylacetic acid and homovanillic acid (both dopamine metabolites) did not correlate with the other two metabolites in narcoleptics, and...
3-methoxy-4-hydroxyphenylethleneglycol (a norepinephrine metabolite) did not correlate with the other three metabolites in patients with idiopathic hypersomnia. These results led to speculation that dysfunction in dopaminergic pathways may exist in narcoleptic patients and noradrenergic pathways may be disrupted in idiopathic hypersomnia (14).

Although narcolepsy is associated with the HLA-DR2 antigen, “essential hypersomnia” is not (15). Among 30 noncataplectic patients with excessive daytime sleepiness or sleep attacks in one study, all six who had at least one SOREM period on a multiple sleep latency test (MSLT) were HLA-DR2 positive, whereas the remainder had a frequency similar to that of controls (16). Of the 18 HLA-tested patients with idiopathic hypersomnia in the study by Bassetti and Aldrich (7), only six were found to be HLA-DR2 positive.

As noted, genetic factors may play a role in idiopathic hypersomnia. Of Bassetti and Aldrich’s 42 patients with idiopathic hypersomnia, two had one relative with narcolepsy–cataplexy and 14 had at least one family member with unexplained excessive daytime sleepiness. In addition, a family history of diabetes was present in 52% of the patients; a link with diabetes has also been observed in narcolepsy (7,17).

Fifteen patients (11 women) diagnosed with the polysymptomatic form of idiopathic hypersomnia and 15 controls were evaluated in a recent study that tracked salivary melatonin and cortisol content for 24 hours (18). The circadian rhythms of both hormones were found to be phase-delayed in idiopathic hypersomnia, and these subjects displayed symptoms of sleep drunkenness and prolonged nocturnal sleep, though they did not have additional evidence of a clinical phase delay. A nonsignificant increase in the duration of melatonin secretion and decreased night-time concentrations of melatonin also were noted in the idiopathic hypersomnia subjects.

**Diagnosis**

Excessive daytime sleepiness is a common symptom, and diagnosis of idiopathic hypersomnia requires exclusion of other known causes of excessive daytime sleepiness. No unique “gold standard” test exists for this disorder. The history comprises a critical portion of the diagnosis. Patients with idiopathic hypersomnia often have severe excessive daytime sleepiness without clear cause for at least three months, prolonged episodes of night-time sleep, long unrefreshing naps, and sleep drunkenness. Idiopathic hypersomnia with long sleep time and idiopathic hypersomnia without long sleep time are differentiated primarily by whether the nocturnal sleep period is greater or less than 10 hours.

The physical examination of a patient with suspected idiopathic hypersomnia may help to exclude alternative reasons for excessive sleepiness. An elevated body mass index, increased neck circumference, or crowded oropharyngeal airway can suggest obstructive sleep apnea. An abnormal neurological exam may suggest a focal brain lesion as a cause of hypersomnia. Evaluation of mood may be helpful, as depression is among the most common causes of complaints of excessive sleepiness.

Laboratory studies are rarely useful in the assessment of excessive daytime sleepiness. Evaluation of blood counts and thyroid function occasionally identifies medical causes of fatigue. As noted above, HLA testing, CSF hypocretin, and other genetic studies may be of help in a diagnosis of idiopathic hypersomnia by helping
to exclude alternative causes of sleepiness, such as narcolepsy. Computed tomography (CT) or MRI should be considered if a central nervous system lesion is suspected.

Nocturnal polysomnography is essential for ruling out other causes of excessive sleepiness. A sleep study should be done when the patient has been free of sleepiness-influencing drugs for at least five drug half-lives and free from rebound effects that follow discontinuation of some agents. The sleep–wake schedule should be consistent for at least seven days. Polysomnographic monitoring may demonstrate prolonged sleep time, usually with normal percentages of NREM and REM sleep, though an increase in slow-wave sleep may be observed. Significant sleep-disordered breathing or periodic limb movements should be absent to make a conclusive diagnosis of idiopathic hypersomnia. In rare cases, long-term sleep monitoring (24–36 hours) can be considered to document excessive sleep time.

A MSLT should be performed on the day following the nocturnal polysomnogram. A meta-analysis has indicated that patients with idiopathic hypersomnia (both types) have a mean sleep latency of $6 \pm 3$ (s.d.) minutes. It should be noted, however, that a mean sleep latency of less than 8 minutes can be found in up to 30% of the general population, so clinical symptoms must be considered when integrating MSLT results into a determination of the most appropriate diagnosis. The patient should have less than two SOREM periods during the MSLT.

**Differential Diagnosis**

Narcolepsy, particularly in the absence of cataplexy, can resemble idiopathic hypersomnia and some believe that idiopathic hypersomnia forms part of the spectrum of narcolepsy. Although the distinction may be semantic, the diagnosis of narcolepsy requires cataplexy or two SOREM periods on an MSLT, whereas the diagnosis of idiopathic hypersomnia requires absence of two SOREM periods. Patients with narcolepsy may be less able to resist daytime sleepiness, though naps are generally shorter than in idiopathic hypersomnia. Sleep paralysis and hypnogogic hallucinations do not help to distinguish narcolepsy without cataplexy from idiopathic hypersomnia (19).

Frank obstructive sleep apnea can cause severe excessive daytime sleepiness and is usually readily evident on a polysomnogram. However, another cause can be more subtle sleep-disordered breathing associated with increased respiratory effort and arousals but few easily observed apneas or hypopneas. Esophageal-pressure monitoring or nasal-pressure monitoring may assist in identification of respiratory event-related arousals that can be a treatable cause of hypersomnolence. When the patient’s history suggests sleep-disordered breathing but the initial polysomnogram is negative, a repeat study with esophageal or nasal pressure monitoring may allow a patient otherwise destined to carry a diagnosis of idiopathic hypersomnia to be classified and treated more appropriately for sleep-disordered breathing (20).

In clinical practice, a common situation in which excessive daytime sleepiness remains unexplained arises when a patient is optimally treated for obstructive sleep apnea, but the sleepiness persists (21). Although still “idiopathic,” this condition is not clearly classified by the ICSD as persistent obstructive sleep apnea, idiopathic hypersomnia, or physiological (organic) hypersomnia, unspecified.

Psychiatric conditions can lead to a complaint of excessive sleepiness, often in association with poor night-time sleep and sometimes without abnormal MSLT
findings. Use of medications, withdrawal from them, illegal substances, or alcohol may cause daytime sleepiness. Behaviorally induced insufficient sleep syndrome may easily be mistaken for idiopathic hypersomnia due to the daytime hypersomnia. However, a careful history and a sleep diary will often lead to the correct diagnosis. In some cases, it may be difficult to distinguish between idiopathic hypersomnia and long sleep syndrome, in which the patient needs more sleep than most persons but does not manage to get enough hours in bed. Patients with chronic fatigue syndrome may complain of persistent fatigue or low energy, but are not necessarily sleepy, and this symptom will usually not resolve with sleep.

Medical conditions may lead to excessive daytime sleepiness, particularly when they involve the central nervous system. Trauma, viral infections, strokes, brain tumors, and neuro-genetic syndromes can cause daytime sleepiness. Encephalopathies, endocrinopathies, and pain may also disrupt sleep and cause daytime sleepiness. Physical examination, laboratory studies, and brain imaging may help to identify such patients.

Treatment

Though Roth generally considered idiopathic hypersomnia to be poorly responsive to treatment, and our incomplete understanding of the pathophysiology of this disorder has not led to specific therapeutic approaches, patients with idiopathic hypersomnia now have several options for symptomatic relief. Roth suggested treatment by increasing the amount of sleep for patients with idiopathic hypersomnia for several consecutive days, but this method was unsuccessful when attempted by Bassetti and Aldrich (7). Pharmacological approaches have resembled those used for narcolepsy, but have been somewhat less successful, particularly in reduction of sleep drunkenness. Many medications have been prescribed, including tricyclic antidepressants, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, clonidine, levodopa, bromocriptine, selegiline, and amantadine (22). Bassetti and Aldrich found that 75% of their patients benefited from stimulant medications, most commonly methylphenidate and dextroamphetamine. Some patients also benefited from antidepressant medications. Subjective improvements in sleepiness were not always reflected by prolongation of the mean sleep latency on the MSLT (7).

Modafinil, a wake-promoting agent that may have fewer adverse effects than stimulants, also appears to improve sleepiness in idiopathic hypersomnia (IH) (23). In one study, 18 patients noted a decrease in drowsiness episodes and sleep episodes per day, with maximal improvement at two months. Several subjects who discontinued treatment after 6 to 12 months continued to have symptomatic improvement for at least one year.

After research suggested that idiopathic hypersomnia patients may have a circadian phase delay (18), 10 patients with “polysymptomatic” idiopathic hypersomnia were treated with 2 mg of slow release melatonin at bedtime. Half of these subjects had an improvement in symptoms, including shorter nocturnal sleep, improved daytime sleepiness, and decreased sleep drunkenness (24).

RECURRENT HYPERSOMNIA: KLEINE–LEVIN SYNDROME
AND MENSTRUAL-RELATED HYPERSOMNIA

Historical Introduction

Kleine–Levin syndrome is often considered the prototype among several different variants of recurrent or periodic hypersomnia. Initially described by Kleine in 1925
and by Levin in 1929 (25,26), the symptoms include episodes of extensive sleep, for
days to weeks, associated with hyperphagia. Kaplinsky and Schulmann (27) wrote
in 1935 of a similar type of hypersomnia, but this disorder was associated with men-
stration. The eponym Kleine–Levin syndrome was put forth by McDonald Critch-
ley in 1942. Diagnostic criteria for this disorder, published in 1962 based on 26
patients, included male gender, adolescent onset, periodic hypersomnia, megapha-
gia, and spontaneous remission (28). Current diagnostic criteria do not use gender
as a discriminating factor (10).

**Epidemiology**

The epidemiology of this rare condition is not well known. More than 200 cases
of recurrent hypersomnia have been reported in the literature. Table 2 lists a
sample of studies that have included multiple Kleine–Levin patients. In Roth’s
series of 642 patients with hypersomnia, only two subjects were considered to
have “typical” Kleine–Levin syndrome, though another five were thought to
have a related disorder with long periods between episodes of hypersomnia (2).
Based on available case series and reports, the ratio of males to females with
Kleine–Levin is approximately 4:1, though the gender ratio is likely 1:1 when recur-
rent hypersomnia is the sole symptom (10,29). Many of the reported cases have
been of Israeli patients; it is not clear whether this is a publication bias or a
genetic vulnerability in people with Jewish heritage(30).

**Clinical Features**

Episodes of hypersomnia are generally separated by weeks or months of normal
sleep. Each episode can last a few days to several weeks (though more typically
three to four days) and can occur as frequently as ten times per year. Although
the recurrent hypersomnia is usually the defining feature, other symptoms often
occur. Table 3 demonstrates the reported frequency of symptoms in Kleine–Levin
syndrome based on a review of 186 case reports. Prodromal symptoms before an
episode can include fatigue, depression, or headache. Triggers for an episode
may include viral infections, menstruation, pregnancy, head trauma, and physical
or emotional stress. During a period of hypersomnia, patients may sleep 16 hours
per day, arising only for eating and elimination. There is no urinary incontinence.
If aroused by strong stimuli during an episode, the patient may respond verbally,
though may be unclear or aggressive. The end of an episode may be associated
with amnesia, transient dysphoria, or elation with insomnia. Between episodes,
sleep and general behavior tend to be normal (10). Polydipsia and water retention
have been seen in some patients with recurrent hypersomnias (2).

<table>
<thead>
<tr>
<th>Table 2 Large Case Studies of Kleine–Levin Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Authors</td>
</tr>
<tr>
<td>Roth and Nevsimalova</td>
</tr>
<tr>
<td>Smolik and Roth</td>
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<tr>
<td>Mayer et al.</td>
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<td>Rosenow et al.</td>
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<td>Gadoth et al.</td>
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<tr>
<td>Dauvilliers et al.</td>
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<tr>
<td>Poppe et al.</td>
</tr>
</tbody>
</table>

*Abbreviations: KLS, Kleine–Levin syndrome; PSG, polysomnography; MSLT, multiple sleep latency test.*
Symptoms of Kleine–Levin syndrome can include hyperphagia and changes in mental status during the periods of hypersomnia. Hallucinations, feelings of unreality, and confusion may occur when awake. Hypersexuality and binge eating have been associated with this disorder, and the patient may gain significant weight in a short period. Generally Kleine–Levin syndrome, particularly when associated with ancillary symptoms, occurs in male adolescents (2nd decade) though childhood and adulthood onsets have been observed (31). Female patients may (10) or may not (32) have a slightly later age of onset. Recurrent events tend to occur every few months for up to 20 years, though in most cases the frequency and severity of the periods of hypersomnia diminish with time (28). Long-lasting short-term memory loss has been observed on neuropsychological testing in some subjects (33). In a few cases, general cognitive decline over the course of the syndrome was also observed (34,35).

Menstrual-related periodic hypersomnia, another subtype of recurrent hypersomnia, has been less commonly reported in the literature. The hypersomnia begins to occur within a few years after menarche, can last one to two weeks per episode, and generally resolves after menses. Measured hormone levels have been normal, including follicle-stimulating hormone, lutenizing hormone, estrodiol, and progesterone (36,37). Too few cases have been reported to understand the long-term prognosis of this disorder. Oral contraceptive treatments have been effective.

Pathophysiology
The pathophysiological mechanism for recurrent hypersomnia is not known. Hypothalamic dysfunction has been postulated, based on clinical features and endocrinological findings. One report followed hormone levels every 20 minutes for 24 hours in the same patient during an asymptomatic and a symptomatic phase that, when compared, demonstrated a significantly lower growth hormone (GH) and higher thyroid-stimulating hormone during symptomatic periods. These findings were interpreted to support an abnormal dopaminergic tone during symptomatic periods (38). Another single case report demonstrated borderline high basal prolactin and a paradoxical increase of GH in response to thyrotropin-releasing hormone stimulation testing (39). A study evaluated five patients, finding that only two had decreased mean 24-hour and nocturnal sleep time growth hormone levels during symptomatic periods. Three subjects had lost the normal tendency to secrete GH during slow-wave sleep. Melatonin levels

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Affected/total</th>
<th>Percent</th>
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</thead>
<tbody>
<tr>
<td>Hypersomnia</td>
<td>168/168</td>
<td>100</td>
</tr>
<tr>
<td>Cognitive disorders</td>
<td>98/102</td>
<td>96</td>
</tr>
<tr>
<td>Confusion</td>
<td>24/47</td>
<td>51</td>
</tr>
<tr>
<td>Amnesia</td>
<td>24/50</td>
<td>48</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>13/93</td>
<td>14</td>
</tr>
<tr>
<td>Eating behavior disorder</td>
<td>125/157</td>
<td>80</td>
</tr>
<tr>
<td>Megaphagia</td>
<td>97/125</td>
<td>78</td>
</tr>
<tr>
<td>Depression</td>
<td>41/86</td>
<td>48</td>
</tr>
<tr>
<td>Hypersexuality</td>
<td>67/155</td>
<td>43</td>
</tr>
</tbody>
</table>

Note: No neurological symptoms present prior to onset.
Source: From Ref. 30.
were increased during periods of hypersomnia, but were still within the normal range (40). Overall, the data demonstrate some endocrinological changes but do not clearly confirm hypothalamic-pituitary dysfunction.

The wakefulness-promoting neurotransmitter hypocretin-1 is absent or severely reduced in narcolepsy with cataplexy, but this observation has not been replicated in the Kleine–Levin syndrome. The mean hypocretin-1 level of four Kleine–Levin syndrome patients studied during asymptomatic periods was within the normal level, though one of the four subjects had a higher than normal hypocretin-1 level. One subject, who also had a Praeder–Willi syndrome, was studied when symptomatic and had a level of hypocretin-1 that was half as high as it was during his asymptomatic period (41). Similarly, in another study, among three patients with recurrent hypersomnia, two had normal hypocretin-1 levels during asymptomatic periods, and one patient tested during a symptomatic period had an intermediate level (42). One set of siblings with Kleine–Levin syndrome was reported; CSF hypocretin measured in one sibling during an episode of hypersomnia was in the normal range (43).

Imaging studies also have not demonstrated consistent findings in these patients. Two patients demonstrated abnormalities in the region of the suprasellar cistern on CT scans (44). Other studies used single photon emission computed tomography (SPECT) imaging to demonstrate hypoperfusion in the right frontal lobe (45), left frontal lobe, temporal lobes, right parietal lobe (46), and left mesiotemporal structures (47). A total of seven patients with the Kleine–Levin syndrome and normal CT and MRI findings were studied with SPECT. Five patients were evaluated during symptomatic periods; all demonstrated hypoperfusion bilaterally in the thalami. Structures less consistently affected included the basal ganglia (4/5 cases) and cortex (3/5). Complete resolution of all thalamic findings occurred when the patients were asymptomatic, though some hypoperfusion remained in cortical structures and in basal ganglia in two of the seven patients studied while asymptomatic (48).

Among 11 patients in three studies of patients with the Kleine–Levin syndrome, only one tested positive for HLA-DR2, a human leukocyte antigen commonly found in narcolepsy. However, one study found three subjects with HLA-DQw2 (corresponding to the DQB1*0201 allele) and the other two studies found two patients with the HLA-DR3 allele, which generally is associated with the DQB1*0201 allele (49–51). This finding is of interest, because the HLA DQB1*0201 allele may be associated with autoimmune disorders (52).

More recently, among 30 patients with Kleine–Levin, CSF cytology and protein were normal in 11 patients studied while symptomatic, as were head CT scans in 8 patients and head MRI in 21. Fourteen of the thirty patients had HLA-DQB1*0201, and the one familial case was found to be homozygous for the allele. Testing for tryptophan hydroxylase and catechol-O-methyltransferase (COMT) gene polymorphisms showed only a tendency for low-activity COMT alleles in Kleine–Levin subjects (52).

Postmortem pathological study of a patient who died during a symptomatic period of Kleine–Levin syndrome showed abundant thalamic infiltrates of inflammatory cells classified as microglia (53). Inflammatory infiltrates in the diencephalon and midbrain also were reported (54), as was a small locus ceruleus with decreased pigmentation in the substantia nigra (55). Another patient had abnormalities in the hypothalamus, amygdala, and temporal gray matter, possibly because of mild, localized encephalitis (56).
Diagnosis
Diagnosis of recurrent hypersomnia is based on clinical symptoms. The ICSD-2 (2005) has delineated new criteria for recurrent hypersomnias. These criteria include recurrent episodes of excessive sleepiness lasting two days to four weeks, at least yearly recurrence of episodes, normal cognition and behavior between attacks, and that no other explanation for the attacks exist. The Kleine–Levin syndrome is one type of recurrent hypersomnia, which includes behavioral abnormalities (binge eating, hypersexuality, odd or abnormal behavior, or cognitive disturbance) during the periodic symptomatic episodes. Menstrual-related hypersomnia is another subtype, which comprises symptomatic periods that correspond to menses, generally beginning within the first few months after menarche (10).

Polysomnograms do not tend to aid in the diagnosis of recurrent hypersomnias. Sleep studies performed on 18 patients during a symptomatic episode demonstrated a mean total sleep time of 11+ hours with a low sleep efficiency (80 ± 12%), mildly decreased slow wave and REM sleep percentages, and significantly increased stage-1 sleep percentage (52). Ten of these patients studied during their asymptomatic periods had a more normal sleep time, but continued to show decreased sleep efficiency and REM sleep amounts. Among another 25 patients with Kleine–Levin syndrome, who underwent sleep studies (18 studies performed during a symptomatic period, 17 during asymptomatic times), sleep structure was normal except for mildly-decreased REM sleep latency, increased total sleep time, and frequent awakenings from stage 2 sleep (29). MSLT during symptomatic phases have demonstrated short sleep latencies (usually less than five minutes) and SOREM periods (57). Routine electroencephalography (EEG) during symptomatic periods may show combinations of background slowing and intermittent generalized slowing in the theta range, and less commonly in the delta range. During asymptomatic periods, the EEG and MSLT are generally normal (57).

Differential Diagnosis
Though recurrent episodes of hypersomnia are not common and therefore are suggestive of the diagnosis, other causes of excessive daytime sleepiness often must be excluded. Disorders such as narcolepsy, idiopathic hypersomnia, obstructive sleep apnea, or insufficient sleep syndrome may cause daily hypersomnia, but not in a periodic manner. Central nervous system injury due to tumors, encephalitis, head injury, or strokes may cause excessive somnolence or decreased levels of consciousness. Third ventricle tumors, which may intermittently obstruct the flow of CSF (such as colloid cysts), can cause recurrent neurological symptoms, such as headaches and impaired consciousness. Prolonged seizures or postictal states can increase sleepiness, but less commonly in a defined periodic manner. Patients with psychiatric disorders have been reported to have periodic episodes of sleepiness; possible diagnoses include bipolar disorder, seasonal affective disorder, or somatoform disorders.

Treatment
No controlled studies have been performed for treatment of recurrent hypersomnia, perhaps in part because of its rarity and variety. Treatments of all types have generally been disappointing in relieving all of the Kleine–Levin symptoms. Stimulants may be helpful in reducing sleepiness, and modafinil has been used during symptomatic periods with limited success. However, stimulants do not
generally help with associated behavioral and cognitive changes (52). Lithium may decrease the number of episodes and some of the behavioral abnormalities (58,59). Use of valproic acid, carbamazepine, moclobemide, and light therapy has been described (60–63). Psychotherapeutic modalities and reassurance of the patient and family may be helpful in nonpharmacological approaches (64). Electroconvulsive therapy has been attempted in multiple cases; it was generally unsuccessful at relieving symptoms and appeared to increase confusion (30). Oral contraceptive therapy has been effective in the few reported cases of menstrual-related hypersomnia (37).

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INTRODUCTION

The motor disorders of sleep represent a frequent challenge in the practice of sleep medicine. They are not, however, a uniform nosological category, as exemplified by the new current International Classification of Sleep Disorders (ICSD-2) in which the “Sleep Related Movement Disorders” section includes the following:

1. Restless legs syndrome (RLS)
2. Periodic limb movement disorder
3. Sleep-related leg cramps
4. Sleep-related bruxism
5. Sleep-related rhythmic movement disorder
6. Sleep-related movement disorders unspecified
7. Sleep-related movement disorders due to drug or substance
8. Sleep-related movement disorder due to medical condition (1)

Moreover, motor behavior is often a predominant feature of other categories of sleep disorders, such as the parasomnias.

This chapter gives an overview of the principal motor disorders of sleep, in which abnormal motor patterns represent the prominent sign. The ICSD-2 is followed here as far as possible.

PHYSIOLOGY OF MOTOR CONTROL DURING SLEEP

Progressive loss of muscle tone develops at the transition from wakefulness to light sleep, reaching full atonia during rapid eye movement (REM) sleep. Especially observed in the antigravity muscles, such as the mental and nuchal muscles routinely monitored during polysomnography, muscle atonia is attended by reduced motor unit firing because of postsynaptic inhibition and dysfacilitation of the spinal and brain stem alpha motoneurons. In the cat, the neuronal membrane hyperpolarizes only slightly during quiet nonREM (NREM) sleep, but to a much greater degree, 2 to 10 mV, during active REM sleep (2), making the motoneuron less excitable. Spontaneous motoneuron activity ceases, recurrent motoneuron discharges are inhibited, and excitatory postsynaptic potentials (EPSPs) induced by Ia fiber stimulation are all reduced during REM sleep, further so during the bursts of REMs, by a mechanism of postsynaptic inhibition. Spontaneous inhibitory postsynaptic potentials (IPSPs) also increase in number during REM sleep, and large-amplitude IPSPs appear during this sleep stage (2). While the neurotransmitter(s) implicated in the origin of the sleep-related inhibition of the EPSPs is still unknown, glycine appears to mediate the IPSPs that develop during sleep.
Atonia is, however, not complete during REM sleep: on the background of a potent inhibition, motoneuron spike potentials, isolated or in short bursts, can still be recorded, usually accompanied by brief motor activity in the shape of myoclonic twitches and jerky movements, especially of the facial or distal limb muscles. These sudden excitatory drives characterize the so-called phasic REM sleep stage, as opposed to the tonic REM sleep from which it arises. The concomitant depolarization of the motoneuron membrane during such volleys is thus due not to relenting inhibition, but to strong excitatory activity descending from supraspinal centers.

The inhibitory influences impinging upon the alpha motoneurons during sleep can instead be reproduced in the experimental animal by electric stimulation of the inhibitory reticular formation. Motor inhibition can be obtained, in particular by activation of the gigantocellularis reticular nucleus, and it is thought that this nucleus is in turn activated, during REM sleep, by neurons of the nucleus pontis oralis (3). Lesions of the latter, in fact, cause a loss of the physiological muscle atonia, typical of REM sleep (4), and provoke peculiar behavior abnormalities whereupon animals display complex motor activities, such as fighting, searching for food, and ambulatory patterns, in the absence of any contact with the environment. The complex neurophysiological mechanisms underlying this so-called “REM sleep without atonia” have been further described by Morrison and coworkers (5) and need not be detailed here. Suffice to say that sleep-related motor inhibition is equally seen in man, associated with loss of tendon jerks and inhibition of the electrically evoked monosynaptic H-reflex of the soleus muscle (6). The H reflex, which is an indirect measure of the excitability of the motoneuronal pool, is progressively lost, in association with muscle tone, beginning from the 10 minutes of NREM sleep preceding the REM sleep stage until it totally disappears during REM sleep. Thus, muscle atonia during NREM sleep in humans seems to parallel the findings in the experimental animal. Likewise, atonia during REM sleep and REM sleep without atonia have been recognized in man following their description in the cat.

PHYSIOLOGICAL MOTOR ACTIVITY DURING SLEEP

In normal humans sleep is not a period of absolute motor quiescence, and some degree of motor activity must be considered as part of normal sleep physiology. Its most elementary form is represented by the so-called physiologic fragmentary hypnic myoclonus (PFHM) described as “partial hypnic myoclonias” for the first time by De Lisi (7) in 1932 in man and animals. PFHM are short jerky contractions of parts of, or of an entire small muscle, resembling fasciculations and occurring mostly in the distal muscles of the hands and the face. They may or may not cause small displacements of the fingers, lips, or eyelids and occur isolated or in short bursts. PFHM usually last less than one second are especially frequent during NREM sleep stage 1 and REM sleep, when they reach a peak, and tend to decrease during deep sleep (8). They closely resemble the brief jerky motor activity observed in the cat during the phasic REM sleep periods and are thought, therefore, to derive from strong excitatory volleys descending from the reticular formation, except that they are not associated to REMs. PFHMs could otherwise be relayed through the cortico-spinal tracts, since they disappear in muscles that are completely paralyzed because of peripheral nerve, spinal, or pyramidal lesion, increase in extrapyramidal diseases and persist unchanged by changes in muscle spindle afferents (9).
“Sleep starts” (otherwise known as “hypnic jerks”) represent another normal accompaniment of sleep. They are actually classified within the section VII of the ICSD-2 (1) that includes “isolated symptoms, apparently normal variants, and unresolved issues,” frequently occurring in normal people and at any age. In some cases, they are a cause for concern and occasionally enter the differential diagnosis of epileptic myoclonic seizures. When particularly frequent and severe, they have been, however, reported as a cause for sleep-onset insomnia (see section “Excessive Sleep Starts”). Oswald (10) described them as sudden contractions of one or more limbs or the entire body, but especially involving the axial muscles, lasting up to one second and especially evident when falling asleep and during light sleep. They are associated with electroencephalogram (EEG) signs of arousal, such as the K-complexes, autonomic activation (tachycardia, tachypnea, and sudomotor activity), and a peculiar sensory feeling of “shock” or “falling into the void.” Though their origin is still unknown, sleep starts are hypothetically due to descending volleys within the pyramidal tracts at the transition from wakefulness to sleep (11).

“Benign neonatal sleep myoclonus” (BNSM), also included in the section VII of the ICSD-2 (1), is another condition in which physiological myoclonic activity during sleep may mimic an epileptic seizure. Described by Coulter and Allen (12), BNSM presents in the first weeks or months of life with repetitive myoclonic jerks, involving one part, one or more limbs or the whole body or migrating between muscle groups, often repeated in clusters and recurring for several minutes. BNSM is especially evident during NREM and least during REM sleep, disappears during wakefulness and remains unassociated with any other neurological or developmental abnormality. EEG is normal. BNSM may rarely persist into childhood, and its mechanisms, whether due to a transient immaturity of the serotonergic system or to changes in activity of the reticular centers at the transition to or during sleep as hypothesized, remain unknown. The condition is self-limited and requires no treatment. Unfortunately, the fact that BNSM is an innocuous and nonepileptic phenomenon is not well recognized and, not uncommonly, it is confused with neonatal seizure disorder, resulting in unnecessary investigations, treatment, and parental anxiety.

Finally, the so-called “gross body movements” represent another normal motor activity of sleep and indicate those global movements and shifts that modify the body position. They occur at least three or four times an hour, in particular during the second part of the night, prior to awakening. They are more frequent at the beginning and at the end of REM episodes, but may also be seen during light and REM sleep, preceded by EEG signs of arousal. Particularly evident during infancy, their decrease with adulthood has been taken to reflect maturational events of the brain and of the sleep-wake cycle.

Mimic acts and gestures, such as smiling, sighing, scratching, or grinding the teeth are also commonly seen during every sleep stage, but especially during light sleep.

SLEEP-RELATED MOVEMENT DISORDERS
Nocturnal Leg Cramps
Nocturnal leg cramps consist of painful involuntary contractions of the leg, especially the triceps surae, or foot muscles, which arise suddenly during sleep or in the transition from wakefulness to sleep. Lasting some seconds, they are
associated with palpable contraction of the muscles involved and subside either spontaneously or after lengthening of the contracting muscles. They may cause insomnia. Nocturnal muscle cramps are especially frequent during NREM sleep and may recur aperiodically for long stretches of time. In some patients, cramps may be present also during wakefulness.

Whereas, the usual cramping conditions during the daytime are often related to electrolyte disturbances or to muscle and endocrine disorders, such as myotonic syndromes, muscle glycogenosis, or hypothyroidism, the exact mechanism underlying the nocturnal leg cramps is still unclear. Pregnancy, Parkinson’s disease, and diabetes mellitus are known factors associated with them. Jacobsen et al. (13) recently described a familiar condition of nocturnal leg cramps, associated with myoclonic jerks and involving also trunk, limb, and face muscles, transmitted as an autosomal dominant trait.

Nocturnal leg cramps should not be confused with the RLS. Although uncomfortable, RLS usually does not involve cramping. Conditions that mimic cramps include simple muscle strain, dystonias, ischemic or neuropathic claudication, nerve root disease, and periodic limb movements of sleep (PLMS). Muscle cramps are a feature of many myopathic and neuropathic conditions in which they are not usually restricted to the night-time or necessarily to the legs.

Pathogenesis of nocturnal leg cramps remained unclear, but in some cases the cramps respond favorably to clonazepam. Carbamazepine, quinine, vitamin E, and local application of botulinum toxin are other medications described as useful in anecdotal reports.

Sleep Bruxism

Sleep bruxism defines pathologic forcible grinding or clenching of the teeth during sleep. Occurring especially during stage 2 of NREM sleep, sleep bruxism is polysomnographically characterized by forceful short (approximately 250 milliseconds) rhythmic or prolonged tonic contractions of the masticatory muscles (14). However, the clinical and polygraphic features of sleep bruxism are not completely clear. Few detailed studies of the motor pattern of sleep bruxism exist; in particular, brief repetitive masticatory muscle electromyographic (EMG) activity, in the form of masticatory or oromandibular myoclonus, has been reported as an isolated finding (15) or associated with sleep bruxism (16).

Grinding and clenching movements of the jaws during sleep bruxism produce a loud annoying noise and, when long-lasting, are a remarkable cause of tooth wear. Sleep bruxism should be differentiated from bruxism during wakefulness, which is silent and moreover characterized by clenching only, and not grinding movements.

Sleep bruxism occurs especially in children aged 3 to 12 years, but also in adults, without any sex prevalence (17). Patients are unaware of the jaw movements and may come to medical observation only because of unexplained dental problems. Polysomnographic recordings demonstrate that bruxism occurs during NREM, especially stage 2 sleep, in particular during arousals and is due to forceful short rhythmic or prolonged tonic contractions of the masticatory muscles (17).

Nocturnal tongue biting and bleeding due to repetitive myoclonic activity of masseter and orbicularis oris and oculi muscles present only during sleep may mimics sleep bruxism and may be familial (18).

Sleep bruxism has been variously ascribed to craniomandibular, such as malocclusion disorders, hyperthyroidism, psychological factors, or even
encephalopathies with basal ganglia disorders or cerebral palsy. It may be favored by drugs, such as levodopa, alcohol, amphetamines, and serotonin reuptake inhibitors. In most cases, however, sleep bruxism remains an isolated condition. Treatment is warranted in those patients in whom bruxism causes severe dental and even mouth and tongue damage. Bite splints, benzodiazepines, and biofeedback therapy may be of help.

SLEEP-RELATED RHYTHMIC MOVEMENT DISORDER

Sleep-related rhythmic movement disorder (SRMD) consists of repetitive and stereotyped movements of the head, neck, and trunk, and sometimes also the legs which occur at sleep onset, during short arousals in light sleep or sustained into light sleep. Also known as jactatio capitis nocturna or “headbanging” or “head-rolling,” the term RMD is preferred as different body areas may be involved in the movement activity. Rhythmic body movements may occur in any stage of sleep, including REM sleep, but most often during drowsiness persisting into light sleep. The head is typically rolled side to side, or may be forcibly banged into the pillow and mattress. The whole body or parts of it, such as hands, arms, or legs, may also be rolled and rocked repetitively (“bodyrocking”). These stereotypic movements may last a few or several minutes, repeated at a frequency of 0.5 to 2 per second. SRMD is seen in otherwise normal children, but it has been reported also in mentally retarded and autistic patients. It usually disappears after the age of three to four years and does not require any medication, though benzodiazepines may be useful in selected severe cases.

The association of SRMD with long-lasting RLS is well known (19,20), and SRMD may also occur in RLS of recent onset (21).

Rhythmic feet movement, formerly hypnagogic foot tremor (0.5–3 Hz), occurring during presleep wakefulness and light sleep may be considered a new kind of SRMD arising in adults, in some cases associated with insomnia (22), sleep apnea, PLMS, and RLS (23).

Brief activations of the tibialis anterior in one leg alternating with similar activation in the other leg, so called alternating leg muscle activation (ALMA), have been described. Such activations, similar to rhythmic feet movements while falling asleep, occur at a frequency of 1 to 1.5 Hz, each lasting up to 0.5 seconds, with sequences of several to 20 seconds and recurring in all sleep stages but particularly during arousals. ALMA has been described in patients with sleep apnoea, PLMS, taking antidepressant medication (24), and with RLS (25).

PARASOMNIAS

According to the American Sleep Disorders Association (ASDA) definition (1), parasomnias are “clinical disorders with undesirable physical phenomena that occur predominantly during sleep.” Parasomnias comprise several subheadings: disorders of arousal (from NREM sleep), parasomnias usually associated with REM sleep, and other parasomnias. Motor features, such as to constitute a true motor disorder during sleep are prominent only in some parasomnias, especially the arousal disorders, parasomnias usually associated with REM sleep, and some other parasomnias. Nightmares, a parasomnia occurring during REM sleep, are not associated to relevant motor phenomenon.
Disorders of Arousal (from Nonrapid Eye Movement Sleep)
Disorders of arousal are attributed to disordered arousal mechanisms and occur typically during NREM sleep. Foremost among them are the so-called “sleep terrors” (pavor nocturnus) and “sleepwalking” (somnambulism), while the “confusional arousals,” in which automatic behaviors associated to mental confusion, impaired contact with the environment and amnesia occur after awakening, by definition have no prominent motor features, in particular no motor agitation or ambulation.

NOCTURNAL FRONTAL LOBE EPILEPSY: PAROXYSMAL AROUSAL, NOCTURNAL PAROXYSMAL DYSTONIA, AND EPILEPTIC NOCTURNAL WANDERING (SEE ALSO CHAPTER 14)
Nocturnal paroxysmal dystonia (NPD) was reported for the first time by Lugaresi and Cirignotta in 1981 (26) under the term hypnogenic paroxysmal dystonia. They described cases of recurrent attacks during NREM sleep characterized by sudden arousal, motor agitation associated with extrapyramidal features, such as tremor, chorea, and dystonic posturing, and ballism of the limbs, in the absence of clear-cut epileptic waveforms on the ictal EEG. Their patients responded to antiepileptic medications such as carbamazepine, but the normal EEG precluded their being considered definite cases of epilepsy arising during sleep (morpheic epilepsy) or rather instances of sleep-related motor disorders. Since patients with NPD often complain of disturbed sleep, NPD has been included within the Appendix A of the ICSD-2, which includes “sleep disorders associated with conditions classifiable elsewhere” (1). NPD attacks of different duration were reported, and short-lasting and long-lasting ones (>2–3 minutes) were later recognized as having different features.

Later studies documented that some patients with short-lasting NPD had epileptic EEG activity detected over the frontal regions by means of sphenoidal electrodes (27), and NPD was recognized as a manifestation of nocturnal frontal lobe epilepsy (NFLE). Meierkord et al. (28) demonstrated that NPD attacks with and without ictal epileptic discharges were indistinguishable, and concomitant studies of frontal lobe epileptic seizures showed that, when arising from the mesial and orbital frontal regions, epileptic seizures are characterized by complex and bizarre motor patterns involving axial muscles and bipedal or bimanual activity with rocking movements and sometimes ambulation, very similar to those observed during short-lasting NPD attacks. The origin of the discharges from deep-seated foci explains why EEG often remains normal even during the attacks.

NPD attacks have been further characterized according to their duration and the motor patterns observed during the videopolysomnographic recordings. Thus, paroxysmal arousals (PA) represent attacks, often recurring several, up to 20 times, during the night, several nights in a row, of stereotypic motor activity, such as abruptly raising the head from the pillow, staring, moving the arms in a dystonic posture, and crying aloud as if in distress, lasting about or less than 20 seconds and associated with autonomic activation (Fig. 1) (29). PA sometimes are accompanied by frank epileptic activity and respond to carbamazepine, sometimes at very low dosages. PA may recur quasi-periodically during NREM, especially light sleep stages, showing a periodicity (every 20–40 seconds) reminiscent of that found in the PLMS (30). That PA and NPD belong to the same spectrum of sleep-related frontal lobe seizures is shown by the fact that in many patients they
recur during the same night, and that PA can be seen on videorecordings to initiate a typical NPD attack. Still, more elaborate and complex motor patterns may be seen in the so-called episodic nocturnal wanderings (ENW) first described by Pedley and Guilleminault (31). Patients with ENW display peculiar attacks of violent motor activity, with screaming, yelling, flailing of limbs, associated with frantic ambulation, such as running about, jumping, and kicking. They may injure themselves or their bed partner, especially when restrained, but they are not in full contact with the environment. The attacks, always arising from NREM sleep, sometimes respond to antiepileptic medications, and this led Pedley and Guilleminault

FIGURE 1  An attack of paroxysmal arousal in a 19-year-old male. The attack starts with sudden flexion of the right arm and leg; the left limbs are later stiffened and the right leg kicked about. The lower panels show excerpts from the polygraphic recordings of the same episode. The electromyographic movement artefacts are preceded by electroencephalogram signs of arousal from stage 2 sleep with tachycardia. (thoracic respiration, left-right deltoid). *Abbreviations:* R.T., thoracic respiration; L-R D, left-right deltoid.
to suppose their epileptic nature. This view was confirmed in three cases in which epileptic activity over the frontal regions was recorded during the ambulatory episode (32). Therefore, ENWs are thought to represent another example of sleep-related seizures, encompassed within the spectrum of NFLE.

The frontal origin of these “nocturnal hypermotor seizures” is also indicated by intracerebral EEG recording (30,34), ictal single photon emission computed tomography (35–37) and interictal fluorodeoxyglucose-positron emission tomography (FDG-PET) imaging (38). However, recent observations highlight how complex anatomic and functional networks participate in the genesis of seizures with predominantly frontal lobe-behaviors (33), including the temporal lobe (39,40) and the insula (41). Therefore, while the typical “hypermotor” nocturnal behavior corresponds to involvement of frontal regions by the epileptic discharges, the latter may actually originate outside of the frontal lobe.

PA, NPD, and ENW pose particular problems in their differential diagnosis, as they may be easily mistaken for NREM parasomnias, such as sleep terrors or somnambulism. The diagnostic problem is worsened by the fact that even ictal EEGs are often unrevealing and by the presence of a familial predisposition for both parasomnias and NFLE. The latter may in fact be inherited in an autosomal dominant fashion (42). An autosomal dominant inheritance is found in 8% to 43% of NFLE patients (43–45) and two genes coding for the α4 and β2 subunits of the nicotinic acetylcholine receptor (nAChR) are responsible for autosomal dominant NFLE (46–48). Useful diagnostic markers for NFLE are, however, the lifetime persistence of the attacks, usually well into adulthood, while parasomnias disappear after adolescence, the high rate, from 20 to 30, of same-night repetition of the episodes, clearly unusual for a parasomnia, and their stereotypical features, that is their recurrence with the same motor pattern over several nights. Moreover, parasomnias do not display dystonic or choreic motor patterns and do not respond consistently to antiepileptic drugs. A high degree of suspicion, repeated polysomnographies, and the use of tentative trials with antiepileptic medications are warranted in those cases that cannot be easily classified. Even after thorough neurophysiological studies, in fact, there remain cases with motor agitation during NREM sleep that cannot in any way be ascribed to epileptic discharges. Patients with NPD of long duration, with episodes that last up to half an hour or more, and children showing puppet-like dystonic-dyskinetic attacks of long duration during both NREM sleep and after prolonged exercise in wakefulness may represent true movement disorders occurring during sleep (49) and should be differentiated from the more common short-lasting NPD epileptic attacks.

ISOLATED SYMPTOMS, APPARENTLY NORMAL VARIANTS, AND UNRESOLVED ISSUES

Excessive Sleep Starts

“Sleep starts” or “hypnic jerks,” listed in the section VII of the ICSD2 (isolated symptoms, apparently normal variants, and unresolved issues) (1), represent a physiological and universal accompaniment of sleep, especially light sleep (see earlier). In some patients, however, they may be so severe and frequent as to represent a cause of sleep-onset insomnia. This condition has been termed “excessive sleep starts” by Broughton et al. (11) and may respond to clonazepam. Its relationship to hyperekplexia and to the propriospinal myoclonus (PSM) observed at the transition from wakefulness to sleep (see later) needs clarification.
Propriospinal Myoclonus at the Transition from Wakefulness to Sleep

PSM was characterized by Brown and coworkers (50) as a form of myoclonus arising within the spinal cord (spinal myoclonus), usually in axial thoracolumbar segments and then propagated at low speed to other spinally innervated muscles presumably along propriospinal multisynaptic pathways intrinsic to the cord. Therefore, PSM, in contrast to the spinal myoclonus, which persists in the same segmentally innervated muscles, is a multisegmental propagated phenomenon, in which the myoclonic jerks travel in a progressive manner to more rostral and caudal segments in a descending and ascending pattern. The myoclonic jerks are usually irregular, last from 150 to 300 milliseconds and only in occasional patients may be evoked by external stimuli. Their propagation velocity along the spinal cord is low, calculated to around 3 to 11 m/sec. PSM must surely originate in subcortical areas, as shown by the fact that the jerks lack any cortical premovement potential (bereitschaftspotential) upon back-averaging studies, and probably in the spinal cord as indicated by the few patients in whom a spinal lesion is found. It shows an effect of posture, being sometimes worsened by sitting or lying down.

Some cases of otherwise typical PSM, however, show a striking relationship of the myoclonic jerks with the state of vigilance of the patient. In these cases, PSM occurs only during the relaxed wakefulness state, when patients are trying to fall asleep lying down on a couch or in bed, and when the EEG alpha activity has spread to involve the anterior brain regions (51,52). In such a situation, the jerks can recur quasi-rhythmically every 10 to 20 seconds and are of such intensity as to propel the patient out of bed or in any case severely impede his falling asleep (Fig. 2). Yet, whenever the patients undergo sensory or mental

![FIGURE 2](image_url)

**FIGURE 2** Videorecordings of a jerk of propriospinal myoclonus in a 41-year-old male. Total duration of the jerk 0.5 seconds. The panels on the right show the electromyographic (EMG) recordings of the same jerk, at low and high speed respectively. The EMG activity originates in the right paraspinous muscles, thereafter propagating to more rostral (rectus abdominis (RA), triceps brachii, biceps brachii, pectoralis, sternocleidomastoideus, masseter, all on the left) and caudal (RA, PS, quadriceps femoris, biceps femoris, tibialis anterior, gastrocnemius) muscles. **Abbreviations:** PS, paraspinous; RA, rectus abdominis; TB, triceps brachii; BB, biceps brachii; P, pectoralis; SCM, sternocleidomastoideus; MAS, masseter; Q, quadriceps femoris; BF, biceps femoris; TA, tibialis anterior; G, gastrocnemius.
stimulation or are asked to perform a mental task, the jerks, together with the EEG alpha activity, disappear. PSM again disappears as soon as the patient finally achieves sleep and remains conspicuously absent throughout all sleep stages. Occasionally, the jerks can show up for a short time also upon awakening in the morning. Only partial improvement is afforded in these patients by the use of clonazepam.

PSM has also been found in patients with a long history of RLS (25). In these cases, PSM jerks arose during relaxed wakefulness, but gave way with the appearance of spindles and K-complexes on the EEG to typical periodic limb movements during sleep with characteristic EMG activity limited to leg muscles.

The peculiar relation of the PSM with the relaxed wakefulness prior to sleep is attributed to supraspinal modulatory influences acting upon the spinal cord where the jerks are thought to originate (51). It also shows that wakefulness prior to sleep represents a peculiar vigilance state with intrinsic mental and neurophysiological characteristics—the predormitum as defined by Critchley (53).

Excessive Fragmentary Hypnic Myoclonus
Excessive fragmentary hypnic myoclonus (EFHM) has been reported as a pathological enhancement of PFHM persisting throughout sleep causing, sometimes, small movements of the finger, toes and/or corner of the mouth and associated with sleep apnea, excessive daytime drowsiness, and insomnia (11,54). Similar motor activity during sleep has been reported in patients with RLS (55), in extrapyramidal syndromes (56) and in patients with REM sleep behavior disorder (RBD) (57), narcolepsy, periodic limb movements during sleep, and fatigue (11). EFHM may be present as an isolated motor phenomenon during relaxed wakefulness, NREM, including stages III and IV, and REM sleep in which “quiver” movements recur throughout the body, affecting primarily the hands and face with some degree of sleep fragmentation. The twitches may occasionally awake the patient. They are absent during wakefulness and EEG–EMG back averaging does not show any cortical potentials related to the twitches (58). The exact origin and significance of the EFHM remain unclear, and despite the myoclonus being a common finding in polysomnography, it is often asymptomatic. EFHM is now classified in the section VII of the ICSD-2 (isolated symptoms, apparently normal variants, and unresolved issues) that lists sleep-related symptoms that are in the borderline between normal and abnormal sleep.

CONCLUSION
The nosography of the motor disorders that arise during sleep has gained much in the last few decades by the widespread use of videopolysomnographic recordings, which enable audio-visual monitoring of the different motor episodes concomitantly with the relevant neurophysiological EEG, EMG, and autonomic features. While permitting the recording and a detailed analysis of the motor episodes, videopolysomnography seldom discloses the pathophysiological mechanisms underlying the motor events. In other words, it is a purely descriptive means and lacks etiological power. Thus, this field is still far from being completely characterized, and even the boundaries between the physiological and the pathological are not always completely clear. The increasing application of molecular biology and
modern imaging techniques, such as functional magnetic resonance imaging or PET imaging will doubtless offer further insight into the pathogenic mechanisms behind many sleep-related motor disorders, with important implications for our knowledge of the sleep mechanisms involved in their origin.

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REFERENCES

The first description of restless legs syndrome (RLS) is usually credited to the XVII century English physician and scientist Thomas Willis (1,2). He considered RLS to be caused by “convulsive distempers,” such as epileptic activity. However, he did not suggest whether it was an inborn or an acquired condition. Progress over the following two and a half centuries was slow, with RLS having been mostly understood as a psychogenic disorder (3–5). In the 1940s, RLS was ascribed to various medical conditions, such as a vascular cause (6) or a familial origin with exacerbation during pregnancy (7).

The first modern description of RLS can be attributed to the Swedish neurologist Ekbom (8). He considered RLS to be secondary to either iron deficiency or vascular causes, and gave an accurate estimate of its prevalence at approximately 5% of the general population. Major steps in our current clinical understanding of the disorder were the first sleep studies (9,10) and the initial description of the therapeutic response to dopaminergic agents (11). Nevertheless, RLS has been ignored throughout history, which might be due to the fact that it involves abnormal sensations and sleep (12). Thus, for many years, it has been considered a nonspecific, psychological disorder. The frequently bizarre and subjective sensations described by the patients might have further contributed to this misunderstanding.

DIAGNOSIS

The diagnosis of RLS is usually based on the patient’s clinical history. The first criteria for diagnosis of RLS were established by the International RLS Study Group in 1995 (13). These were redefined in 2003 in a National Institutes of Health (NIH) sponsored workshop (14). Apart from principal criteria, three supportive and three associated clinical features were included for the RLS diagnosis (Table 1).

The clinical evaluation is based primarily on the information provided by the patient and the bed-partner during the interview. All four essential criteria must be met in order to establish the diagnosis of RLS.

Essential Criteria

*Urge to Move the Legs Associated or Not to Dysesthesias*

The urge to move the legs is usually accompanied or caused by uncomfortable or unpleasant sensations in the legs. The urge to move can be present without the uncomfortable sensations; sometimes the arms or other parts of the body are involved in addition to the legs. Even when motor and sensory symptoms can be described separately (urge to move vs. uncomfortable sensations), most RLS
patients experience both motor and sensory symptoms. There are two typical findings: sensations are perceived to originate from deep inside the leg and involve a perception of movement within the leg. Many patients describe painful sensations (15,16). RLS symptoms may also involve other parts of the body. Although they are usually noticed first in the lower extremities, they can spread to hip, face, trunk or upper extremities, usually coinciding with an increase in the severity of symptoms. Arms have been reported to be affected in a range of 34% to 50% of the RLS cases (17–19). Generally, RLS symptoms begin in the distal parts of the legs even when RLS is associated to neuropathy (20). Symptoms can be present unilaterally or bilaterally, alternating or simultaneously in one or the other side. The urge to move should not be confused with repetitive movements such as foot tapping, a motor behavior that habitually occurs without any acute distressing awareness of an urge to move.

**Onset or Exacerbation with Rest**

The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting. Generally, symptoms begin with a delay of minutes up to an hour when the patient is lying or sitting. Rest generates RLS symptoms, like lying in bed, sitting for long journeys in the car, plane, or train. Rest includes physical immobility and decreased central nervous system activity, factors that contribute to the onset of symptoms (21). Evidence of this feature was studied by the group of Montplaisir (22,23), who used the suggested immobilization test (SIT). The SIT evaluates periodic leg movements during wakefulness (PLMW) (Fig. 1) associated to self-reported sensory symptoms that the subjects experience while remaining immobile for an hour. In RLS sufferers, these symptoms increase throughout the test. It is important to differentiate these from circulatory compromise, pain or stiffness due to prolonged lying or sitting.

**Relief with Movement**

The urge to move or the unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues. Improvement of symptoms occurs immediately or soon after the beginning of the activity. This is a typical feature of RLS that discriminates from other disturbances, particularly those associated with pain. Depending on the intensity of the

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**TABLE 1** National Institutes of Health Criteria for Diagnosis of Restless Legs Syndrome

<table>
<thead>
<tr>
<th>Principal criteria</th>
<th>Supportive criteria</th>
<th>Associated clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urge to move</td>
<td>Family history</td>
<td>Natural clinical course following certain identifiable patterns</td>
</tr>
<tr>
<td>Onset or exacerbation with rest</td>
<td>Dopaminergic responsiveness</td>
<td>Sleep disturbance</td>
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<tr>
<td>Relief with movement</td>
<td>Periodic limb movements</td>
<td>Normal medical evaluation/physical examination</td>
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symptoms, relief is present while movement persists, but it can resume as soon as the physical activity ends. Types of voluntary movements consist in walking, stretching, bending, rubbing the legs, and flexing the extremities. Another usual strategy to reduce the intensity of symptoms is to take hot or cold baths in the limbs (24), and is reported to be effective in 82% of the patients (25). As the severity of the disease progresses, relief with movements becomes less effective, and subjects may not obtain any improvement. Relief with movement is a criterion that must be present or have been present in the course of the disease, and in severe cases it can be assessed only retrospectively in the past history.

Circadian Pattern

The urge to move or unpleasant sensations occurs in the evening or at night. In some cases they occur also earlier (sometimes during the entire day), but are worse in the evening or at night. When these symptoms are very severe, the worsening at night may not be noticeable, but must have been previously presented in the patient’s history. Circadian pattern of RLS symptoms have been studied in the last years, measuring the impact of both recumbence and rest (21,26,27). Most patients have a period during the day when the RLS symptoms are less pronounced, during which they can sleep or rest. In severe RLS cases the circadian pattern disappears, and symptoms are present 24 hours a day, without any apparent daily variation. Again, this criterion must be present or have been present in the course of the disease, at least as a historical feature. In one study (21), patients were monitored by the SIT and polysomnographic recordings. Results showed a peak in RLS restlessness between the hour immediately after midnight and a reduction in the late morning hours (10:00 AM to 11:00 AM). The highest number of periodic limb movements (PLMs) occurred during the falling phase of the circadian core-temperature curve, whereas the smallest during the rising phase of the curve.
In severe cases there is no daily variation, and a retrospective analysis might be required. In some cases, subjects only experience RLS symptoms during prolonged inactivity and rest, such as prolonged trips. A recent study that measured night to night variability in 28 untreated RLS patients, showed that index and nocturnal pattern of PLM occurrence were highly reliable across the nights, suggesting that a single-night study may be sufficiently sensitive to confirm the diagnosis and the associated sleep disturbances in these patients, with an individual inter-night variability (28,29).

Supportive Clinical Features
These clinical features are not necessary for RLS diagnosis, but their presence can resolve cases with diagnostic uncertainty.

Family History
First-degree relatives are affected in idiopathic RLS in more than 50% of the patients. Subjects with RLS are three to five times more likely to have a family history of RLS in comparison with nonaffected subjects (20,25,30,31).

Response to Dopaminergic Therapy
Almost all patients with RLS experience improvement during the initial period of treatment with dopaminergic drugs, using very low doses in comparison with the therapy for Parkinson’s disease (PD), as it has been documented in several trials (32–36). This initial response is not universally maintained during treatment (37).

Periodic Limb Movements
PLMs occur in sleep or wakefulness in up to 80% of the patients (38), but they are not obligatory for RLS diagnosis. PLM can appear in many other disorders, and in the normal elderly population (39–42).

Associated Clinical Features
Natural Clinical Course
The clinical course of RLS is variable. Typically, early onset tends to be insidious with a fluctuating course, and onset occurs at 50 years or older (16,20,43). Secondary RLS usually remits when the comorbid condition is resolved. Examples of these situations are improvement of uremic RLS following renal transplantation or RLS secondary to pregnancy (44–46).

Sleep Disturbance
Complaints on initiating and/or maintaining sleep are referred by over 90% of the RLS patients. Sleep disturbance represents the common major morbidity for RLS, and is often the first reason why the subjects seek medical evaluation. Objective measurements with polysomnographic recordings evidence increased sleep latency, increase of PLM arousals/awakenings and a decrease in sleep efficiency, total sleep time, and slow-wave sleep (12). Reduced sleep efficiency correlates with clinical severity of RLS. A patient moderate to severely affected can sleep less than five hours per night, with an important impact in his/her quality of life (47).
Normal Medical Evaluation

Physical and neurological examination is generally normal, except for RLS comorbid conditions. Anemia, neuropathy, or radiculopathy can be evidenced by clinical examination in order to determine secondary causes of RLS that should require different approaches of treatment (20,48,49).

It is also important to rule out potential mimics of RLS like leg cramps, vascular insufficiency, peripheral neuropathy, intermittent claudication, painful legs and moving toes, arthritic conditions (involving lower limbs), neuroleptic-induced akathisia, pruritus, anxiety disorder, and/or agitated depression.

SLEEP LABORATORY EVALUATION IN RESTLESS LEGS SYNDROME

The diagnosis of RLS can be supported by the sleep laboratory evaluation (14). The sleep laboratory evaluation is useful to investigate increased sleep latency, decreased sleep efficiency, and PLM-associated arousals/awakenings in RLS. Patients sleep less than 50% of the time they spent in bed. More than five PLM per hour of sleep is compatible with RLS, and the frequency of PLM is used as a measure for disease severity and response to treatment. The PLM index (PLMI) is detected by electromyogram (EMG) recording, usually measured at the anterior tibialis muscle (12,50).

PLMD is a nosological entity that may cause sleep disorders and daytime symptoms and is frequently associated with RLS. However, it is important to know that both are independent entities: RLS can occur without PLM during sleep, and isolated PLMD without complaints of RLS is a frequent finding. PLMs are also found in other sleep disorders, particularly when these involve dopaminergic dysfunction (i.e., narcolepsy, REM sleep behavior disorder) or even in sleep apnea syndrome, and in uncomplaining subjects with advancing age.

Polysomnography

PLMs are a laboratory finding present in the vast majority of patients with RLS (Fig. 2). The electrophysiologic features of PLMs are described in another chapter. When PLMs are intense, they can cause electroencephalographic (EEG) arousals. If these PLM arousals are numerous, PLMs alone can lead to nonrestorative sleep. In sleep studies, the PLMI is defined as the number of PLMs per hour of sleep. The PLMI threshold for RLS has been established at 11/hr by some authors (50) and 15/hr by International Classification of Sleep Disorders—2nd Ed (ICDS-2) (50a).

However, the presence of high number of PLMs is by no means specific to RLS, as PLMs cooccur in a wide range of sleep/wake complaints, including narcolepsy, sleep apnea, and REM sleep behavior disorder. Further, an abnormally high number of PLMs have also been found in otherwise physically and mentally healthy subjects. PLMs can also occur during sleep but without any sensory-motor symptoms while awake. As many as 12% of RLS patients do not have marked PLMs when recorded for two or more nights (38). When recording for two consecutive nights, a cut off score of 11 PLMs/hr provides a diagnostic sensitivity and specificity of approximately 80%. Thus, the presence of an abnormal number of PLMs during polysomnography (PSG) supports a clinical diagnosis, but does not suffice by itself to establish a firm diagnosis.

PLMI can be used to assess disease severity, although sleep efficiency, another parameter obtained routinely during PSG, correlates better with clinical rating of
RLS (12). Sleep efficiency might reflect RLS severity but it is a nonspecific marker of disturbed sleep.

Three parameters in the PSG require special consideration in the evaluation of RLS:

1. PLMI: number of PLMs per hour of sleep
2. PLM arousal index: hourly number of PLMs associated with microarousals
3. PLMW index: number of PLM per hour of nocturnal wakefulness, starting at lights off (beginning of the study), and finishing at lights on (end of the study)

PLMI is probably the most frequently used PSG parameter by clinicians and researchers to support the diagnosis of RLS. In a recent study, the authors showed that the PLMW index is more sensitive and specific than the PLMI, and when the PLMW index is assessed separately or together with the mean subjective leg discomfort score during the SIT (SIT MSD), the accurately obtained data discriminates patients with RLS from healthy control subjects, with high levels of sensitivity (82%) and specificity (100%) (50). These represent direct measures of the two major complaints presented by RLS patients: (i) unpleasant leg sensations, and (ii) motor restlessness occurring at rest, in the evening or during the night.

PSG is recommended for patients with probable or definite RLS in the following cases (51):

1. Clinical data suggesting probable RLS, but symptoms appear atypical or are influenced by other disorders
2. There is an ongoing severe insomnia and/or a lack of efficacy in patients with typical RLS symptoms during treatment with sufficient dosages of dopaminergic agents

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**FIGURE 2** Polysomnographic recording in a patient with restless legs syndrome. Sleep fragmentation as a result of the sensory and motor disturbance is observed. The patient remained awake a significant part of the night.
3. Patient complains about daytime sleepiness as a leading symptom in order to rule out other causes of daytime sleepiness

4. Patient is younger than 30 years, suffer from severe RLS and should be treated daily with dopaminergic agents, in order to support the diagnosis with a prospect of a life-long treatment with medication

5. In severe RLS an opioid medication is conceivable. In this case severity of insomnia and occurrence of PLMs should be documented, and pre-existing sleep-related respiratory disorder that might worsen during treatment should be excluded

6. Patient is diagnosed with RLS and an additional sleep-related disorder, but complains about persistence of RLS symptoms during pharmacotherapy.

7. An expert report is needed for legal purposes

In summary, even although the diagnosis of RLS is based on clinical information, nocturnal polysomnographic assessment remains an important supportive tool in the evaluation of RLS, and nowadays it is used in most sleep laboratories in the world.

**Suggested Immobilization Test**

RLS symptoms are primarily observed during wakefulness, especially when the patient is at rest in the evening or at night. Thus, objective tests have been performed to assess symptoms during wakefulness (PLMW). The occurrence of PLMW and the quiescentogenic nature of RLS provided the basis for developing a test aimed to be more specific for RLS (52). The SIT is a 60 minutes test to be performed in the evening 90 minutes before bedtime. Patients are reclined in bed and are instructed not to move or fall asleep. However, immobility is not enforced, but just suggested. Legs activity is recorded using standard bilateral anterior tibial surface EMG. EEG is recorded simultaneously. Every five minutes patients fills out a visual analog scale for sensorial discomfort. The criteria of PLM scoring differs from the classical Coleman’s criteria in the duration of each movement, between 0.5 and 10 seconds (53). The use of this criterion allows to consider the longer duration of leg movements during wakefulness, resulting in a voluntary contraction of leg muscles that follows the shorter, involuntary contraction to relieve dysesthesias.

PLMW are more common during the second half of the SIT, both in patients and controls, with a significant difference in RLS patients ($P < 0.05$) (22), suggesting that PLM increase with duration of immobility.

**Actigraphy**

An actigraph is a small portable device capable to sense physical motion and to store the resulting information. It is widely used to evaluate rest-activity cycles in the normal healthy population, and in sleep disturbances like insomnia, circadian-rhythm disorders, obstructive sleep apnea syndrome, and PLMD. Modern actigraphs have a movement detector and sufficient memory to record for long-time periods.

The use of actigraphy in sleep disorders like RLS with PLM has gained popularity. The information can be taken out of the laboratory setting and be recorded over several days, thus taking care of day to day variation in symptoms (27).

The devices called actigraphs (or actimeters) are used to record limb movements (wrist or ankle). The term PLMs refers to leg movements of the same type
that occur either while the patient is awake or asleep, therefore, the quantification of
PLM is independent of sleep stages or wakefulness. Even when PLMs occur in an
isolated fashion in (periodic leg movement disorder, PLMD) and also in certain
percentage of patients with various sleep disorders, the movements are closely
related to RLS. The data collected are displayed on a computer and are examined
for activity versus inactivity and analyzed for wake versus sleep. Kazenwadel
et al. (54) found a high reliability between EMG and actigraphy for the number
of leg movements per hour of sleep.

Actigraphy should be associated with a sleep diary, and several studies
observed that it can substitute laboratory or ambulatory PSG.

The advantages of actigraphy are its simplicity, the ability to record for long-
time periods (from minutes to several days), low cost monitoring in all environ-
ments (excluding water), ability to be used in a home environment, minimizing
laboratory effects that may alter a patient’s typical sleep patterns, and reliability
in all kinds of patients (including demented patients and those not compliant
with PSG, like small children) (55,56).

Two studies have employed actigraphy in the evaluation of treatment efficacy
of RLS. In the first study, a placebo-controlled crossover design, the effects of
levodopa (L-DOPA) therapy for idiopathic and uremic RLS, using both PSG and acti-
graphy at baseline and at the end of the treatment, was investigated (33). L-DOPA
treatment resulted in a significant reduction of leg movements, measured by both
methods (actigraphy and PSG) in both types of patients (idiopathic and uremic
RLS). The data of both measures showed that the improvement was limited to
the first four hours of recording time. Parallel to these objective indices, subjective
measures like sleeping diaries and quality of life ratings, showed similar improve-
ment in response to treatment. Actigraphy was continued for two additional nights
after the PSG study, and so the authors were able to confirm the stability of this
treatment effect.

In the second study, Collado-Seidel et al. (57) conducted a similar study of
L-DOPA and slow-release L-DOPA efficacy, but without simultaneous use of
PSG. The authors found significant treatment-related effects for most actigraphic
variables, including movements per hour and number of movement episodes,
and only the change in the time without movements in the first half of the night
failed to reach significance. Subjective improvements also have been seen in
patients reporting increases in sleep quality and overall well being, decrease in
number of awakenings, time awake, and reports of daytime fatigue.

When used for RLS and PLMs, actigraphy has certain limitations (55) in
patients with RLS and PLMs. Thus, it might underestimate the frequency of legs
movements during sleep, and there is no information about the exact sleep
stages. Additionally, the limits on the categorization of movements, the lack of
means to quantify the intensity of movements, and the different patterns do not
allow actigraphy to evaluate specific physiologic or abnormal movements.
Overall, actigraphy is best at estimating total sleep time (i.e., normal subjects);
but when sleep became more fragmented (i.e., in RLS with high PLMI and an
increase of awakenings) the actigraph became less accurate in the detection of
sleep and wake, overestimating sleep and underestimating wake, particularly
during the day when an individual is more likely to sit quietly while awake.
Furthermore, as there is no accurate marker of bedtime, the determination of
sleep latency or variables whose calculations depend on it (sleep efficiency and
wake after sleep onset) become unreliable.
Additional Medical Evaluation
Several relatively simple procedures are planned to exclude secondary causes of RLS, particularly iron deficiency and peripheral neuropathy. It is important to exclude these two conditions before RLS is labeled as primary.

Basic Laboratory Evaluation
The laboratory parameters include complete blood cell count, markers of renal and hepatic function, iron metabolism, inflammation, endocrine function, vitamins (B12 and folic acid), and magnesium. Also a basic biochemistry is needed with plasma determinations of glucose, creatinine, urea, potassium, calcium, and sodium.

Regarding the iron metabolism, there are two variables of special interest:

1. Serum ferritin: low levels of serum ferritin may precede a decrease in serum iron level. Level lower than 50 ng/mL (<50 μg/L) have been associated with RLS, even in the absence of decrease hemoglobin or serum iron levels (58,59). The depletion of iron stores, even in the absence of serum iron deficiency, could lead to a RLS.
2. The concentration of soluble transferrin receptor (sTR) reflects the total body mass of cellular transferrin receptor (60). A high sTR concentration is considered to be the initial response to declining body iron supply (61).

Urine Tests
Besides urinalysis, it is also recommended to perform a 12- or 24-hour urine collection for creatinine clearance, reflecting the glomerular filtration rate (GFR) in patients at risk for kidney disease. A declining renal function is associated with increasing prevalence of RLS (62).

Electromyography and Nerve Conduction Studies
RLS is not infrequent in several neurologic conditions such as spinal cord dysfunction [Charcot-Marie-Tooth type 2, Spinocerebellar ataxias (SCA 1-3)]. These studies should be performed primarily when peripheral neuropathy is suspected on clinical grounds, even if the results of neurologic examination are apparently normal (63).

Rutkove et al. (64) reported a 5.2% prevalence of RLS in miscellaneous peripheral neuropathies. Some types of peripheral neuropathy, such as cryoglobulinaemic neuropathy, Charcot-Marie-Tooth type 2, diabetic neuropathy, and amyloid neuropathy are especially prone to trigger RLS; often as an early manifestation (65).

Other Tests
In certain cases, extensive complementary tests (MRI, special CSF and serum determination, venous ultrasound of the legs) should be carried out in order to confirm the existence of other factors and conditions that may contribute to secondary RLS, such as lumbosacral radiculopathy, lyme disease, monoclonal gammopathy of undetermined significance, myelopathy or myelitis, and so on or to make a differential diagnosis with other diseases, such as deep venous thrombosis, chronic venous insufficiency.

Epidemiological Studies
In his initial work, Ekbom suggested a 5% prevalence rate in the population. Although early population studies in Australia reported prevalence rates of 2.5%
(66), later studies have steadily shown higher rates in western countries, thus confirming Ekbom’s initial estimates. A study conducted among 2000 Canadians showed a 15% of responders with “sleep onset difficulties and restlessness in their legs” along with a further 10% of subjects with “unpleasant leg sensations after awakening from sleep.” Although no gender differences were found in this study, francophone Canadians were significantly more affected than anglophone Canadians (67) suggesting a possible genetic effect that would be associated with ethnic differences. Since then, several studies, carried out in western countries, have shown high rates of prevalence in different populations (30,61,68–74). Yet, recent studies have found lower prevalence rates in Asian populations (75–78), further reinforcing the concept of ethnic differences possibly driven by genetic factors.

Most of the studies found significant higher prevalence of RLS in the female population, with prevalence frequently twice as high as for men (61,68,69,79–82). It has been found that prevalence rates also increase with age (69,81,83,84). Yet, no age related changes were found in the prevalence rates of 65 to 69-year-old subjects compared to those over 75 years.

Prevalence rates have also been investigated in special populations. Neuropsychiatric complaints, for example, depression (81,85), headache, and work-related fatigue (74) are more common with RLS. Other conditions that have been found to be related to RLS are iron deficiency (59,79) and end-stage renal disease (33,86–88). It has been also suggested that peripheral neuropathy might be related to RLS, although this issue remains controversial (20,64).

SECONDARY RESTLESS LEGS SYNDROME

Pregnancy

Occurrence of RLS during pregnancy has been documented by several authors, particularly in the third trimester, and has been found to be related to familial RLS cases, lower hemoglobin levels, folate deficiency, and hormonal changes (46). In the majority of cases, RLS symptoms remit after delivery.

Uremia (End-Stage Renal Disease)

Uremia is one of the best described comorbid conditions for RLS, with high prevalence in these populations (89–92). In renal disease, false negatives and false positives are common because of individual differences in the selfappraisal of symptoms and the common presence of itching, neuropathy, and legs cramps. Both RLS and a PLMI greater than 20 had been documented as significant independent predictors of mortality in this population. Impaired quality of life has also been reported (93). Dialysis improves RLS symptoms, and renal transplantation represents the most effective treatment for uremic RLS (44).

Iron Deficiency

There is an evident correlation between iron deficiency and RLS (94). Iron deficiency may be present in primary and secondary forms. Low ferritin levels (serum and CSF) seem to be implicated in RLS development, and values of ferritin lower than 50 μg/L are common in RLS patients (62). Iron status should be investigated in all subjects with idiopathic RLS.

Other deficits have been reported (vitamin B12, folate, magnesium), with no clear evidence for an association to RLS (95).
Parkinson’s Disease
Both RLS and PD share many issues: responsiveness to dopaminergic therapy, affected (different) dopaminergic pathways, and increase prevalence of PLMs. In PD up to 20% of patients have symptoms of RLS (96,97).

In PD, RLS symptoms should be differentiated from akathisia, a purely motor restlessness without sensory symptoms, tremor, and a motor disorder with specified frequency (98). There is no documented association between the risk of development of RLS and PD disease (97).

Miscellaneous
Other medical conditions, which have been associated with RLS are: (i) rheumatologic diseases (99), (ii) myelinopathy (61), (iii) antidepressants such as mirtazapine (100), and (iv) agonists blockers (101).

PSYCHIATRIC SYMPTOMS IN RESTLESS LEGS SYNDROME
RLS might be confounded with several neuropsychiatric disorders. Furthermore, comorbidity is not uncommon (102). RLS might be associated with some features of depression but not with the full spectrum of a depressive disorder (85). In another very recent study, authors found that RLS patients have an increased risk of having specific anxiety and depressive disorders (103).

GENETICS
The implication of genetic factors in the etiology of RLS is supported by the following findings.

High Prevalence of Restless Legs Syndrome in First Degree Relatives of Affected Patients
The presence of RLS in the family of RLS patients varies between 42% and 90% according to different studies (20,25, 30,38). The mode of inheritance has an autosomal dominant pattern in more than one-third of the familial cases (104,105). Some families show a possible anticipation with each (104,106).

High Concordance Rates Observed in Monozygotic Twins
The only study available in twins showed a high concordance rate (83.3%) and a high penetrance. It also evidenced variation between identical twins regarding the age of onset and symptom severity (107).

Identification of Susceptibility Locus in Families with Restless Legs Syndrome
There have been different model-based linkage analyses reported for RLS:

1. Desautels et al. (108) identified an autosomal-recessive RLS locus on chromosome 12q22-23 in a single French-Canadian family.
2. Bonati et al. (109) mapped an autosomal-dominant RLS locus to chromosome 14q13-21, also in a single Italian family. More recently, the locus on chromosome
14q previously reported, was replicated in 1 out of 14 other French-Canadian families (110).

3. Chen et al. (111) identify a significant linkage to RLS on chromosome 9p24-22 in 15 large North American families, but could not detect mutation in any of the three genes analyzed (MUPP1, SLC1A1, and KCNV2). Moreover, their results provided indirect confirmation of the mapping of an RLS gene on chromosome 12q22-23, reported before (108).

However, none of these loci are clearly related to the dopaminergic system. Desautels also analyzed eight relevant candidate genes involved in dopaminergic transmission and metabolism: (i) DA-receptors D1 to D5, (ii) dopamine transporter (DAT), (iii) tyrosine hydroxylase (TH), and (iv) dopamine β-hydroxylase (DBH), but none of them were directly involved in the etiology of RLS (Desautels, 2001 218 id).

Although some authors base the genetic etiological theory of RLS on a single major gene acting in a autosomal-dominant manner with a multifactorial component (105), the hypothesis that RLS may present a polygenic basis, with interactions between genes and environmental factors, is not completely excluded, especially if we consider the identification of these three genetic loci for RLS on three diverse chromosomes 12q22-23 (108,109,111).

Nevertheless, there is no clinical distinction between the familial and sporadic RLS cases, presenting similar symptomatology, examination, and evolution. The only differences between these two groups consist of a significantly earlier age of onset, and a more frequent worsening during pregnancy in patients with hereditary RLS (105).

**PATHOPHYSIOLOGY**

Although the pathophysiology of RLS remains largely unknown, dopaminergic mechanisms are believed to play a central role. The hypothesis of an impaired central dopaminergic transmission in RLS is supported by the involvement of the dopaminergic system in motor control and by a successful therapeutic response of these conditions to dopaminergic agents (112,113).

Brain imaging studies have reported heterogeneously and with partial inconsistent data abnormalities of central dopaminergic systems in RLS. Two studies have shown a mild reduction in postsynaptic dopaminergic status in RLS (114,115). Moreover, two of the three [18F]-DOPA PET studies showed a slight but significant decrease in striatal [18F]-DOPA uptake in RLS patients compared to healthy controls (115,116), suggesting a presynaptic dopaminergic dysfunction in the striatum. The remaining [18F]-DOPA PET studies showed normal values for presynaptic dopaminergic function (117), as well as the SPECT studies (114,118). Furthermore, studies trying to determine the genetic substrate of this hypothesis have not been able to identify a relation between RLS and several genes coding for receptors and enzymes related to dopaminergic transmission (119). In addition, metabolites of dopaminergic and serotonergic pathways in both the cerebrospinal fluid and plasma were not different between RLS and controls (120,121).

Ultimately, another link between RLS and a potential brain dopaminergic dysfunction might be provided by research into altered iron metabolism in this disorder (122). Dopamine synthesis requires iron; hence iron deficiency could lead to dopaminergic abnormalities underlying RLS (94). In the 1950s, Ekbom described iron deficiency as a potential cause of secondary RLS.
Several findings support the association of the RLS etiology to brain iron deficiency, including:

1. Decreased iron concentrations in the substantia nigra and less significantly in the putamen, have been suggested in a MRI study of patients with RLS, both in proportion to RLS severity (123). These findings may indicate that brain iron insufficiency affects certain brain regions in patients with RLS.

2. Immunocytochemical autopsy studies have produced evidence of impaired iron metabolism in neuromelanin cells of the substantia nigra (124,125). Substantia nigra neurons with positive iron staining were reduced in RLS patients compared to control examinations. In neuromelanin cells from brains of RLS patients, heavy chain ferritin staining was absent and light chain ferritin staining was present, but was morphologically distinct from control examinations. Transferrin receptors were not upregulated in brains from patients with RLS, indicating impaired brain iron acquisition in RLS (125). A later study detected a decrease of iron regulatory protein 1 (IRP-1) and transferrin receptor expression, with an increase of transferrin in neuromelanin cells of RLS patients, concluding that IRP-1 deficiency could be responsible for the lack of adequate transferrin receptor up regulation in RLS and in consequence of cellular iron deficiency (Connor, 2004 141 /id).

3. Decreased levels of ferritin and increased levels of transferrin have been found in the CSF of patients with RLS (126).

Also a dysfunction of other dopamine-dependent pathways, such as the diencephalospinal pathway, has been suggested as an alternative mechanism for RLS (20,127).

**Treatment**

Since the first report by Akpinar (11,128) of the therapeutic effects of L-DOPA, dopaminergic drugs have become the treatment of choice for RLS (112,129). Since then, several controlled studies have shown the clinical efficacy of L-DOPA when administered in combination with a decarboxilase inhibitor. The usual daily dosage of L-DOPA ranges between 50 and 250 mg given as a single dose one hour before bedtime. All of the published studies have reported a subjective improvement of symptoms and sleep quality. In addition, some studies also showed a shortening of sleep latency and a reduction in PLMs. Still, treatment with sustained release L-DOPA alone is probably not sufficient, as effective peak plasma concentrations might not be reached before the patient falls asleep (32). In addition, the short half-life of L-DOPA poses a practical problem as some patients with severe RLS might require multiple doses during the day as well.

Long-term treatment with L-DOPA has been investigated for periods up to two years, and sustained efficacy has been observed in over 70% of the patients (130). Hitherto, no L-DOPA induced dyskineties have been found in RLS patients. Furthermore, studies with \[^{18}F\]-DOPA PET showed normal nigro-striatal binding capacities after more than five years of treatment (117) in patients with RLS. Neither does PD become more likely in RLS patients when treated with L-DOPA (97,131,96).

In general terms, L-DOPA is well tolerated in RLS patients, and the most frequently reported side effects are nausea and dry mouth. Yet, in the course of long-term treatment with L-DOPA, rebound and augmentation may result in
serious problems (132,133). Rebound refers to the reappearance of symptoms at a time coinciding with the end of the half-life period of the drug, usually early in the morning. The presence of rebound is more common when the used drug has a short half-life, as it is the case for L-DOPA. Following rebound, a symptom-free interval of variable length can be observed before the next evening symptoms begin. If the presence of rebound symptoms wakes up the patient during the night, the addition of a further dose of medication to the treatment regimen during these awakenings might be helpful. An alternative approach would consist of using a drug with a longer half-life such as a dopamine agonist.

Augmentation frequently represents a more serious problem and can become a therapeutic challenge for the treating physician. Augmentation was originally described as comprising four possible features (132): (i) an earlier onset of time at which symptoms start, compared to the pretreatment period, (ii) a shorter latency to symptoms when at rest, (iii) an overall increase in severity of symptoms with a shorter duration of treatment effect, and (iv) an expansion of symptoms to the upper limbs and trunk. In general terms, augmentation reflects an overall increase in symptom severity as a result of long-term dopaminergic treatment. The likelihood of augmentation has been associated to the severity of RLS at baseline, to the type and daily dosage of medication, and to the length of treatment, as it has not been observed so far under nondopaminergic treatments (133). Among dopaminergic drugs, augmentation occurs with particular frequency during treatment with L-DOPA in 50% to 85% of the cases. Augmentation needs to be differentiated from rebound in clinical practice, particularly because the increase in daily dose typically carried out to treat rebound will inevitably lead to a worsening of augmentation.

At present, dopamine receptor agonists are the treatment of choice for RLS, particularly if daily treatment is needed or the condition is severe (112,129). This is mainly due to their longer elimination half-life, which makes repeated administration during the night unnecessary, to their better tolerance and to the lower frequency of long-term complications. Several dopamine receptor agonist drugs have been studied under controlled conditions, showing efficacy for ropinirole (134–136), pramipexole (137,138), pergolide (139–141), cabergoline (142,143), rotigotine (144), and bromocriptine (34). In addition, more large-scale controlled studies are currently being carried out for several new dopaminergic agonists.

Opiates were already described by Willis (1,2) as being effective for RLS, and today they are generally used by clinicians as a second choice option or for conditions with augmentation problems. Hitherto, all of the few opiates studied, such as oxycodeone (145) or propoxyphene (146) have been found to be effective. Yet, the required dose was relatively high—often in the higher end of the analgesic range.

Anticonvulsants such as carbamazepine and, more recently, gabapentin, are also effective drugs for RLS. The latter seems to exert therapeutic effects at dosages between 1400 and 1850 mg/day, and is particularly effective for cases including pain or an associated peripheral neuropathy (36,147–150). Some benzodiazepines, such as clonazepam, have also been reported to be effective for RLS (129,151–153). However, their therapeutic effects at the usual dosage (0.5–2 mg/day) are mild, and, if applied at higher dosages, can cause sedation and other side effects. Furthermore, the effects of benzodiazepines might be mediated by sleep induction rather than by direct suppression of RLS symptoms.

The medical treatment choices for RLS do not differ between secondary and primary RLS, except for the need to correct the cause of the disorder, whenever
possible, and for the limitations imposed by the secondary condition (e.g., pregnancy, renal insufficiency). In general, treatment will always depend on the disorder’s severity. Mild cases may only need assistance with sleep, such as sedative hypnotics (clonazepam) or behavioral treatments like circadian rhythm adjustment allowing sleep at a later time of the day. An alternative treatment option for mild cases consists of using a low dose of either L-DOPA/carbiDOPA or 0.25 to 0.5 mg pramipexole. Any of these treatments can be adjusted and used intermittently “as needed” rather than every night, although no empirical validation of this treatment method has been performed yet. More severe RLS cases require the use of higher L-DOPA dosages, or preferably, either a dopamine receptor agonist; or even an opiate.

In addition to symptomatic medication, it is important to ascertain that the body iron stores are adequate. Oral iron is recommended whenever serum ferritin levels are lower than 45 to 50 μg/L (48). Oral absorption of iron increases if simultaneously taken with vitamin C on an empty stomach. Furthermore, an early study showed that repeated administration of 200 mg iron intravenous led to a complete remission of patients (154,155).

In conclusion, recent advances in the treatment of RLS have significantly improved the available treatment options. As a result, RLS has become a manageable condition. It is to be expected that further efforts in education, will make diagnostic recognition accessible to the entire medical community, and help make these therapeutic advances available to the vast majority of patients.

REFERENCES


PERIODIC LEG MOVEMENTS IN SLEEP

Periodic leg movements (PLMs) are repetitive, stereotyped flexor-withdrawal–like movements of the legs which occur during sleep. They can involve the arms and are thus called periodic limb movements of sleep (PLMS). PLMs can also occur during wakefulness [periodic limb movements of wake (PLMW)], especially in patients with restless legs syndrome (RLS) (1,2). Formerly, PLMS were called nocturnal myoclonus (3) due to their occasional myoclonic jerk character. With the purpose of emphasizing their repetitive periodicity and the fact that most PLMs did not reach the speed of a myoclonic phenomenon, the term periodic movements in sleep was introduced (4) later. After some time, the term was modified to PLMs in sleep: these movements involve the lower limbs in almost every case and were originally described as affecting exclusively the legs. However, the term periodic limb movements in sleep is better recommended, because in severe cases, the upper limbs and even the trunk can also be involved, that is, periodic arm movements (5).

PLMs are defined by their electromyographic (EMG) characteristics during polysomnographic (PSG) recordings. Recording of PLMs involve EMG surface electrodes placed in one or both anterior tibialis muscles. PLMS are scored only when they occur in series of four or more consecutive movements with a duration of each EMG burst for 0.5 to 5 seconds. The amplitude of each EMG burst should be equivalent to 25% of the biocalibration signal and separated by intervals of 5 to 90 seconds during any sleep stage (wake excluded) (4,6) (Fig. 1). PLMs occur mainly during the first half of the sleep period, in stages 1 to 2 (Fig. 2).

These movements consist of dorsi-flexion of the foot, extension of the big toe, and frequently also flexion of the knee and hip. Thus, PLMs of sleep closely resemble the spinal flexor reflex (FR) (4). Therefore, PLMs have been compared to the triple withdrawal reflex (7). Nevertheless, some recent studies based on surface EMG findings have not confirmed this point (8,9). After all, these classical descriptions were based on clinical observations of muscles moving during sleep. In these studies, nearly all muscle movements occurred randomly and not in the classical sequence. Hence, it was proposed to eliminate the term “stereotyped” of the PLMs definition (9). The movement speed is typically moderate, similar to a voluntary movement, but can vary from one sustained tonic contraction to one or more brief myoclonic bursts, and it can occur in combinations of sustained tonic phase with myoclonic bursts at the beginning or at the end of the movement (4,7,10,11). PLMs are often bilateral, involving both legs, but may be predominant in one leg or alternate between legs (12), and occur in a series of similar movements during a variable period (from few minutes to several hours).
PLMS are also frequent in normal subjects without sleep disorders complaints, especially in the elderly (13–16). The prevalence increases with age in healthy subjects. Furthermore, PLMS have a night-to-night variability. PLMS are rare in normal subjects younger than 30 years; however, when polysomnography is performed across several nights, approximately 30% of subjects between 40 and 60 years and over 50% of those over 65 years show a significant number of PLMS (16–19).

**CLINICAL FEATURES OF PERIODIC LEG MOVEMENTS IN SLEEP AND WAKEFULNESS**

PLMW are the basis of the suggested immobilization test (SIT), particularly in patients with RLS. PLMW during SIT are scored according to the same criteria as those used for PLMS (4), but include a few modifications. Any movements lasting between 0.5 and 10 seconds, with an intermovement interval of 4 to 90 seconds are scored.

PLMs are scored as bilateral if the interval between the offset of movement in one leg and the onset of movement in the other leg is lower than four seconds. The use of these criteria differentiates PLMW from myoclonia (due to their duration)
and from continued EMG tonic bursts (due to the required intermovement intervals). Furthermore, according to Coleman’s criteria, any leg movements to be scored have to be part of series of at least four consecutive movements and thus be periodic. However, during wakefulness, the longest duration for leg movement to be scored as such is 10 seconds, whereas during sleep the maximal duration is five seconds. The longer duration of leg movements during wakefulness is justified as being the result of a voluntary contraction of leg muscles that follows the shorter, involuntary one, in order to relieve the dysesthesias, which usually take place within two seconds of the onset of PLMW (20).

Periodic Limb Movements of Sleep Disorder

Periodic limb movements disorder (PLMD) is defined as the presence of an abnormal number of PLM in PSG studies with the simultaneous presence of insomnia (difficulties in initiating and/or maintaining sleep) and/or, occasionally, daytime fatigue or sleepiness, and with the exclusion of other causes of sleep disturbances (21). The main criterion used for the diagnosis of PLMD is the index of PLM per hour (PLMI) on PSG recording in the sleep laboratory or ambulatory sleep recording. Usually, an additional measure of severity is the index of PLMS associated with arousal (PLMAI) (22). Classically, a PLMI greater than five per hour was considered abnormal. However, some doubts have risen on the clinical validity of this threshold: although it may be maintained for children, later reports suggested that in adults the normative abnormal minimal value of PLMI should be greater than 15 per hour (21). Furthermore, sleep-related breathing disorders and, more specifically, upper airway resistance syndrome (UARS) need to be excluded using a pressure transducer airflow monitoring or esophageal pressure, before the diagnosis of PLMD can be made (23–25). The classical classification of severity for PLMD is: mild (PLMI between 15 and 24 associated with mild insomnia or...
sleepiness), moderate (PLMI between 25 and 50 associated with moderate insomnia or sleepiness), and severe (PLMI greater than 50 or PLMAI greater than 25 associated with severe insomnia or sleepiness).

Actigraphy is also a valid method for the detection of PLMs. While EMG detects electrical potentials, actigraphy records movements. More recent actigraphs with high sampling rates can determine whether movements meet criteria for PLMs and include light detectors or position detectors that helps to distinguish PLMs from repetitive voluntary limb movements (26). The main advantage of actigraphy is that it is more economic than PSG, can be performed in any environment, and is easily used on a long-term basis (22). Its main disadvantage is that it provides less information about the context of the movement.

The prevalence of PLMD is not well-determined; in a recent cross-sectional study performed in five European countries with telephone interviews of subjects aged 15 to 100 years old, the prevalence of PLMD was 3.9%. Specific associated factors were: being a shift- and/or a night-worker, snoring, high daily coffee intake, use of hypnotics, and stress (27). No sex difference has been described, and a typical age range is not known (21), although PLMD is probably more frequent in the elderly. It is a matter of ongoing discussion whether PLMD is a preclinical form of RLS or a completely separate entity (28–30).

Periodic Limb Movements of Sleep Associated with Other Conditions
The first descriptions of PLMS were made in patients diagnosed with RLS (31,32). In fact, 70% to 87% of the patients with RLS studied by PSG have a significant number of PLMS (five per hour of sleep or more) (10,33) and RLS is the most common condition associated with PLMS (22). In RLS, the mean PLMS index increases with age (34,35). Furthermore, independently of the age factor, PLMS index increases with RLS severity (5).

In RLS, the temporal pattern of PLMS index across the night is the “decrescendo type” (36,37): most movements take place during the initial part of the sleep period and their frequency decreases as the night progresses. Furthermore, according to several reports, in RLS, PLMS are more frequent and longer during non-REM sleep stages (34). The individual night to night variability of PLMS is most frequent and occur to the highest extent in RLS patients than in non-RLS patients (38).

PLMS are a habitual finding in other primary sleep disorders, most frequently narcolepsy and REM sleep behavior disorder (RBD). PLMS are very common in narcoleptic subjects (33,39–41), with an estimate of PLMI of five or more in 45% to 60% of the subjects. This percentage varies with age, and increases to 90% in narcoleptic individuals older than 60 years (42). The linkage PLMS–RBD is also well-documented (43,44), with a reported PLMI greater than 10 per hour in about 70% of the patients. Both, narcolepsy and RBD have frequent PLMS in all stages of sleep, with a trend to have more PLMs during REM sleep. These features are probably a manifestation of motor control dysfunction with a lack of REM sleep motor inhibition, presumably secondary to an impaired dopaminergic system.

PLMS has also a well-documented relationship with the obstructive sleep apnea (45,46). It occurs most frequently in association with respiratory events but can be independent, in which case the intermovement interval of PLMS is reported to be shorter (47). The PLMS index can decrease after treatment with nasal continuous positive airway pressure (N-CPAP), although it frequently remains elevated.
Pathophysiology of Periodic Limb Movements of Sleep

Although most studies have been performed on patients with PLMS that also had RLS, it is thought that both conditions (PLMD and RLS/PLMS) share the same pathophysiology, as they frequently coexist and both respond to the same therapeutic agents (62,63). The final common pathway mediating PLMs are neural pathways within the spinal cord, as lesions below the pons (infarction, transaction, or other spinal pathology) can contribute to their occurrence (7,64–66).

A single neurophysiologic mechanism underlying PLMS is unlikely. In general, the main deficit manifests as brainstem or spinal reflex “hyperexcitability” (67–69). The origin of this enhancement of motor excitability is not known, but must derive from a source that accounts for the circadian variation and for the state dependency of spinal cord excitability. In that sense, state dependent changes have been described in spinal cord excitability (68). These changes manifest as a decreased threshold of the FR and as a segmental spread of the FR (from proximal to distal muscles). It should be noted that the FR can be modified by muscle and cutaneous afferents, Renshaw cells, presynaptic inhibition of afferents by intraspinal interneurons, and multiple supraspinal pathways (70–74).

Periodic limb movements do not reside in the principal sensory and motor elements, as waking EMG activity, resting motoneuron excitability, simple reflexes, and sensory evoked potentials are generally normal (67,75–78). However, diffuse peripheral nerve dysfunction is common and may be an important modifier of PLMS expression (79–82). The most powerful and consistent influences originate from outside the spinal cord in supraspinal, premotor circuits of the central nervous system. In spinal cord injury, pharmacologic agents effective in treating RLS/PLMS and dampening FR responses via local spinal circuits are generally, but not universally, ineffective (63,83). Thus, the primary benefit is mediated by dopamine-sensitive pathways that are located supraspinally. However, although some brain imaging studies have shown reductions in dopamine uptake into presynaptic axons and D2 receptor binding, suggesting a relative excess of extracellular dopamine, the magnitude of these changes is small (84–86).

Periodic limb movements also occur when the striatum is depleted of dopamine axons (13,57). This can occur either in experimental setting or in neurodegeneration such as in Parkinson’s disease. Nevertheless, it is surprising that the prevalence of RLS in Parkinson’s disease (PD) lacking nigrostriatal pathways does
not differ substantially from that observed in the general population (87,88), and could point out to the main pathophysiology residing in alternative dopaminergic pathways such as the diencephalo-spinal pathways. These pathways terminate in the dorsal horn where they inhibit superficial and deep tissue afferents.

PLMs can be modified by other central pathways. Rather than exhibiting a unique pathologic condition, PLMs can arise from several central sources. Factors favouring PLMs expression can be categorized into two groups: the first reflecting disinhibition resulting from interruption of descending inhibitory pathways, for example, through modulation by the pyramidal motor system, as patients with hemiplegia due to cerebrovascular disease exhibit PLMs that predominate in the hemiplegic limbs (89).

The second mechanism would consist in facilitation from direct enhancement of neural activity, such as is the case during administration of monamines. For example, PLMS can be exacerbated by serotonin reuptake inhibitors (90). The specific neural substrates mediating these effects are not known, given the ubiquitous nature of monaminergic innervation, but they could be mediated by direct enhancement of motoneuron responsiveness, serotonin (5HT2)-receptor mediated facilitation of the FR (91), or medullary raphe-mediated enhancement of spinal nociceptive transmission (92). It remains also possible that decrements in monoaminergic neural integrity with aging (specially dopaminergic nigrostriatal cells) might also play a role, given the fact that the prevalence of PLMs increases steadily across the life-span. In summary, the heterogeneity of causes for PLMs and in treatment responses could be due to a redundancy in sensori-motor networks as well as a lack of neurons necessary and sufficient to generate PLMs.

Treatment of Periodic Limb Movements of Sleep

There is a general consensus that the presence of PLMS per se, when not accompanied by insomnia, fragmented sleep, daytime symptoms (fatigue, somnolence), does not necessarily require treatment. Most studies on the treatment of PLMD have been performed in patients with RLS. In any case, treatment should only be considered when PLMS is part of a broader disorder in which sleep complaints (PLMD) are present. Although no large studies have been performed on the treatment of PLMD, most agents have been used in PLMS associated to RLS. Many agents have been suggested to be effective in PLMS (Table 1). Among these, the non-ergot dopamine-agonists are the most often recommended agents for PLMS (93,94). Ropirinole at 1.5 to 4 mg/day has a high efficacy in reducing

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<th>Table 1</th>
<th>Effective Medications for the Treatment of PLMS in Restless Legs Syndrome</th>
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<td>Dopaminergic agents</td>
<td>Dopamine agonists</td>
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<td>L-DOPA</td>
<td>Nonergot derivatives: ropinirole, pramipexol</td>
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<td></td>
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Abbreviations: PLMS, periodic limb movements of sleep; L-DOPA, levodopa.
PLMI in relation to placebo (76% vs. 14%) (95). Pramipexole at 0.375 to 1.5 mg before bedtime is also effective in reducing PLMS (96). Common side effects are somnolence, nausea, dyspepsia, muscle weakness, and headache. Ergotamine derivatives like cabergoline 0.5 to 2 mg/day or pergolide 0.4 to 0.55 mg/day can also be used to treat PLMS (97,98). Bromocriptine 7.5 mg/day was reported as effective in PLMD associated with narcolepsy (99). During long-term treatment with ergotamine derivatives, an increased risk of valvular heart disease and fibrotic reactions has been reported. L-DOPA seems to be effective for PLMS (associated or not to arousals) (100–102), but is less frequently used by sleep specialists. Gabapentin at 600 to 1800 mg/day has been reported as effective, reducing the PLM index by 9.8 events (103,104). Minor side effects like dizziness, drowsiness, and enhanced alcohol effects were reported. Clonazepam at 0.5 to 1 mg/daily also has been reported effectively in reduce PLMS and PLM associated to arousals (by 32%) (105,106). The side effects of benzodiazepines should be considered (morning sedation, tolerance, memory dysfunction, somnolence, dizziness) before administering cloazepam. Opiates like oxycodone can improve PLMS reducing PLMI (by 34%) and PLMA (by 23%) (107). Other agents—baclofen, iron sulfate, magnesium, melatonin, erythropoietin, selegiline, apomorphine—used for the treatment of PLMD associated or not to RLS have no demonstrated efficacy.

REFERENCES


Disturbed sleep in patients with Parkinson’s disease (PD) was noted by James Parkinson in his original description of the disorder in 1817 (1). Since that time, considerable knowledge and experience has accumulated regarding the interaction of sleep with PD as well as with other extrapyramidal disorders. The steady growth in this body of knowledge has paralleled our evolving understanding of the physiology of sleep and the etiopathogenesis of clinical disorders of the extra-pyramidal system. More is known about the relationship between sleep and PD than about the interaction between sleep and other extrapyramidal disorders because PD is the most prevalent and the most extensively studied condition of this class of clinical disorders.

MECHANISMS OF INTERFERENCE WITH SLEEP

There are a variety of mechanisms through which extrapyramidal disorders can interfere with sleep. In many instances, particularly in advanced stages of illness when there is severe motor and cognitive dysfunction that require intense pharmacotherapy, sleep may be disrupted concurrently by several different mechanisms that are operative in a single patient.

One of the most basic ways that these conditions impact sleep is through disruption of sleep architecture. Abnormalities in the sequence or duration of sleep stages have been noted in PD and several other extrapyramidal disorders. When a disturbance of sleep architecture occurs in an individual receiving drug therapy for an underlying extrapyramidal syndrome, it is often difficult to determine whether the abnormality represents a primary neurobiological effect of the neurologic disorder or a medication effect. Two additional mechanisms by which sleep may be disturbed in extrapyramidal disorders are: (i) disruption of circadian rhythm and (ii) the appearance of one or more parasomnias. In the latter circumstance, the appearance of a parasomnia may antedate the onset of the typical neurologic signs associated with the underlying basal ganglia disorder. Lastly, the motoric symptoms that are present in most extrapyramidal disorders have significant potential to interrupt sleep. In this regard, either hyperkinetic or hypokinetic abnormalities can interfere with sleep onset or maintenance. One final mechanism of sleep disturbance is associated not with extrapyramidal disorders, but rather with the medications prescribed to treat them. These drugs may exert their influence either through a primary effect on sleep, by exacerbating a previously existent parasomnia, or by inducing nocturnal motoric or behavioral side effects.

To devise a rational corrective therapy for sleep dysfunction appearing in the context of an extrapyramidal disorder, it is critical to recognize which of
these mechanisms, singly or in combination, is contributing to disturbed sleep. At the same time, it is important to avoid choosing a therapy that may exacerbate the underlying neurologic illness. With these considerations in mind, understanding the spectrum of sleep abnormalities that can occur in each of the common extrapyramidal disorders is the next step in planning effective therapy.

PARKINSON’S DISEASE
The Effect of Parkinson’s Disease on Sleep
It is widely accepted that sleep abnormalities are common in PD (2–6). In three large surveys, prominent complaints of sleep disturbance were noted in 74% (3), 82% (7), and 93% (4) of PD patients. In these studies, and most others, it is often difficult to ascertain whether the reported sleep disturbance is related to PD itself or the medications used to treat it. For those patients in whom the sleep disturbance is clearly related to PD alone, it may be difficult to discern which of the many ways that PD can impact sleep is at play. Specifically, it may be difficult to determine whether sleep disruption unrelated to drugs is caused by nocturnal akinesia, nocturnal rigidity and pain, re-emergence of tremor, associated parasomnias, disruption of the circadian rhythm, or a primary alteration of sleep architecture. Some studies have suggested that there are no sleep abnormalities inherent to PD and have found that sleep parameters in untreated PD patients are not different from a normal, age-matched population (8). It should be noted however, that untreated PD patients are those in whom motoric abnormalities such as rigidity, tremor, and akinesia are almost always very mild and nondisabling. To the extent that nocturnal re-emergence of these symptoms contributes to disrupted sleep, mild untreated patients would be expected to suffer from fewer sleep disturbances. Other studies have clearly indicated that there is a disruption of sleep architecture in PD that correlates with disease duration (9). Therefore, most of the mechanisms by which PD can impact sleep can be expected to become more prominent as the illness progresses, again explaining why studies of mild PD patients may not uncover the full spectrum of sleep disturbances in PD. The accurate study of sleep disruption in PD in the future will be aided by the recently developed PD Sleep Score (10,11).

Sleep Fragmentation
Parkinson’s disease patients suffer from an increase in nocturnal arousals (2) and the degree of this abnormality appears to correlate with the severity of the underlying neurologic disorder (12). This propensity to frequent arousals may stem in part from abnormalities in sleep architecture that are present in PD, including reduction in total slow-wave and REM sleep (2,12,13), and a decrease in sleep spindle density (13). The cardinal motor signs of PD, tremor, rigidity, and bradykinesia, also play a role in sleep fragmentation (5,14), and complaints such as immobility in bed and pain related to nocturnal rigidity correlate with abnormalities of sleep. What is not clear is the exact sequence of events that leads to awakening in patients with nocturnal symptoms. Polysomnographic studies suggest that the appearance of tremor (15) usually occurs in stage 1 or 2 sleep, after arousals, and during sleep stage transitions, but occasionally with no relationship to any of these events (15–17). When tremor appears during sleep it is often in an attenuated form consisting of lower amplitude movements and repetitive, but nonalternating muscle activity of the previously tremorous muscles (18,19). The mild tremor which occurs during
sleep stage 1 or 2 may not result in an awakening, but more severe tremor can appear shortly after an awakening that occurs without any particular cause (20), and is often reported by patients to be associated with sleep disturbance. By the same token, severe tremor may prevent patients from initiating sleep at bedtime. Bradykinesia can also contribute to disturbed sleep. In some patients, especially those with advanced disease in whom the effect of dopaminergic medication wears off as the night progresses, sleep is disturbed because of severe immobility and inability to shift to a comfortable position (14). Lees et al. (4) found this to be present in 65% of PD patients surveyed, and to be the most troublesome parkinsonian sleep complaint in 39%. As another indication of the impact of nocturnal bradykinesia, 79% had the need to void at night, yet 35% were unable to get out of bed unaided. Similarly, patients in whom significant rigidity appears during an awakening may complain of associated pain which prevents the resumption of sleep.

The potential for the re-emergence of motoric parkinsonian symptoms to disrupt sleep suggests that nighttime dosages of anti-Parkinson medications might improve sleep. There is some controversy, however, about whether a bedtime dose of levodopa or a dopamine agonist improves sleep in PD (5). One large survey (4) indicated that sleep complaints in PD are not related to the timing of the last daily dosage of anti-Parkinson medication. But this study did not separately analyze this relationship in advanced patients whose sleep is more likely to be interrupted by immobility, rigidity, or tremor. In many moderately severe to advanced PD patients, nocturnal amelioration of significant motoric signs of PD is often an important therapeutic goal in attempting to normalize sleep (21,22). The most useful strategy to achieve this goal is the use of a bedtime dose of a dopaminergic agent with a relatively long efficacy half-life. Long-acting dopamine agonists are useful for this purpose, and perhaps even more useful are the sustained release levodopa preparations (23,24). The use of a catechol-ortho-methyl-transferase (COMT) inhibiting agent along with levodopa at bedtime might further prolong the dopaminergic effect during the night. Bedtime dosing in PD patients with nocturnal disabilities results in less tremor, reduced rigidity, improved mobility, and fewer awakenings, at least during the early part of the night and often through the entire night (21,22,24). Some patients may require additional dosing of a sustained release or standard levodopa preparation after early awakening to allow uninterrupted sleep for the remainder of the night.

The question remains as to whether bedtime dopaminergic agents are useful in PD patients with milder disease and less potential for sleep-disrupting motor symptoms. Low dosages of levodopa can promote sleep in some PD patients with insomnia unrelated to nocturnal emergence of tremor or immobility (25). However, higher bedtime dosages in such patients can be counterproductive and may actually prolong sleep latency (20). Van Hilten et al. (5), for example, found that in less severe PD patients, sleep disruption was positively correlated with the total daily dosage of levodopa or dopamine agonist. A caveat is that a bedtime dose of a dopaminergic medication, irrespective of its purpose, has the potential to induce vivid dreaming and nocturnal hallucinosis, both of which are often associated with reduced sleep efficiency, less total sleep time, and a reduction in REM sleep (26). This side effect, should it occur, can be dealt with by reducing or eliminating the bedtime dose of the offending dopaminergic drug or by appropriate pharmacotherapy, as will be discussed later.

Many PD patients, or their physicians, in the belief that anti-Parkinson medication is required round the clock, initiate bedtime dosing of levodopa or a
dopamine agonist in the absence of nocturnal motor symptoms or PD-related sleep disturbance. This practice should be discouraged because it unnecessarily raises the dosages of medication and, in some patients, dopaminergic drugs can actually interfere with sleep by inducing dyskinesias (see below) or through the aforementioned tendency for high dosages to induce insomnia. Bedtime dosing with dopaminergic medications can either improve or interfere with sleep and a clinical judgment in individual patients needs to be made to determine which effect is likely to prevail. In general, advanced PD patients who experience nocturnal emergence of motoric symptoms, but do not suffer from hallucinations, are more likely to benefit from bedtime dosing, and milder patients stand a greater chance of experiencing medication-related sleep disturbance.

In addition to pharmacologic treatment of the sleep-disrupting motoric features of PD, several nonpharmacologic strategies are also useful. To minimize the effect of nocturnal immobility, the use of satin sheets can be recommended as a means of reducing friction between the body and bed sheets and allowing easier mobility in bed. Ambient stimuli (noises, drafts, a restless bed partner), which might lead to brief arousals followed by a major emergence of tremor or rigidity and pain should be avoided to the extent possible.

**Depression**
Depression occurs in over 40% of PD patients (27). Depressed PD patients have a higher incidence of sleep complaints than those who are not depressed (28,29). The typical clinical and polygraphically defined sleep changes of depression, including shortened REM sleep latency, increased arousals, and early awakening, occur more frequently in depressed than nondepressed PD patients (30).

The relative contributions of depression and the underlying features of PD to disturbed sleep can be difficult to separate. Menza and Rosen (29), while noting poorer overall sleep in depressed PD patients, found that compared to depression, age, illness-related variables, and levodopa dose were major determinants of sleep disturbance in this population. Starkstein et al. (28), on the other hand, found that depression correlated with sleep disturbance more than any motor or demographic variable. Furthermore, these investigators and others (31) found a graded relationship between sleep dysfunction and depression, the greatest sleep disruption appearing in the most seriously depressed PD patients. Depression-related sleep disturbances in PD are treated in much the same manner as those in the non-PD population, with only minor differences in choices of drugs. The sedating antidepressants such as amitriptyline or doxepin administered at bedtime are very useful for this purpose (32). For some PD patients, especially those with dementia, agents with lower anticholinergic properties such as nortriptyline are a better choice to avoid exacerbating their cognitive deficit. There is some controversy as to whether the selective serotonin reuptake inhibitor (SSRI) drugs exacerbate PD in a small percentage of patients (33). Also, the use of either SSRI or tricyclic antidepressants in patients receiving selegiline for PD has been reported to cause a severe, potentially fatal interaction in a small number of patients (34). However, a recent survey of PD specialists revealed that these adverse interactions were quite rare and SSRI agents were the first choice of therapy for depression in PD for 51% of the respondents (35). In this same survey, the most common reason to choose tricyclic antidepressants instead, was their potential to improve sleep.
Circadian-Rhythm Disorders
Reversal of the sleep cycle is common in PD, especially in elderly patients with advanced disease. Typically, affected patients experience frequent napping during the day and are awake at night. The cause for this circadian abnormality is multifactorial. Many of the standard external markers of diurnal rhythmicity such as mealtime and scheduled activities are altered by PD and by the timing of medications used to treat the disease. For example, meals may be scheduled at unusual times to coincide with peak drug effect or to avoid an adverse drug interaction at scheduled medication dosing times. Also, periodic immobility can occur during the day as a result of fluctuations in response to dopaminergic medications. Similarly, a natural circadian pattern of worsening and improvement in dopamine-dependent functions (36,37) may dictate certain periods of the waking day when the patient is ambulatory and active (typically the early morning) and other times when there is relative immobility and a tendency to nap (typically late afternoon). Factor et al. found that circadian changes in symptom severity were most common in more advanced PD patients (38). Lastly, the sedative effect of anti-Parkinson medications experienced by some patients leads to daytime somnolence and napping, with resultant nighttime wakefulness. To reverse the sleep cycle toward normalcy, attempts should be made to restore mealtime to a typical morning, noon, and early evening pattern and to plan scheduled activities during times of predicted somnolence, whether drug-induced or related to the patient’s spontaneous diurnal cycle. The sedating effects of anti-Parkinson medication can be countered to some extent by administration of a daytime dosage of selegiline (39,40). This drug, which is metabolized to amphetamine derivatives, has potential alerting properties. Occasionally, stimulant agents such as pemoline, methylphenidate, or dextroamphetamine are used (32), but tachyphylaxis and the occasional induction of hallucinosis in the elderly or cognitively impaired PD patient limit their use. The potential for PD patients to develop hallucinosis when using wake-promoting drugs might be avoided through the use of an alerting drug such as modafinil, which has little or no dopaminergic activity (41), and has been shown to be safe and effective in treating somnolence associated with PD (42,43).

The advanced sleep phase syndrome, although relatively common in the general elderly population, is even more prominent in PD. In some patients, the final daily dosage of anti-Parkinson medication is so early in the day that there is wearing off of its motoric benefit well before bedtime, leaving the patient relatively immobile and unstimulated in the early evening. The advanced sleep phase may coincide with this period of evening immobility, leaving the PD patient at risk of falling asleep for the night. In this circumstance an additional evening dosage of levodopa or dopamine agonist two to three hours prior to the desired bedtime may ameliorate the problem. In refractory cases, the use of nighttime phototherapy as a zeitgeber can be considered to shift the endogenous clock governing sleep toward a more normal time of the night (44). Of interest is the recent discovery that this endogenous clock can be entrained by light application to extra-retinal sites on the body such as the popliteal space where photoreceptors in intravascular hemoglobin are stimulated (45).

Respiratory Disorders
Significant respiratory dysfunction is not seen in mild PD (46), but in more advanced patients there may be an increased frequency of obstructive and
central apneas and arterial oxygen desaturations during sleep (47). In at least one study, sleep apnea was not observed in any PD patients irrespective of the severity of the underlying illness, although tachypnea during REM sleep was commonly observed (48). However, in a more recent case-control study, subtle signs of sleep apnea were found in nearly half of PD patients consisting of an increased apnea hypopnea index without associated evidence of oxygen desaturation (49). In the same study, PD patients with high body-mass index were more likely to have overt sleep apnea. Although there is little exact clinical data, it is common clinical experience that obstructive sleep apnea is more common in multiple system atrophy than in idiopathic PD.

The Effect of Anti-Parkinson Drugs on Sleep

Although, as mentioned, anti-Parkinson drugs can improve sleep by lessening the nocturnal motor symptoms of PD, they also have the potential to impact sleep adversely in three ways: (i) by inducing unwanted sleep, (ii) by inhibiting normal sleep, (iii) by resulting in motoric or behavioral side effects that interrupt sleep.

Daytime Somnolence Related to Anti-Parkinson Drugs

Most of the commonly used anti-Parkinson medications including levodopa, amantadine, dopamine agonists, COMT inhibitors, and anticholinergic agents have some potential to induce excessive daytime somnolence (EDS). Selegiline, on the other hand is virtually never associated with excessive daytime sleepiness. Among the anti-Parkinson drugs, levodopa, the most commonly used agent, can cause medication related somnolence. In PD patients evaluated by polysomnography (PSG), the total daily levodopa dose has been found to be predictive of daytime somnolence. Typically, patients complain of an irresistible desire to sleep within 30 minutes of a dosage of standard or sustained release carbidopa/levodopa. Nau-sieda (3) found that polysomnographic study in such patients demonstrated a transition from stage 1 to stage 2 sleep within 30 to 60 minutes of a dosage of levodopa, but multiple sleep latency tests in these patients were normal if evaluated while they were not under treatment with levodopa. The pathogenesis of this phenomenon is unclear since levodopa infusion, at least at high levels, suppresses REM sleep (50). It is likely that in some PD patients exhibiting this apparent relationship, the appearance of EDS simply reflects the high incidence of this problem in a normal aged population that occurs independently of levodopa administration. In these patients, a cause-effect relationship between levodopa and somnolence can be mistakenly assumed by the patient or the physician. In one study comparing PD patients and age-matched healthy individuals, the incidence of daytime somnolence was identical in both groups (51). While some excessive daytime somnolence in PD undoubtedly occurs independent of medications being administered, the striking temporal relationship between somnolence and the administration of the last dosage of levodopa in some patients suggests that at least in these circumstances a true cause-effect relationship exists.

Recently, a potentially dangerous form of somnolence leading to serious motor vehicle accidents has been reported in patients being treated with dopamine agonists. Eight PD patients taking pramipexole and one receiving ropinirole fell asleep while driving (52). Similar episodes have also been described in patients being treated with the dopamine agonists bromocriptine, pergolide, and lisuride (53). Because of the suddenness of sleep onset in some cases, these episodes are sometimes labeled
“sleep attacks.” A meta-analysis of 20 publications reporting similar episodes in parkinsonian patients concluded that the attacks are a class effect for a variety of dopaminergic medications, but they have been most commonly reported in patients receiving either pramipexole or ropinirole (54). Some investigators question whether these attacks, or somnolence in general, are related to pharmacotherapy, as opposed to the underlying pathology of PD (55), whereas others have found excessive daytime sleepiness to correlate with both disease severity and Parkinson medications (56). In the earliest and mildest patients, however, the role of the underlying disease may be minimal since untreated de novo patients do not differ from healthy controls in Epworth Sleepiness Scale scores (57). Ambulatory polysomnography in PD patients has confirmed that patients experiencing sleep attacks do have a higher degree of daytime somnolence in that they have higher Epworth Sleepiness Scale scores, and a higher proportion of micro-sleeps and intentional naps (58). Further ambulatory polysomnography study has shown that sudden sleep occurring against a background of wakefulness (i.e., sleep attacks), do occur in Parkinson patients, albeit rarely (59). In one patient experiencing sleep attacks, PSG documented slow eye movements and K-complexes only 10 seconds after documented wakefulness and progression to sleep stage 2 within 60 seconds (60). It is clear that EDS in general and sleep attacks in particular, are a risk factor for falling asleep while driving with resultant accidents (61).

The treatment of this problem can be difficult. One simple strategy to control medication-related somnolence is to alter environmental stimuli and planned activity schedules in the immediate postdose period, when somnolence is most likely to occur. During this at-risk period dark, quiet, poorly ventilated rooms should be avoided and planned vigorous activities such as a morning or afternoon walk can be scheduled. Fortunately, from a motoric point of view, many PD patients are best able to engage in such physically demanding activities immediately after a dosage of medication, when they are “on.” If this strategy fails, an attempt can be made to change to another anti-Parkinson drug. Some patients may be less somnolent on standard carbidopa/levodopa than on the sustained release preparation (32) and in a small percentage of patients the reverse is true. Similarly, the available dopamine agonists may each have different potential to induce somnolence in a given patient. Stimulant drugs are occasionally indicated to combat EDS in PD, but must be used with caution in this patient population, especially because of the risk of behavioral side effects (32). As mentioned previously, there is some reason to believe that stimulant drugs without dopaminergic properties may be better tolerated (41). Accordingly, Modafinil, shown to be effective in treating EDS in PD in two controlled studies, is a good choice for this purpose (42,43).

**Insomnia Related to Anti-Parkinson Medications**

Anti-Parkinson drugs can also result in insomnia. Selegiline, because of its potentially alerting metabolites can result in insomnia, especially when administered later in the day than noon (32). Levodopa has the potential to alter sleep architecture at least in the period immediately after the initiation of therapy (51,62) and possibly chronically (63). As discussed previously, in some patients, dopaminergic agents administered at high dosages late in the evening have the potential to increase sleep latency and result in sleep fragmentation (50). Accordingly, for most patients, if a late evening dosage of levodopa or dopamine agonist is not required to control nocturnal motoric symptoms, it should be eliminated, decreased, and/or distanced from bedtime.
Nocturnal Neuropsychiatric Disturbances Related to Medication

A variety of behavioral side effects are possible as a result of anti-Parkinson therapy, including memory loss, confusion, paranoia, psychosis, hallucinations, and vivid dreaming (32). Among these adverse effects, nocturnal hallucinations and vivid dreaming have the greatest potential to interrupt sleep. After chronic dopaminergic therapy, some patients report that dreams become increasingly vivid, although dream content remains unchanged. In Lees et al.’s survey of 250 PD patients, 48% acknowledged experiencing vivid dreams or nightmares and 9% identified this as their major sleep complaint (4). Medication-induced vivid dreams not only have the potential to interrupt sleep, but are considered by some to be a premonitory sign of hallucinations and advanced psychosis (3,64), suggesting that they not be left untreated. This progression is most likely to occur in PD patients who are aged, cognitively impaired, and already have disturbed nocturnal sleep of any cause (65,66). A recent study, however, suggested that vivid dreams are common among patients who hallucinate, but vivid dreams among PD patients who are not already hallucinating have little predictive value for the development of this complication (67). Medications are major contributors to the appearance of hallucinations in PD. Therefore, when nocturnal hallucinations appear, it is advisable to reduce the bedtime dosage of anti-Parkinson medication and/or distance it from bedtime. Although levodopa and the dopamine agonists are the most common offenders, anticholinergic drugs, including the anticholinergic antidepressant agents and amantadine, can also result in this syndrome and should be adjusted at first before attempting to taper the more clinically effective primary dopaminergic agents. Ultimately, a strategy of downward titration of late evening and bedtime anti-Parkinson medications is undertaken while being vigilant for the inevitable re-emergence of disabling motoric signs of PD. If downward titration of anti-Parkinson drugs cannot be successfully accomplished without seriously exacerbating parkinsonism, small dosages of an atypical antipsychotic agents such as quetiapine can be administered at bedtime, usually without fear of significantly worsening the underlying illness (68). Similarly, olanzapine (69) and risperidone (70), each with reduced potential for extrapyramidal side effects, can be used at bedtime. If these strategies fail, low dosages of the atypical neuroleptic clozapine (12.5–50 mg/day) can be administered (71). All of these agents can cause daytime somnolence if taken other than at bedtime. Clozapine must be used with caution because of its potential to induce agranulocytosis in a small percentage of patients.

Medication-Induced Involuntary Movements and Restlessness

Dyskinesias related to dopaminergic therapy are usually choreiform or dystonic. In some patients both patterns are found (72). Typically, choreiform dyskinesias occur when the dopaminergic agent is manifesting its greatest central effect (peak dose dyskinesia); less commonly they occur when the central effect is just beginning to be manifest and again when it is just beginning to wane (biphasic dyskinesia). Choreiform dyskinesias, irrespective of their temporal pattern of occurrence, tend not to persist to a major degree or emerge during sleep and are seldom the cause of self-reported sleep disturbance. Dystonic dyskinesias, on the other hand, are more likely to impact sleep. While dystonia can also occur de novo in PD, it is more commonly related to the administration of dopaminergic medications. Dystonic dyskinesias, like the choreic form, can occur concurrent with the peak effect of dopaminergic agents or in a biphasic pattern. Even more commonly,
these abnormal movements occur exclusively at the end of an interdose period when the central effects of medication have nearly or totally worn off. End-of-dose dystonia can be especially prominent upon awakening in the morning after a prolonged medication-free interval while asleep. In this pattern of occurrence, referred to as early morning dystonia, the lower extremities are usually involved with painful plantar flexion of the feet and curling of the toes. Less commonly, the facial and upper extremity musculatures are affected as well. One-third of PD patients surveyed by Lees et al. experienced nocturnal dystonia and 20% experienced early morning foot dystonia (4). Since nocturnal or early morning dystonia is most commonly related to the waning central effect of levodopa as the night progresses, the most useful treatment is to institute bedtime therapy with a relatively long-acting dopaminergic agent such as controlled release carbidopa/levodopa, or a long-acting dopamine agonist. Pahwa et al. (22) noted resolution of early morning dystonia in 8 of 14 patients, after changing from standard to controlled release carbidopa/levodopa. In some patients, a bedtime dosage of baclofen will also ameliorate this symptom. An additional strategy employed by some patients to prevent early morning dystonia is to set their alarm so that they can administer a dose of levodopa 30 to 45 minutes earlier than their usual waking time and then return to sleep to awaken permanently after the medication has begun to take effect. Botulinum toxin and apomorphine have been used successfully to treat early morning dystonia (73). Another form of dystonia, blepharospasm, occurs in PD patients at the beginning of the night, but is not clearly related to dopaminergic medications (74).

Levodopa-induced myoclonus occurs predominantly, but not exclusively at night (75). It typically involves axial and proximal muscles and can appear during non-REM sleep, as often as 30 times per night. These movements usually emerge only after chronic administration of levodopa. Surprisingly, they seldom interrupt the sleep of the PD patient, but can pose a problem for the bed partner. It has been postulated that levodopa-induced myoclonus is related to enhanced central serotonergic activity, since serotonin blocking agents have been reported to be an effective treatment (75).

Akathisia, an irresistible internal desire to move, is seen in some PD patients receiving levodopa and, very rarely, in the untreated patient. It can be distinguished from the restless legs syndrome by its lack of relationship to recumbency, by the absence of associated sensory phenomena, and by its involvement of the entire body, not just the legs. Although not totally confined to bedtime, it is commonly nocturnal and can inhibit sleep initiation (76). In individual patients, akathisia has a variable relationship to the timing of levodopa administration and can occur in either the “on” or “off” state (77). Accordingly, in treating PD patients with severe nocturnal akathisia it is sometimes necessary to experiment by first increasing and then decreasing the evening dosage of dopaminergic medication. Should both approaches fail, a bedtime dosage of the atypical neuroleptic clozapine is very effective in treating this symptom, keeping in mind its potentially severe hematologic side effects (76).

Parasomnias in Parkinson’s Disease
Parkinson’s disease patients can experience abnormal movements and behaviors during sleep (parasomnias) among which are somnambulism, somniloquy, nightmares, night terrors, REM sleep behavior disorder (RBD), and periodic limb movements of sleep (PLMS) (78,79). Since all of these sleep-related phenomena can also
occur in an ostensibly healthy population, the question remains as to whether their incidence is greater in PD patients. The exact frequency of their occurrence in PD is not totally certain but the two parasomnias that are most frequently reported in parkinsonian patients are RBD and PLMS.

In RBD there is a failure of the normal suppression of electromyographic (EMG) activity during REM sleep and an absence of atonia (78). Affected individuals physically act out their dreams, often incurring serious injury as they move, run, or dive out of bed in the course of a dream. That RBD appears in PD is well established, (26,80), and, in fact, it is probably more common than realized, as evident by the report of Comella et al. (26) who unexpectedly discovered RBD in 50% of ten PD patients undergoing screening polysomnography as part of a research protocol. A case has been reported in which there were no parkinsonian features in life, but Lewy bodies were found at postmortem in the locus ceruleus and substantia nigra (81). Another report detailed three PD patients in whom clinically apparent RBD emerged only after beginning selegiline therapy (82). The notion that there is an inter-relationship between PD and RBD has been strengthened by several reports demonstrating that patients with RBD often develop PD later in life (83,84). Schenck et al. (84) followed 29 older men with RBD and found that 38% developed PD at a mean interval of 13 years after the diagnosis of their parasomnia. In a series of 33 unselected PD patients undergoing polysomnography, 58% had REM sleep without atonia and of these 42% had no behavioral manifestations of RBD, suggesting that they have a preclinical form (85). The relationship of RBD to Lewy body pathology was also demonstrated by a patient who developed diffuse Lewy body disease 17 years after onset of RBD (86). The presence of RBD in PD has been found to be associated with an increased risk of manifesting hallucinations (87,88). Most hypotheses explaining the cooccurrence of RBD and PD have centered around the fact that there is involvement of the pedunculopontine nucleus in both conditions, a structure that plays a major role in REM atonia and is reciprocally connected to the substantia nigra (83,84). The finding of pontine pathology on magnetic resonance imaging in RBD patients supports this notion (89).

Because of the potential for serious injury to the patient and for disruption of both the patient’s and bed partner’s sleep, serious attention should be given to treating this disorder in PD. The potential for injury while acting out a dream while standing is even greater than average in PD, since these patients may be especially prone to fall in the middle of the night when anti-Parkinson medications have worn off. For PD patients with RBD, the treatment is much the same as in non-PD patients, namely clonazepam at bedtime. Because of the long efficacy half life of clonazepam, a bedtime dosage can result in daytime somnolence. Accordingly, it is often useful to experiment with dosage times as far in advance of bedtime as possible in order to avoid this potential complication. Parkinson’s patients, who are not yet on levodopa therapy, may occasionally find that this preparation ameliorates both their PD symptoms and RBD (83).

The syndrome of periodic limb movements of sleep (PLMS) is commonly encountered in PD patients although there is little documentation in the literature as to its exact incidence in this population (90). In one study, the incidence of PLMS in PD patients increased in proportion to the severity of the parkinsonian symptoms (91). This syndrome, often erroneously referred to as nocturnal myoclonus, consists of stereotypic movements of the lower extremities characterized by extension of the great toe and ankle and flexion at the knee and sometimes the
hip. Rarely, the upper extremities are involved. The patient may or may not be aware of these movements. Occasionally, only the bed partner is disturbed by them. PLMS is especially common in patients suffering from the restless legs syndrome (RLS). The incidence of RLS seems definitely greater in PD; one recent study found RLS in 12% of PD patients versus 2% of controls (92). Almost all patients with RLS also experience PLMS, but not all patients suffering from PLMS have RLS. As is the case with RBD, the treatment of PLMS in PD is similar to that in the non-PD population (93) with one exception. Levodopa is the drug of choice for occasional RLS and PLMS in the non-PD population, but PD patients may already be receiving this medication. In this case, a bedtime dosage of sustained release levodopa should be added, if not already a part of the patient’s regimen. Levodopa is best avoided to treat daily occurring RLS/PLMS since frequent administration is associated with an incidence of augmentation (symptoms appearing progressively earlier in the day) as high as 82% (94). Dopamine agonists administered at bedtime are the most useful therapy for this condition when it occurs nightly, since there is a much lower incidence of augmentation (95,96). Clonazepam is the next most effective therapy followed by opioids such as oxycodone or propoxyphene. Benzodiazepines, other than clonazepam, such as triazolam are useful, especially for reducing PLMS-related arousals (97). Combination therapy with two agents is sometimes required in these patients (93).

Another parasomnia, somnambulism, has been reported to appear with increased frequency in PD. Merello et al. (98) reported a 5% incidence of sleep walking among 312 PD patients studied, which is twice the frequency observed in a study of a large non-PD population (99).

Effect of Sleep on Parkinson’s Disease
Sleep typically has a salutary effect on the symptoms of PD. The most common diurnal pattern of symptom severity in PD is that of improvement in motoric function in the morning just after arising. This is paralleled by improvement in nonmotoric dopamine-dependent functions at the same time of day (36). In one study, 25% of PD patients reported a greater than 40% improvement in PD symptoms following nocturnal sleep, with a duration of benefit ranging from one-half to three hours (100). This effect was most prominent in younger and milder patients. Young patients with autosomal recessive parkinsonism due to Parkin gene mutations are especially likely to demonstrate sleep benefit (101). However, two subsequent studies found sleep benefit of this type to be most common in patients with longer disease duration (98,102). In these two surveys the incidence of sleep benefit was still higher, ranging between 33% and 55% of PD patients.

The beneficial effect of sleep on the symptoms of PD can be so prominent in some patients as to eliminate the need for anti-Parkinson medications for the first half of the day. The mechanisms underlying this phenomenon are not yet fully understood. Comella et al. (100) hypothesized that sleep benefit may result from the effect of sleep on residual dopamine storage, while Currie et al. (102) suggested that patients taking higher dosages of levodopa have higher residual tissue levodopa levels in the morning. Merello et al.’s results (98) argue against both of these theories. Their findings indicated that sleep benefit does not correlate with the use of controlled release levodopa, which would be expected to enhance residual tissue levodopa in the morning. They also noted that PD patients with the least restful sleep and the most nocturnal awakenings appear to have the
greatest sleep benefit, arguing against the hypothesis that the restorative properties of sleep improve dopamine storage.

**MULTIPLE SYSTEM ATROPHY**

Multiple system atrophy (MSA) is a degenerative extrapyramidal disorder characterized by parkinsonism, symptoms of cerebellar dysfunction, and autonomic failure, each to various degrees of severity in individual patients. The condition is felt to represent the combined clinical and histologic result of its component disorders, striatoni gral degeneration (resulting in parkinsonism), olivopontocerebellar atrophy (resulting in cerebellar signs), and Shy Drager syndrome (resulting in prominent autonomic symptoms) (103). Although these component symptoms can occur in any combination, parkinsonism is present in the great majority of patients, followed in frequency by autonomic failure and cerebellar dysfunction.

Disrupted sleep patterns are common in MSA. Manni et al. (104) studied patients with MSA and autonomic failure and found their sleep to be characterized by reduced total sleep time, less REM sleep time, and prolonged REM latency. They also noted either obstructive, central, or mixed sleep apnea in approximately half of this patient population. Patients with the most severe autonomic dysfunction were at greatest risk for developing abnormal breathing during sleep. Ghorayeb et al. (105) compared the incidence and types of sleep disorders between PD and MSA in 62 and 57 unselected patients, respectively. Seventy percent of MSA patients complained of sleep disorders compared with 51% of those with PD. Among MSA patients, the most common sleep problems were vocalization (60%), sleep fragmentation (53%), REM sleep behavior disorder (48%), and nocturnal stridor (19%). The incidence of these sleep disorders was higher in MSA than PD, in every instance except sleep fragmentation. In general, sleep problems in MSA were associated with more severe motor symptoms, longer duration of disease, and longer levodopa treatment.

A serious and potentially fatal sleep related breathing disorder in MSA is nocturnal vocal cord abductor paralysis (106–108). This symptom has been found to be the presenting sign of MSA in as many as 4% of such patients (109). In the early stages of this dysfunction, vocal cord movement may be normal during wakefulness and only exhibit paradoxical movements during sleep. At this stage, suspected vocal cord paralysis can only be confirmed reliably by laryngoscopy performed during sleep (108). With further progression there may be both daytime and nighttime inspiratory stridor. At night, this manifests as peculiar snoring which is different in pitch from ordinary soft palate snoring, due to its origin from the vibrating glottis (107,108). Sudden nocturnal death has occurred in several MSA patients with this vocal cord syndrome, presumably due to respiratory arrest (107,110). Because of the potential seriousness of this syndrome, careful investigation, possibly including sleep laryngoscopy, is indicated in the MSA patient exhibiting loud, high-pitched snoring. If vocal cord abductor paralysis is demonstrated, there should be consideration of early tracheostomy (106,107,110). More recently, continuous positive airway pressure (CPAP) has been successfully used to treat nocturnal stridor, with reduction in mortality due to this complication (111). However, more advanced patients may be less tolerant and compliant with this therapy (112).

Another sleep related disorder that has become increasingly recognized in MSA is RBD. The high incidence or RBD in MSA, PD, and dementia with Lewy
bodies has led to the belief that RBD is a clinical marker for all of the synucleinopathies (113), although some investigators have recently questioned the validity of this association (114). As in the case in PD, RBD can occasionally be the presenting symptom of MSA (115). In addition, its overall prevalence in clinically established MSA is probably much higher than previously suspected. Plazzi et al. (116) reported the results of polysomnography in 39 consecutive patients with MSA. Sixty-nine percent of these patients reported nocturnal paradoxical episodes related to dreams, suggesting RBD. By polysomnographic evaluation 90% of these patients were felt to have RBD. Twelve of the patients in this study reported symptoms of RBD for at least one year preceding the clinical onset of MSA, again confirming the notion that RBD not infrequently antedates the extrapyramidal disorders with which it is associated. Other forms of sleep disturbance were documented in this study. Six patients demonstrated obstructive sleep apnea, eight had laryngeal stridor, and ten had periodic limb movements of sleep. Based on these results, the authors suggested that RBD may be the most common sleep disorder in MSA rather than sleep breathing disorders. The finding of absent REM atonia in a high percentage of MSA patients without sleep complaints supports this notion (117). An important and practical consideration is whether clonazepam, one of the most useful therapies for RBD, can be used in this patient population since it could exacerbate nocturnal stridor or OSA. In such MSA patients with coexistent OSA or stridor and RBD, melatonin has been suggested as an alternative therapy (118).

Another potential sleep related problem in MSA is nocturnal hypertension. Patients with Shy Drager syndrome frequently require medications such as fludrocortisone or midodrine to counteract orthostatic hypotension occurring during the day. These agents may result in significant hypertension while the patient is asleep and recumbent. It is usually advised that patients requiring these agents not take a large dosage close to bedtime. In addition, elevation of the head of the bed is often required to reduce the potential for nocturnal recumbent hypertension.

PROGRESSIVE SUPRANUCLEAR PALSY

Progressive supranuclear palsy (PSP) is a degenerative central nervous system disorder characterized by supranuclear gaze palsy, parkinsonism, axial dystonia and rigidity, and early gait disturbance (119). The most consistent sleep abnormality reported in PSP is an absence or severe reduction of REM sleep (114,120,121). This reduction in REM sleep results from REM periods that are both fewer in number and shorter in duration. Additionally, PSP patients have been found to have shorter total sleep time, reduced sleep efficiency, a marked reduction in sleep spindles, and atonic slow-wave sleep (121). REM sleep atonia, on the other hand, has classically been noted to be preserved in PSP (121), although at least one survey found that 27% of PSP patients had more than 50% of REM sleep without atonia and 13% had overt RBD (114). Frequent nocturnal awakenings are common in PSP (120–123), and several studies have concluded that the number of awakenings and reduction of sleep time in PSP is proportional to the severity of the underlying neurologic symptoms (120,122). Sleep related respiratory disorders are typically not a source of major disability in PSP. Aldrich et al. (120) found only mild central, obstructive, or mixed apneas in PSP and noted that they did not constitute a major source of sleep disability. Arnulf et al. (114) noted similar apnea/hypopnea indexes in PSP patients and normal control subjects. Other
investigators were unable to detect evidence of even mild nocturnal respiratory
dysfunction in PSP patients, including those with severe underlying neurologic
dysfunction and those with a significant daytime disturbance of voluntary
respiration (122).

OTHER PARKINSONIAN SYNDROMES

A variety of other neurologic conditions may be associated with parkinsonian
symptoms. Conditions such as corticobasal degeneration, neurodegeneration
with brain iron accumulation, and X-linked dystonia parkinsonism (Lubag) are
relatively uncommon and their potential interaction with sleep has not been well
documented or studied. To the extent that patients with these disorders manifest
nocturnal rigidity and akinesia, they are susceptible to the same types of sleep dis-
ruption caused by these motor symptoms as those experienced by PD patients.
Another parkinsonian syndrome, diffuse Lewy body disease, is characterized by
parkinsonian features and early dementia. These patients are even more susceptible
to drug induced nocturnal hallucinosis and vivid dreaming than PD patients. In
this syndrome, similar to other synucleinopathies such as PD, RBD can appear
years before typical motor or cognitive symptoms (86).

DYSTONIA

Dystonia is an abnormal involuntary movement characterized by sustained and
twisting postures. The pattern of body parts involved may be focal or generalized.
One of the most common generalized dystonias is idiopathic torsion dystonia, and
the most common focal dystonias are spasmodic torticollis and writer’s cramp.
Considerable investigation has centered around the degree to which dystonia per-
sists or is altered during sleep. Most observers have suggested that in both gener-
alized and focal dystonias the abnormal movement seen in the waking state is
improved during sleep, and in some cases totally abolished (15,123–125). Fish
et al. (15) noted that dystonic movements, although greatly attenuated during
sleep, were still present in stage 1 and 2 sleep, as well as during awakenings and
lightening of sleep. In a parallel study the same investigators demonstrated that
dystonia disappears during REM sleep, and normal REM sleep atonia is main-
tained. This was further documented by the demonstration of reduced motor
responses to scalp magnetic stimulation during REM sleep (126). Similarly, in
two studies, oromandibular focal dystonia improved, especially in deeper sleep,
but never totally disappeared (123,124).

The sleep benefit in spasmodic torticollis may be considerably more striking.
In this condition, Lobbezoo et al. (125) demonstrated that patients experienced a
significant decrease in abnormal cervical muscle activity immediately upon lying
down, with subsequent disappearance of all abnormal muscle activity during the
transition to light non-REM sleep. In this form of dystonia, which exclusively
involves axial postural muscles, the beneficial effects of recumbency appeared to
considerably enhance the primary benefit derived from sleep.

Although dystonic movements are typically improved at night, patients with
this condition still suffer from a variety of sleep disturbances including increased
sleep latency (125,127), reduced sleep efficiency (124,127), and reduced slow and
REM sleep (124). Treatment of the underlying dystonic disorder may influence
these sleep abnormalities. Jankel et al. (128) noted that unilateral stereotactic thalamotomy for idiopathic torsion dystonia, not only improved the abnormal involuntary movements but also normalized previously experienced sleep abnormalities such as reduced REM sleep. Whether improvement in sleep parameters in this circumstance reflects a primary physiologic effect of the thalamic lesion or simply corresponds to the benefit of less severe nocturnal dystonia after treatment remains uncertain.

Two forms of dystonia deserve special mention because of their unique relationship to sleep. Nocturnal paroxysmal dystonia (NPD) is a symptom complex occurring during non-REM sleep. It is characterized by sudden onset of axial and appendicular dystonic posturing often associated with a variety of seemingly purposeful movements or vocalizations (129). Occasionally, similar episodes occur during the day while awake. Despite the fact that the electroencephalogram is often normal during these attacks, their clinical resemblance to frontal lobe epilepsy, their excellent response to carbamazepine, and the appearance of typical seizures in the same patient at other times suggest that NPD is epileptic in origin and not truly a primary movement disorder (130,131). A preferred name for this syndrome is nocturnal frontal lobe epilepsy (NFLE), although for many patients in this category, nocturnal paroxysmal dystonia is an appropriate descriptive term, if physiologically imprecise. In a study of 40 patients with an autosomal dominant form of NFLE, over 42% were found to manifest dystonic or dyskinetic movements during the typical nocturnal episodes (132). In many instances, these patients had previously been diagnosed as having a parasomnia based on their abnormal nocturnal movements and behavior.

Dopa responsive dystonia (DRD) is an autosomal dominant, heritable condition characterized by a marked diurnal variation in severity of symptoms. In this condition, dystonia is typically least severe in the morning and then worsens as the day progresses, only to be relieved by sleep. DRD is known to be remarkably responsive to small dosages of levodopa. The known genetic basis for this condition explains the marked benefit derived from levodopa. The responsible gene for DRD encodes GTP cyclohydrolase I, which is the rate limiting enzyme in the synthesis of tetrahydrobiopterin, an important cofactor in the metabolic pathway for dopamine (133). Levodopa, which bypasses this synthetic blockade, not only has the potential to completely reverse dystonia in DRD but may also improve the insomnia which sometimes accompanies this disorder.

HUNTINGTON’S DISEASE AND CHOREA

The great majority of sleep investigations in choreic disorders have been performed in patients with the relatively common adult condition Huntington’s disease (HD). Polysomnographic evaluations in HD have revealed a variety of sleep disturbances including reduced sleep efficiency (134–136), prolonged sleep latency (135), reduced slow-wave sleep (134–136), frequent awakenings (135), and increased sleep spindle density (13,135,136). Chorea improves during sleep, but never completely disappears (15,136), often appearing after awakenings, during lightening of sleep, or in stage 1 sleep (15). One group of investigators found that sleep abnormalities in HD correlated with the duration and severity of clinical symptoms of the disorder as well as with the degree of caudate atrophy, demonstrated by neuroimaging (134,135). Respiration during sleep in HD is normal (137), although daytime respiratory dyskinesias are common.
Although other forms of chorea are somewhat rarer and may have a different pathophysiologic basis, sleep abnormalities in these conditions are very similar to those found in HD. Sleep evaluation in a patient with vascular hemichorea revealed reduced total sleep time, prolonged sleep latency, and reduced slow wave and REM sleep (138). After treatment with haloperidol, all of these sleep parameters improved. These observations suggest that a bedtime dose of antichorea medication such as haloperidol and perhaps reserpine, can improve disturbed sleep in the choreic patient. This may be particularly true in vascular hemichorea-hemiballism in which the involuntary movement itself may be so violent as to inhibit initiation or continuation of sleep.

TOURETTE’S SYNDROME

Tourette’s syndrome (TS) typically manifests in childhood with a succession of motor and phonic tics, often associated with obsessive compulsive behaviors and attention deficit hyperactivity disorder (ADHD). It is most common in boys and in many cases improves as the patient passes into adulthood (139). Tics in this disorder are characterized as being either simple or complex. Simple motor tics are meaningless motions such as a shoulder shrug, while complex motor tics are more purposeful and integrated movements such as jumping. Simple phonic tics are sounds or articulations without meaning such as throat clearing, while complex vocal tics are understandable utterances such as a word or phrase. Perhaps most disabling are vocal tics known as coprolalia, in which the vocal utterance contains socially unacceptable obscene words. To a certain extent, motor and phonic tics are suppressible in the waking state. Based on polysomnographic studies, both kinds continue to appear during all stages of sleep, especially stage 1 and 2, but are decreased in frequency (140). Other studies have suggested that tic frequency was higher in REM sleep than in non-REM sleep (141). Just as in the waking state, phonic tics may take the form of coprolalia during sleep as well (142). A variety of sleep disturbances have been documented in TS including night terrors (143), somnambulism (143,144), PLMS (145), reduced sleep time (145,146), longer sleep latency (141,146), and number of awakenings (141). In one study, the existence of sleep disturbances in patients manifesting both TS and ADHD was especially high (41%) compared to those with TS alone (26%) (147). Sleep apnea can appear in TS and has been reported to be as frequent as 24% and 67% in two surveys (140,148). It has been suggested that the TS gene confers a life-long susceptibility to disorders of ventilatory control during sleep, resulting in a higher incidence of such conditions as infantile apnea and sudden infant death syndrome early in life and sleep apnea in adults (149).

MYOCLONUS

Myoclonus can originate at several different levels within the central nervous system including the cortex, the brainstem, and the spinal cord. It is difficult to make a global statement about sleep and the myoclonic disorders because they are of such diverse etiologies and anatomic origin and each interacts with sleep somewhat differently. The myoclonus of Creutzfeldt-Jacob disease is of cortical origin and continues to appear during sleep, just as in wakefulness (150). Reticular reflex myoclonus, a form of brainstem myoclonus, was documented to persist during sleep in a patient with levodopa resistant parkinsonism (151). While it is
relatively easy to discern the effect of sleep on myoclonus, this case illustrates the difficulty of determining the effect of myoclonus on sleep. In this patient with parkinsonism, sleep architecture was markedly abnormal, but assigning causality to myoclonus is not possible since it represented only one symptom appearing within a syndrome with much broader neurological dysfunction. The relationship of myoclonus and sleep is much easier to understand in patients with palatal myoclonus since this is a monosymptomatic syndrome. There are two basic categories of palatal myoclonus—essential palatal myoclonus (EPT), in which no structural pathology of the central nervous system is apparent, and symptomatic palatal myoclonus (SPT), which arises from a lesion in the Guillain Mollaret triangle of the brainstem. The clinical syndromes of EPT and SPT are only slightly different but their interaction with sleep is dissimilar. During sleep, EPT ceases while SPT continues, with only a slight change in frequency of the repetitive movements (152,153). Neither appears to have very much effect on sleep. In fact, many patients are unaware of the syndrome except for an audible ear click, which usually accompanies each palatal movement in EPT.

Spinal myoclonus is affected variably during sleep, depending on the precise etiology and location of the causative lesion. Although the generator for this form of myoclonus is within the spinal cord, it is almost always subject to supraspinal influences, which may in turn be modified by sleep. In essential spinal myoclonus, in which there is no apparent structural spinal cord pathology, the abnormal movement may disappear entirely during sleep and only reappear during arousals (153). Supraspinal influence is very apparent in propriospinal myoclonus, a syndrome characterized by abnormal activity spreading both rostrally and caudally within the spinal cord. In three patients with this condition, myoclonus only appeared during mental relaxation and mild drowsiness, but then disappeared entirely during sleep (154). The myoclonus appearing during drowsiness was a major cause of insomnia in these patients. Rarely, this type of myoclonus can persist and worsen during sleep, resulting in continuous focal myoclonic activity approximating a myoclonic “status” state (155). As would be expected, spinal myoclonus originating in segments below a complete spinal cord transection is deprived of supraspinal control and is not influenced by sleep (156).

**PRINCIPLES OF TREATMENT**

Each of the specific sleep disorders appearing in the movement disorders discussed here merit individual analysis and appropriately tailored treatment strategies. There are, however, some general principles of therapy that are useful in approaching sleep dysfunction appearing in the context of an extrapyramidal disorder. The simplest and one of the most useful principles is based on the observation that hyperkinetic or hypokinetic movements that persist into the night can themselves disrupt sleep. Accordingly, the first goal of therapy should be to ameliorate nocturnal symptoms such as severe tremor, dystonia, rigidity, chorea, ballism, and hypokinesia. The same pharmacologic treatment strategy used to control these symptoms during the waking day can be applied at bedtime. Having done this, the second principle of therapy is to weigh the potential that any medication being used for this purpose at bedtime has for producing a direct adverse effect on sleep. For example, as discussed previously, levodopa given at bedtime may ameliorate nocturnal rigidity, tremor, and hypokinesia on the one hand, but can also prolong sleep latency, induce vivid dreaming, or result in nocturnal
hallucinosis all of which are counterproductive. Another principle of treatment is that the therapy required for parasomnias associated with extrapyramidal disorders is usually similar to that used for the same parasomnias in the general population. Thus, clonazepam is useful in RBD associated with extrapyramidal disorders, and dopamine agonists or opioids are useful for PLMS, provided they do not adversely interact with the predominant underlying neurological condition. A final principle of therapy has to do with the adjustment of medications that are required for control of the waking movement disorder but may have adverse effects on sleep. In this circumstance, it is critical to attempt to distance the last medication dosage of the day as far away from bedtime as is feasible. Parkinson’s patients with insomnia for instance, should take their last required dosage of selegiline no later than noon. Similarly, Shy Drager patients requiring therapy for hypotension should have their last daily dosage of medication administered as early in the evening as possible to avoid nocturnal hypertension. Adherence to these general guidelines will often enable the clinician to make significant strides in improving the sleep of patients with extrapyramidal disorders.

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INTRODUCTION

Sleep and epilepsy are both active processes of the central nervous system. Although sleep is a normal physiological state, epilepsy is the result of a wide range of pathophysiological mechanisms. The interaction of sleep and epilepsy exemplifies the dynamic relationship of normal neurophysiology and central nervous system dysfunction. These processes have reciprocal effects upon each other. Sleep may influence the expression of interictal and ictal discharges in humans and alter the rate of kindling in animals. Epilepsy and epileptic discharges modify the regulation and continuity of sleep. Additionally, therapeutic interventions for epilepsy also alter the brain and disrupt the states of sleep and wakefulness.

The interaction of sleep and epilepsy may take multiple forms and can translate into a variety of complaints. Individuals with epilepsy may frequently complain of symptoms referable to disturbed sleep such as excessive daytime sleepiness, insomnia, or nocturnal events, or they may express more subtle complaints of this interaction such as an increase in seizure frequency or behavioral changes. Thus, these symptoms may be an indication of an underlying sleep disorder, an expression of the epilepsy, or a result of the therapy. Clinicians should delineate the potential contribution of sleep disorders, sleep dysfunction related to epilepsy, and side effects of therapy with the goal to improve the patient’s symptoms. In this chapter, we will explore these intricate relationships of sleep and epilepsy.

EPILEPSY

Epilepsy is a chronic condition hallmarked by recurrent unprovoked seizures. The term epilepsy is derived from the word “epilambanien” which, in Greek, means to seize or attack (1). Epileptic seizures are currently defined as the clinical manifestations of pathological excessive hypersynchronous neuronal activity that results in a morbid experience or behavioral change. Within this definition, we typically divide epileptic seizures into partial seizures and primary generalized seizures (2). Partial seizures begin in one focal region and potentially spread to other areas of the brain. Partial seizures may be classified as simple partial (retention of memory and consciousness), complex partial (impairment of memory or consciousness), or secondarily generalized. Primary generalized seizures appear to involve both hemispheres at the onset and may involve Absence seizures, characterized by brief staring episodes; Atonic seizures, sudden loss of postural tone;
Tonic seizures, producing generalized increase in muscle tone; Clonic seizures associated with repetitive jerking; Tonic Clonic seizures, which start with tonic activity that progress to clonic activity; or Myoclonic seizures, involving quick single jerks.

In contrast to provoked or isolated seizures, the clinical diagnosis of epilepsy is defined as the chronic condition of recurrent unprovoked epileptic seizures. Individuals with epilepsy can have multiple types of seizures that subsequently are represented as a single form of epilepsy. Epilepsies can be divided into the focal onset epilepsies and the primary generalized epilepsies, but both types of epilepsies can have specific relationships to the sleep wake cycle.

**EFFECT OF EPILEPSY ON SLEEP**

Epilepsy actively disrupts the regulation of sleep through the occurrence of seizures and interictal activity. Frequent nocturnal seizures interrupt sleep and alter its regulation. Patients with some types of frontal lobe seizures may experience between 5 and 20 brief seizures in a single night (3). Beyond the obvious disruption caused by seizures, sleep architecture is frequently disrupted in patients with epilepsy. Even away from the time period of the seizures, Touchon (4) demonstrated that patients with epilepsy have greater sleep “instability,” with more frequent spontaneous arousals and awakenings prior to treatment with anticonvulsants. Thus, the epileptic condition may play a role in the patient feeling unable to feel rested.

**EFFECTS OF SEIZURES ON SLEEP**

The occurrence of a seizure acutely changes the brain neurochemical balance. This neurochemical change may be manifested by symptoms related to sleep and wake. Patients frequently complain of postictal somnolence or insomnia, and have the perception of disrupted sleep the following night (Table 1). These complaints are founded as shown by Bazil (5), who demonstrated that patients with nocturnal seizures are subjectively and objectively sleepy on the day following a seizure. Objectively, seizures and the postictal state produce sleep fragmentation and suppression of rapid eye movement (REM) sleep. Baldy-Moulinier (6) showed in an earlier investigation that individuals with partial or generalized seizures had less total amount of REM sleep on nights with seizures. Touchon’s study of 77 subjects with primary or secondarily generalized tonic-clonic seizures showed that subjects had reduced total sleep time, a decreased percentage of REM sleep, increased wake time after sleep onset, and increased stage 2 sleep on nights

**TABLE 1** Epilepsy Effects on Sleep

<table>
<thead>
<tr>
<th></th>
<th>Symptoms</th>
<th>Polysomnographic findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizures</td>
<td>Somnolence and insomnia</td>
<td>Suppression of REM and slow wave sleep and lower sleep efficiency</td>
</tr>
<tr>
<td>Interictal discharges</td>
<td>Potentially produce insomnia and daytime sleepiness</td>
<td>Sleep fragmentation Mild REM suppression</td>
</tr>
</tbody>
</table>

*Abbreviation: REM, rapid eye movement.*
following seizures as compared to seizure-free nights (4). He extended these observations by showing that recurrent partial seizures during sleep decreased the relative proportion of REM sleep. Besset (7), similarly, reported that patients with seizures had a reduction in total sleep time and REM sleep, when compared to patients without seizures. Nunes (8) extended this observation in children noting that children who had seizures during the night had reduced REM sleep. Yet, these observations may raise the potential that these patients have a baseline low amount of REM sleep. To account for this, Bazil utilized the patients as their own control, and found nighttime seizures continued to reduce sleep efficiency, REM sleep, and slow wave sleep and prolong the REM latency. This effect appears to extend beyond the traditional postictal period. Bazil (5) also found that diurnal seizures reduced REM sleep and stage 4 sleep on the ensuing night.

EFFECTS OF INTERICTAL ACTIVITY ON SLEEP

Seizures may be the most prominent manifestation of the epilepsy but the epileptic focus is active between seizures. The epileptic state may promote sleep disruption beyond that seen directly from seizures (Table 1). Touchon (4) showed that sleep is disrupted in patients with epilepsy on seizure free nights as compared to nonepileptic controls. These patients were found to have lower sleep efficiencies, increase in sleep stage shifts, and periods of wakefulness when compared to normal controls (4). Touchon (4) also found more stage shifts, arousals, and less deep sleep in individuals with focal onset seizures than those with primary generalized epilepsies. He noted that sleep fragmentation by awakenings was greater in untreated, newly diagnosed patients than those receiving treatment. These findings were improved after treatment with carbamazepine for one month.

The cause of the epilepsy associated sleep disruption is unclear. The electrical event of the interictal discharge may cause a direct or indirect effect on the regulation of sleep. Evidence for this is still lacking in humans, but in animals the link appears to be suggested. In humans, interictal activity can be associated with limited physiological changes. Peled (9) showed that bursts of generalized spike-wave complexes can appear in stages 2 and 3 of nonrapid eye movement (NREM) sleep and occur with K-complexes producing movements and arousals. The patients who were subsequently treated with antiepileptic medications showed reduced paroxysmal events during sleep, increased REM sleep, increased sleep efficiency, and improvement in daytime sleepiness. However, in temporal lobe epilepsy, Malow et al. (10) found that interictal discharges were rarely associated with arousals from sleep. This study utilized surface electrodes and did not look at other features such as autonomic arousals or other physiological parameter shifts. Yet, the discrepancy raises the question if the interictal discharges have an effect on brain function. Evidence for this exists in the realm of autonomic regulation. Interictal discharges have been reported to change the cardiac cycle times and, in animals, may produce significant changes in hypothalamic function (11,12). In animal studies, discharges from the amygdalae or mesio-temporal structures can produce arousals (13). Although the exact mechanisms for these arousals are unclear, the rich anatomical connections of the frontal and temporal lobe structures to hypothalamic and brainstem components that regulate sleep make this disruption expected. Using this information, Bastlund showed that rats, who attained spontaneous seizures after hippocampal kindling via electrical stimulation, had more sleep fragmentation and architectural changes. They also found that these
animals had neuronal cell loss in the dorsomedial hypothalamus, suggesting a more long-term effect of epilepsy on the sleep wake regulation (14). These anatomical connections also provide opportunity for potential therapeutic avenues directed to maintaining wakefulness or promoting sleep induction.

**ANTICONVULSANT THERAPY AND SLEEP**

Anticonvulsant therapies have a broad pharmacodynamic effect, altering receptor binding, ion channel function, or second messenger systems. The lack of specificity of these therapies influences multiple functional networks within the central nervous system potentially diminishing cognition, fine motor skills, and sleep. Unfortunately, these medications do not discriminate between neurons contributing to seizures and those functioning normally. In addition to the lack of discretionary effect, the overall influence of these medications on sleep is difficult to pinpoint. As we have mentioned before, epilepsy is a heterogeneous group of disorders all culminating to a symptom of recurrent seizures. Therefore, the underlying pathology may be very different and the effect of medications in those pathologies may be unique. Also, the effects on sleep regulation may be different in the medication initiation phase compared to the chronic phase of therapy, as well as probable dose-dependent differences. Nonetheless, a brief review of the current information may provide at least some insight to the complexities of the therapies for epilepsy on sleep.

Traditional anticonvulsants are frequently associated with complaints of sedation and fatigue, and insomnia may occur with other agents. Antiepileptic medications also may influence sleep architecture (Table 2) (15). The sleep effect of these medications may be in part related to the mechanism of action for seizure suppression. Phenytoin alters conduction of sodium and calcium channels, thus suppressing neuronal excitability. The drug appears to increase the amount of light NREM sleep, but decrease sleep efficiency and sleep latency (16,17). Yet, carbamazepine, another medication altering sodium channel conductivity, appears to improve sleep fragmentation and reduced awakenings in newly diagnosed patients with epilepsy (4). Gigli (18) reported that in the acute phase, the use of controlled release carbamazepine in patients with epilepsy had a reduction in REM sleep and an increase in the number of sleep stage shifts. This REM suppression may be related to the structural similarity of carbamazepine to tricyclic antidepressants that have known REM suppressant effects. Long-term studies, however, showed these effects were not sustained (18). Ethosuximide, which alters low threshold calcium channel function in thalamic neurons, appears to increase stage 1 sleep at the expense of slow wave sleep in patients with epilepsy (19). Benzo-diazepines similarly cause neuronal hyperpolarization by increasing the frequency, the chloride channel is opened when GABA binds to its receptor. This medication appears to shorten sleep latency, and decrease the number of arousals in patients with epilepsy, with minimal change on slow wave sleep (16). Phenobarbital hyperpolarizes the neuronal membrane by increasing the duration of the chloride channel opening, once gamma amino butyric acid (GABA) binds to its receptor. This drug potentially increases stage 3 and 4 sleep in normal subjects (21). Ehrenberg (22) observed a similar increase in
<table>
<thead>
<tr>
<th>Traditional antiepileptic medication</th>
<th>Subjective sleep effect</th>
<th>Sleep use</th>
<th>Sleep latency</th>
<th>Total sleep time</th>
<th>Sleep efficiency</th>
<th>Arousals</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3/4</th>
<th>REM sleep</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Increased sleepiness</td>
<td>May decrease epileptic aurasals Used as tertiary agent in RLS</td>
<td>Decreased</td>
<td>No change</td>
<td>Increased</td>
<td>Decreased</td>
<td>No change</td>
<td>No change</td>
<td>Increased</td>
<td>Unknown</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>Insomnia</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Increased</td>
<td>No change</td>
<td>No change</td>
<td>Decreased</td>
<td>Increased</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Increased sleepiness</td>
<td>Somnogenic</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Increased</td>
<td>No change</td>
<td>No change</td>
<td>Decreased</td>
<td>Increased</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Increased sleepiness</td>
<td>Increased</td>
<td>No change</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Increased</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Valproate</td>
<td>Increased sleepiness</td>
<td>May help with RLS</td>
<td>No change</td>
<td>No change</td>
<td>Increased</td>
<td>Decreased</td>
<td>No change</td>
<td>No change</td>
<td>Increased</td>
<td>No change</td>
</tr>
</tbody>
</table>
slow wave sleep in patients with periodic limb movements, but the effect in patients with epilepsy is unclear.

The newer antiepileptic medications may have less effect on sleep (Table 3). These medications may have benefits over more traditional sedating medications. Some medications may offer opportunities for improvement in sleep, but this also needs further investigation. Felbamate, a carbamate compound, is found to have stimulant-like effect in patients with epilepsy and cause some patients to complain of insomnia (23,24). Lamotrigine, which appears to alter presynaptic cation channels, has also been reported to cause a dose-dependent insomnia, but polysomnographic investigation of lamotrigine showed it had little effect on sleep architecture with a mild increase in percent of REM sleep (25,26). Gabapentin has been reported to increase sleep efficiency, slow wave sleep, and REM sleep while decreasing arousals, but this medication is occasionally associated with daytime sleepiness (27). In a study using normal volunteers, Foldvary (28) found that gabapentin increased slow wave sleep and improved sleep efficiency compared to placebo. Levetiracetam has also been reported to induce sleepiness and appears to increase stage 2 sleep, but decrease stage 4 sleep (29). Levetiracetam improved the patients’ subjective perception of sleep with fewer recognized awakenings, but subjects felt less alert in the morning. In another study in normal controls, however, Bazil (30) found little effect of the drug on sleep architecture. Topiramate, a medication with multiple mechanisms of action, has been found to induce complaints of daytime fatigue and its effects on sleep. Bonanni (31) found in drug naive patients with partial onset seizures that 200 mg of topiramate per day did not change the mean sleep latency on multiple sleep latency test (MSLT) after two months of therapy. The effect of this medication on nighttime sleep has not been extensively studied. Zonisamide is also noted to provoke insomnia in some patients, but no studies of effects on sleep have been published. Pregabalin, similarly to gabapentin, binds to the alpha 2 delta protein. This medication appears to acutely decrease the frequency of awakenings and increase the amount of slow wave sleep in normal controls (32). It is unknown if this effect persists and if similar results can be found in patients with epilepsy.

Vagus nerve stimulation (VNS) has a mixed effect on sleep. Valdes-Cruz (33) showed in animals, an increase in REM sleep with an increase in pontogeniculate occipital waves (a correlate for REMs) density with VNS. In cats, Puizillout (34) also demonstrated a relationship of VNS to sleep onset REM sleep. They found that stimulation induced sleep cycle and early onset REM sleep. However, human studies, to date, have been insufficiently powered to be conclusive and have shown little consistent effect of VNS on sleep architecture. Rizzo (35) found in 10 patients, a reduction in REM sleep and an increased number of awakenings and percentage of time in stage 1 sleep and wake, in epilepsy patients with stimulation currents over 1.5 mA. Armitage (36), however, found in seven patients with depression that VNS increased the amount of stage 2 sleep and decreased stage 1 sleep and the amount of wakefulness after sleep onset. Age may play a role, as found by Hallbrook. He found that 10 of 15 children with epilepsy had an increase in slow wave sleep with VNS therapy and eight of those had concurrent improvement in their daytime behavior (37). Hallbrook postulated that this may be related to improvement in daytime alertness.

To study alertness, Malow (38) performed MSLT on patients before and after VNS implantation and found that low intensity stimulation improved daytime alertness, but was also associated with an increase in sleep onset REM in daytime
### TABLE 3  Newer Antiepileptic Medication Effects on Sleep

<table>
<thead>
<tr>
<th>Newer antiepileptic medication</th>
<th>Subjective sleep effect</th>
<th>Sleep use</th>
<th>Sleep latency</th>
<th>Total sleep time</th>
<th>Sleep efficiency</th>
<th>Arousals</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3/4</th>
<th>REM sleep</th>
</tr>
</thead>
<tbody>
<tr>
<td>Felbamate</td>
<td>Insomnia</td>
<td>Stimulant effect</td>
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<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Sleepiness</td>
<td>Improve RLS</td>
<td>No change</td>
<td>Increased</td>
<td>Increased</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Insomnia</td>
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<td>No change</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td>Unknown</td>
<td>Unknown</td>
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<td>Unknown</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Sleepiness</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td>Unknown</td>
<td>Unknown</td>
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<td>Unknown</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Sleepiness</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
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</tr>
<tr>
<td>Pregabalin</td>
<td>Sleepiness</td>
<td>Mild decrease</td>
<td>Increased</td>
<td>Increased</td>
<td>Increased</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
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</tr>
<tr>
<td>Tiagabine</td>
<td>Insomnia</td>
<td>May increase stage 3 and 4 sleep</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
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</tr>
<tr>
<td>Topiramate</td>
<td>Sleepiness</td>
<td>No change</td>
<td>No change</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>Sleepiness</td>
<td>No change</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
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</tr>
<tr>
<td>Zonisamide</td>
<td>Sleepiness</td>
<td>May increase RLS</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Abbreviations: REM, rapid eye movement; RLS, restless legs syndrome.
naps. Galli (39) also found a mild increase in mean sleep latency after six months of VNS with currents less than 1.5 mA, suggesting that VNS may have an effect on daytime alertness.

VNS also appears to affect sleep-related respiration. In some patients, VNS may increase sleep-related respiratory disturbance. Malow and Holmes (40-42), independently, have shown selected patients developing obstructive events during stimulator activation. Zaaimi (43) also found that respiratory frequency changed during the stimulation in children. Yet, these effects may not be universal and clearly need further explanation (44). The conflicting results on sleep and sleep-related physiology may in part be related to different populations, underlying pathophysiology and duration of VNS. The maximal benefit in seizure reduction is not seen, until two to three years. This implies that long-term changes are occurring in the central nervous system.

Most of the newer therapies have not undergone extensive polysomnographic investigation in patients with epilepsy nor the respective pathological subgroups. Studies, such as these, would provide significant insight to improving sleep and sleep-related complaints in patients with epilepsy. These unique effects may additionally provide the clinician with the opportunity to improve sleep and wakefulness. The clinician may consider the judicious use of therapies to augment the sleep wake cycle. Antiepileptic medications that promote sleep or improve sleep disorders may require tailored dosing schedules to maximize their benefit, whereas medications that promote wakefulness may be best dosed away from the sleep period. This philosophy can be extended to drug development. To improve seizure control and quality of life, the next generation of antiepileptic medications must augment normal physiological regulation of sleep.

**THE INFLUENCE OF SLEEP ON EPILEPSY AND SEIZURES**

Sleep has a strong influence on seizures. Even in the second century, Galen was aware that sleepiness may aggravate seizures (1,45). The relationship of seizures in sleep was further examined by Gower, in 1881, who determined over 20% of his patients had seizures solely during sleep and 42% had seizures only during the awake state sleep (46). The remainder of the patients had seizures diffusely distributed through both the awake and asleep states. Janz (47,48) also found similar results, of state dependence with seizures and discovered a group of individuals who had seizures primarily in the first two hours after awakening, coining the term “awakening” epilepsies. Many of these individuals with “awakening epilepsy” had a form of primary generalized epilepsy known as Juvenile Myoclonic Epilepsy. This form of epilepsy is in contrast to Benign Epilepsy of Childhood with Centrotemporal Spikes and Autosomal Dominant Nocturnal Frontal Lobe Epilepsy that are focal onset epilepsies that primarily occur during sleep. Each of these epilepsies is influenced by the sleep/wake state in different ways, reinforcing the premise that epilepsy can occur through various mechanisms.

Sleep stage also plays a significant role in the occurrence of seizures. Herman and Minecan (49,50) in separate papers showed that most sleep-related seizures begin in NREM sleep with stage 2 sleep having the highest seizure rate per hour and REM sleep having the lowest rate of seizures (Table 4). This antiseizure property of REM sleep appears to hold true for both the overall sleep time and the seizure rate per hour of sleep, when compared to other sleep wake states (50). Certain regions of the brain also may have greater ties to the sleep state
influence on seizure occurrence. Herman (49) and Janz (47) separately found that frontal lobe seizures are more likely than other locations to occur during sleep (Table 5). Some frontal and temporal lobe seizures occur near an arousal or awakening from sleep and this finding raises a question if the seizures cause the arousal or did the arousal promote the seizure. Shouse (51) has speculated that thalamocortical activation with arousal may promote seizure propagation, but Malow (52) also has postulated that seizure initiation may also produce arousal as evidence by stimulation of the mesiotemporal structures. By either account the dynamic effect may be dependent upon the underlying mechanism and location of the epileptic focus.

The underlying circadian rhythm has an apparent effect on epilepsy and seizure occurrence. Quigg and Stewart (53,54), separately, demonstrated a peak in seizure expression in the mid-afternoon in both rats and humans with focal onset seizures (53,54). This finding is most striking because the humans and rats have diametrically opposed sleep and temperature cycles, but adds to evidence of the potential direct influence of the circadian rhythm on the seizure occurrence. Manfredini (55) also found a circadian influence on simple febrile seizures with the peak incidence of seizures are over four-fold greater between 6 and 11:59 PM than 6 to 11:59 AM. Although this peak is slightly later in the day than found by Quigg, the influence of the circadian rhythm is clear. The relative contribution of sleep and circadian cycles will require more elaborate investigation to understand these dynamics. Despite the circadian and sleep influences on seizure occurrence, sleep may have more subtle effects on the activity between seizures.

**TABLE 4** Distribution of Seizures Across the Sleep Stages

<table>
<thead>
<tr>
<th>Author</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3/4</th>
<th>REM sleep</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herman</td>
<td>23</td>
<td>68</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Minecan</td>
<td>20</td>
<td>61</td>
<td>14</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Author</th>
<th>Seizure rate adjusted for time szs/hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minecan</td>
<td>0.34 0.38 0.29 0.09</td>
</tr>
</tbody>
</table>

Source: Adapted from Refs. 49, 50.

**TABLE 5** Frequency of Nocturnal Seizures by Location of Onset

<table>
<thead>
<tr>
<th>Author</th>
<th>Frontal</th>
<th>Temporal</th>
<th>Parietal</th>
<th>Occipital/parietal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Janz</td>
<td>58%</td>
<td>25%</td>
<td>21%</td>
<td>NR</td>
</tr>
<tr>
<td>Herman</td>
<td>57%</td>
<td>43%</td>
<td>NR</td>
<td>13%</td>
</tr>
</tbody>
</table>

Abbreviation: NR, not reported.
Source: Adapted from Refs. 47, 49.
entrance into the deeper stages of NREM sleep (10). These interictal discharges have greater spatial variance and occur more frequently with the onset of the deeper stages of sleep. One potential explanation of this is that the deeper stages of sleep, physiologically activates fewer neurons leaving more neurons in the resting membrane state to be activated by epileptic activity. The state change may facilitate greater synchronization of thalamocortical relay neurons, participating in propagation of the interictal discharges. Steriade (57) postulated that thalamocortical neurons participating in sleep oscillations may also contribute to the spread of seizure discharge. These theories, however, are not supported by neuronal recordings in humans. In patients with depth electrodes placed in the mesial temporal lobes, Staba (58) showed that single neurons had significantly higher burst rates and synchronous discharges during episodes of slow wave and REM sleep and not wakefulness when compared to nonepileptic hippocampal neurons. Although, these findings suggest that the epileptogenic site may be more autonomous than other areas of the brain and thus less influenced by sleep regulation, Shouse (59) postulated that the availability of neurons to be recruited into the epileptic discharge may be an important factor into the effect of sleep on discharge occurrence. This activation hypothesis has been applied to explain the decrease of epileptic activity in REM sleep.

Several investigators have postulated the corollary hypothesis that the increased activity in REM sleep leaves less neurons available for recruitment into an epileptic discharge. Yet, REM sleep has antiepileptogenic effect beyond temporal activation of the neurons. Animal models have also shown that REM–NREM sleep stages to have complex influences on seizure activity. As in humans, NREM sleep and slow wave sleep have been associated in animals to promote the propensity of interictal discharges and REM sleep to suppress seizure discharges. In the kindling model, animals kindled in NREM sleep require less overall current and sessions than those kindled in REM sleep. Selective deprivation of REM sleep in animals reduces the required current to elicit seizure activity in other stages of sleep and awake. The converse of this is also true. Kumar (60) increased REM sleep through microinjection of cholinergic agonist, and demonstrated significant increase in threshold to produce after discharges in the amygdala during the subsequent period of wakefulness. These findings suggest that REM sleep has broader reaching antiseizure effect than immediate activation of the cortex.

INFLUENCE OF SLEEP DEPRIVATION ON INTERICTAL ACTIVITY

For decades, epileptologists relied upon sleep and sleep deprivation to provoke epileptic-related electroencephalographic activity. Subsequent work has shown that both sleep and sleep deprivation have been useful. Degen and Degen (61) showed sleep deprivation to increase interictal discharges in patients with epilepsy. They found that only 19% of their cohort had interictal discharge on routine electroencephalography without sleep deprivation, but 64% had abnormalities with sleep deprivation. These works sparked a debate as to the mechanism of sleep deprivation increasing these discharges. Entering sleep may promote interictal activity in approximately one-third of epileptic patients and up to 90% of subjects with sleep-wake related, or state-dependent, epilepsies (13,62,63). Gilbert (64) found only a mild increase in interictal discharges in children who were sleep deprived, but Fountain (65) found that 52% of patients with epilepsy who had no interictal discharges on routine electroencephalogram had discharges on studies performed
following sleep deprivation (64,65). Additionally, Rowan (66) found in patients with normal routine electroencephalograms and suspected seizures that only 14% of patients had new abnormalities when sleep was obtained by sedation, whereas 44% had new abnormalities following sleep deprivation. This suggests that activation of interictal activity by sleep deprivation may be a result of direct activation from the sleep loss beyond promotion of the onset of sleep.

Sleep deprivation promotes seizure activity in some patients with epilepsy, whereas other patients have little response (47,48,67). Tan (68) showed that 9% of their cohort of patients hospitalized for recent seizures believed they had sleep deprivation as a precipitating factor. This influence may be related to the underlying type of seizures. Janz found that sleep deprivation frequently provokes seizures in juvenile myoclonic epilepsies. This observation was extended by Manganotti (69), who showed using transcranial magnetic stimulation, that these individuals have hyperexcitable corticospinal neurons of motor cortex following sleep deprivation. Yet, this may also play a role for some focal onset epilepsies. Rajna and Veres (67) found, in patients with temporal lobe epilepsy, that nine, of their cohort of 14, were more likely to incur seizures on the days following acute sleep deprivation. This is in contrast to Malow et al. (70), who showed that individuals in the epilepsy monitoring unit were just as likely to have seizures with sleep deprivation as without. One explanation for the divergent views in these studies is the divergent patient populations and underlying pathologies. Population studies attracting a general pool of individuals may have epileptic foci that are more vulnerable to sleep wake influence than patients with intractable epilepsy who have epileptic foci that are more independent of state changes in the brain.

For the patient, these studies indicate important clinical lessons regarding the need of adequate time for sleep. Sleep deprivation may occur from a variety of avoidable and unavoidable causes. Further investigation may delineate the subgroup of epilepsies that may have significant sensitivity to sleep deprivation. Yet, clinicians must be aware that even schedule limitations, medication effect, the epilepsy, or other dyssomnias may promote sleep deprivation and that the symptoms of these may be reflected in the seizure frequency. No matter what the cause, the clinician should counsel the patient that sleep deprivation may increase seizures, and that correcting potential causes of sleep loss may improve the seizure frequency.

THE EFFECT OF SLEEP DISORDERS ON EPILEPSY

Patients with epilepsy frequently complain of sleep-related symptoms. Miller (71) found that over two-thirds of patients with epilepsy seen at a university center had complaints regarding sleep, and 35% complained their sleep issues interfered with their daytime performance. Malow et al. (72) showed using the Epworth Sleepiness Scale that 28% of 158 adult epilepsy patients surveyed had an elevated score (>10 points) with 44% of subjects reporting a moderate or high tendency to fall asleep while watching television. Hoeppner (73) also elucidated in a survey of 30 independently living adults with partial or generalized seizures and 23 normal controls that those who had at least one seizure a month were more likely to have sleep complaints. This increase in sleep complaints in patients with epilepsy may be related to the disruption of the regulation of sleeps, in the perception of sleep/wake-related symptoms or increase in other sleep disorders.
Sleep disorders in patients with epilepsy may have a significant impact on the other aspects of the epilepsy. Malow (74) showed that nearly one-third of patients with medically refractory epilepsy had a respiratory disturbance index of greater than 5 and approximately 10% of the patients had a periodic limb movement index greater than 20 events per hour. Additionally, Newell (75) found one-third of patients in their cohort had abnormalities on overnight sleep studies. Unfortunately, these studies involved relatively small numbers of patients and include a high percentage of patients with intractable epilepsy. Yet, sleep disorders may produce daytime symptoms but may also exacerbate the epilepsy. This may be best exemplified by the relationship of obstructive sleep apnea and epilepsy.

Obstructive sleep apnea may influence the recurrence of epileptic seizures. Seizures as a direct result of apnea are rare. Kryer (76) reported on one patient who had an apnea in sleep that caused a seizure after severe oxygen desaturation and cardiac arrest. This is probably a rare event. However, recurrent seizures are more commonly reported in individuals with obstructive sleep apnea (77,78). Sonka (78) found that approximately 4% of patients with obstructive sleep apnea had reported seizures. Over three-fourth of the seizure patients in their cohort had seizures only during sleep and most of the events were generalized seizures. This study may be skewed by variances in referral patterns and confirmation of the diagnosis of seizures. Nonetheless, the potential elevated prevalence raises the prospect of sleep apnea provoking seizures or unmasking an underlying tendency for seizures.

The implication that treatment of sleep apnea in patients with epilepsy may reduce seizure frequency was first reported by Wyler and Weymuller. In 1981, they (79) reported a patient with epilepsy and sleep apnea, following tracheotomy, ceased having generalized seizures and improved the frequency of partial seizures. Subsequent reports reinforce the potential benefits for patients with epilepsy, once the sleep apnea is treated (80–83). In our own cohort, we found that 40% of our cohort attained seizure freedom with treatment of the obstructive sleep apnea, but many of these patients had state-dependent seizures that may be more amenable to improvement in sleep (81). Other investigators have found similar results, and further trials are needed to support this benefit. These observations, however, promote the view that obstructive sleep apnea increases the seizure frequency in patients with epilepsy.

The reason sleep apnea may increase seizure expression is unclear. Current work focusses on two primary etiologies: sleep loss and oxygen desaturation. Obstructive sleep apnea causes sleep deprivation and sleep fragmentation. This sleep disruption deprives the patient of the beneficial effects of maintaining sleep, as well as increases the time spent in the lighter more vulnerable stages of sleep vulnerable. The oxygen desaturation associated with obstructive sleep apnea may promote seizure initiation. In animals, oxygen desaturation is noted to decrease potential seizure inhibitory mechanisms, but the human case series have not demonstrated a relationship (84).

Sleep apnea may be more likely to occur in patients with epilepsy because of the central nervous system disease and the therapies. Other disorders of the central nervous system may also alter regulation of respiration during sleep (85). Our therapies may increase the likelihood of sleep apnea by direct or indirect means. Weight promoting medications such as valproate, vigabatrin, and gabapentin may increase obesity and increase the likelihood for sleep apnea (86). Additionally,
respiratory suppressant medications such as benzodiazepines and barbiturates may decrease responsiveness to carbon dioxide and oxygen desaturation and increase upper airway musculature relaxation (87). Stimulation therapies for epilepsy, such as VNS, may increase airway disturbance or change central nervous system respiratory regulation during sleep in some patients, producing periodic breathing and sleep apnea (40–44). Although all of these studies are compelling, larger cohorts are needed to elucidate the true prevalence and age and gender distribution of sleep apnea in patients with epilepsy.

The prevalence of restless legs syndrome (RLS) in patients with epilepsy is unknown. Polysomnographic studies, to date, do not demonstrate unexpectedly high values of periodic limb movements, but the subjective complaints of RLS are unstudied in this population (72). In a study of 39 patient with temporal lobe epilepsy, de Almeida (88) found that 15% of their patients had symptoms of RLS. This appears to be similar to control populations. Because of the baseline prevalence of RLS, some patients with epilepsy will have RLS and periodic limb movements of sleep. Clinicians need to be conscious that patients may have worsening of these symptoms, related to zonisamide or phenytoin use (89,90). Patients with RLS should also be examined for potential causes of their symptoms, such as anemia, uremia, and neuropathy.

Some antiepileptic medications may be chosen to aid with both the epilepsy and RLS. Gabapentin, clonazepam, and carbamzepine have been used to improve symptoms in some patients and may improve both the epilepsy and sleep disorder (91).

GENERAL CLINICAL MANAGEMENT OF PATIENTS WITH EPILEPSY AND SLEEP COMPLAINTS

As with all patients with sleep complaints, the majority of sleep complaints can be divided into one of three major categories: excessive daytime sleepiness, insomnia, or unusual events at night. Though these complaints may appear divergent, they may have common underlying etiologies. Therefore, a systematic approach to elucidating the cause may prove to be the most efficient path to a directed therapy and improve the patient’s quality of life. The clinician should obtain a detailed sleep history including information regarding the clinical course, the sleep-wake schedule, observations of the bed partner, daytime sequelae, beliefs regarding sleep, dietary and activity schedule, medications (including timing and dosage schedule, over-the-counter agents, caffeine and herbs), seizure frequency intensity, and impact upon the patient. The physician should also look for potential causes of sleep disturbance from three groups: effect of epilepsy on sleep, effect of medication on sleep, and the presence of another sleep disorder.

As outlined above, the interaction of epilepsy and sleep is dynamic. Patients with epilepsy may develop obstructive sleep apnea, RLS, periodic limb movements of sleep, narcolepsy, idiopathic hypersomnolence, and circadian rhythm disorders (Table 6). Clinicians should be astute to the diagnosis and treatment of these disorders, knowing that therapy to improve sleep may improve the sleep-related complaints, quality of life, and seizure frequency. We have found that thorough explanation and written materials of the treatment plan with both the patient and a family member aids the patient and family in participating in therapy. Whatever the cause, improving the sleep and daytime alertness of
individuals with epilepsy may have benefits reaching beyond traditional symptoms of sleep disorders.

**APPRAOCH TO EXCESSIVE DAYTIME SLEEPINESS IN EPILEPSY**

Patients with epilepsy frequently complain of excessive daytime sleepiness, and this complaint is frequently dismissed as a side effect of therapy (71–73,92). Yet, this symptom may provide an important clue. Clinicians should routinely ask their patients regarding their daytime alertness and the situations in which the patient falls asleep. They should also look for evidence of sleep deprivation, disruption, and dysfunction. Sleep deprivation may be voluntary or related schedule disturbances or meeting other obligations. In patients with epilepsy, this sleep deprivation may enhance the sedating effects of medications and be promoted by the lack of outside activities. A sleep diary, similar to a seizure calendar, is the first mechanism to document bedtime and wake time and is an excellent tool for reviewing time management.

Sleep may be disrupted from external and internal factors. Clinicians should ask their patients to describe the environment they sleep in and what potential opportunities for disruptions exist. Patients may have stimulating activities in the sleep environment. These factors should be addressed with education regarding sleep hygiene.

---

**TABLE 6 Classical Sleep Disturbances**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Potential therapies</th>
<th>Potential concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstructive sleep apnea</td>
<td>CPAP, positional therapy, surgery, dental device&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Postictal vomiting, confusion</td>
</tr>
<tr>
<td>VNS induced sleep apnea</td>
<td>Reduce current intensity, pulse width or signal frequency</td>
<td>May blunt respiratory response</td>
</tr>
<tr>
<td>Restless legs syndrome</td>
<td>Gabapentin, valproate, dopamine agonists</td>
<td></td>
</tr>
<tr>
<td>Drug-induced hypersomnia/insomnia</td>
<td>Move medication timing to minimize effect</td>
<td>Monitor time of seizure recurrence in relation to dosage</td>
</tr>
<tr>
<td>Narcolepsy</td>
<td>Stimulants SSRIs for cataplex</td>
<td>Differentiate cataplex from atonic seizures</td>
</tr>
<tr>
<td>Epileptic-related insomnia</td>
<td>Increase the nocturnal antiepileptic therapy</td>
<td>Toxic side effects of medications</td>
</tr>
<tr>
<td>Primary Insomnia</td>
<td>Cognitive behavioral therapies, Newer hypnotic agents</td>
<td>Monitor seizure frequency and timing</td>
</tr>
<tr>
<td>Circadian rhythm disorders</td>
<td>Chronotherapy</td>
<td>Avoid sleep deprivation</td>
</tr>
<tr>
<td>Parasomnia—RBD</td>
<td>Clonazepam, melatonin</td>
<td>Confirm diagnosis and monitor nocturnal event frequency</td>
</tr>
<tr>
<td>Parasomnia—disorder of arousal</td>
<td>Behavioral therapy, judicious use of medication therapy</td>
<td>Confirm diagnosis and monitor nocturnal event frequency</td>
</tr>
</tbody>
</table>

<sup>a</sup>See text for safeguards.

*Abbreviations: CPAP, continuous positive air pressure; VNS, vagus nerve stimulation; RBD, REM sleep behavior disorder; SSRIs, selective serotonin reuptake inhibitors.*
Internal causes for sleep disruption may exist in the form of underlying sleep disorders. Clinicians should direct questions regarding symptoms of unrefreshing sleep, snoring, gasping, observed apnea, and excessive movements at night. For some patients who are not aware of their symptoms, a family member or caregiver may provide a more reliable witness to the functional degree of the symptoms. The Epworth Sleepiness Scale, although not validated in patients with epilepsy, can be a helpful metric in patients aware of their symptoms (92). Using the Epworth Sleepiness Scale, Malow (70) showed that elevated scores in epilepsy patients were more commonly associated with symptoms of obstructive sleep apnea and RLS, than the number or type of antiepileptic medication or seizure frequency. Patients with unexplained symptoms of excessive daytime sleepiness should have an overnight polysomnogram to evaluate the potential of an underlying sleep disorder.

As discussed before, the epileptic process may also provoke sleep disruption. Frequent nocturnal interictal discharges and seizures cause significant sleep disruption and result in daytime sleepiness (71). Clinicians may choose to utilize extended electroencephalographic montage or video-electroencephalography with polysomnography to evaluate the extent of this disruption (93). In these patients, treatment with more effective anticonvulsant agents or the use of sedating antiepileptic medication prior to the sleep period may prove beneficial.

At times, the antiepileptic therapy may be causing the daytime sleepiness. In this situation, the medication dosage may be reduced during the day and increased at night, completely withdrawn or substituted with a less sedating medication. Scheduling soporific medications to maximize the peak effect during the usual sleep period may reduce the perceived side effects. Similar philosophy can be utilized with stimulating medications, so that higher dosages should be taken at the beginning of the period of wakefulness and reduced prior to the expected sleep period. This is also a viable technique for the treatment of nocturnal seizures when the patient can tolerate much higher drug levels. Clinicians should remember the pharmokinetics of delayed released preparations, since these may extend beyond the desired period of effect.

CLINICAL MANAGEMENT OF INSOMNIA IN EPILEPSY

Insomnia is a relatively frequent complaint endorsed by approximately 40% of individuals with epilepsy (71). A systematic approach to these complaints may also be helpful in defining the etiologies. The clinician should review the issues of sleep schedule, sleep environment, attitude and beliefs toward sleep, and sleep hygiene. Patients with epilepsy are generally more likely to be withdrawn and reclusive or have sedentary lifestyles that may perpetuate insomnia. Some patients focus their lifestyle in their bedrooms, avoiding going out in public by increasing stimulating distractions such as television, video games, and computers in the bedroom. This along with other maladaptive behaviors will promote the insomnia. These factors may be amplified by the effect on the circadian rhythm issues. Many of these patients have limited exposure to light, physical activity, and social interactions. The lack of exposure to clear zeitgebers at the appropriate time, promote circadian and sleep disruption. Patients should be counseled on the use of bright light and exercise to promote alertness. Alternatively, melatonin may provide some benefit in promoting sleep in patients with circadian disorders and potentially improve the individual’s seizure control (94).
Patients with seizures may develop anxiety regarding sleep for fear of recurrence of seizures, and sleep with the light on or in uncomfortable settings to decrease their apprehension. Some patients may also utilize caffeine to counteract the sedating symptoms of the antiepileptic medications and inadvertently promote wakefulness during the sleep period. Patients with epilepsy may choose altered schedules due to driving restrictions and availability of social support. Thus, their timing of activities such as exercise or eating may lead to disrupted sleep. With education, these factors can be addressed to promote a healthy sleeping environment.

For patients with persistent anxiety over sleep, relaxation techniques, biofeedback and stimulus control therapy, and other forms of cognitive behavioral therapy may be helpful. These patients need clinical supervision, since the insomnia may promote or be the first symptom of an underlying affective disorder. Affective disorders are common in epilepsy (95). The clinical distinction of these processes is difficult, but affective disorders may contribute to the patient’s experience of insomnia (95). In these cases, therapy directed at the affective disorder, such as antidepressant and antianxiety medications, may benefit both the affective disorder and sleep disorder (96).

Several anticonvulsants such as felbamate, ethosuximide, zonisamide, and lamotrigine are reported to cause insomnia in some patients. The use of these medications may be essential to seizure control, but peak dosing of the medication early in the wake period may lessen the symptom of insomnia. Insomnia may also be experienced by patients undergoing withdrawal of medication. This is especially true when removing sedating medication. In our clinical experience, this effect may be expected and may be lessened with slower tapering schedules.

The epileptic process and frequent seizures may also cause frequent arousals and insomnia. Higher dosages of sedating antiepileptic medication at night and optimization of seizure control may improve these patients’ symptoms. Clinicians should also question their patients with insomnia about symptoms suggesting sleep apnea and excessive movement, and consider polysomnography when symptoms are present. Clinicians may also consider polysomnography for insomnia failing multiple medication trials.

THE CLINICAL MANAGEMENT OF NOCTURNAL EVENTS IN EPILEPSY

Distinguishing nocturnal events can be a daunting task. For clinicians faced with differentiating nocturnal events in patients with epilepsy, the approach should include a high suspicion that these nocturnal events may be related to the epileptic seizures or initiated by epileptic events. As discussed in other chapters, nocturnal events can occur from a wide array of etiologies. Historically, the clinician may use the key features of age of onset, time of occurrence, presence of memory for the event, frequency of events, and type of behavior (Table 7). These key features are helpful but not absolute rules. Therefore, the clinician should always have a low threshold for diagnostic evaluation.

Individuals with Disorders of Arousal, like sleepwalking and sleep terrors, typically start having events in childhood and do not incur events every night. Most of these events are present in the first half of the sleep period. Although these nonstereotypic events may be very dramatic, the patients have no memory for the event. With these events, the clinician must consider what is causing the partial arousal. Certainly other sleep disorders such as sleep apnea should be
**TABLE 7  Nocturnal Seizure Differentiation**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Nocturnal simple partial seizures</th>
<th>Nocturnal complex partial seizures</th>
<th>Nocturnal generalized seizures</th>
<th>NREM parasomnia</th>
<th>REM behavior disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of onset</td>
<td>Anytime</td>
<td>Anytime</td>
<td>Anytime</td>
<td>Usually childhood</td>
<td>Usually late adulthood</td>
</tr>
<tr>
<td>Time of occurrence</td>
<td>Anytime</td>
<td>Anytime</td>
<td>Anytime (may be soon after awakening)</td>
<td>First third of night</td>
<td>Latter half of sleep period during REM</td>
</tr>
<tr>
<td>Memory of event</td>
<td>Usually</td>
<td>Usually none</td>
<td>Usually none</td>
<td>Usually None</td>
<td>Dream recall</td>
</tr>
<tr>
<td>Stereotypic movements</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Frequency of events</td>
<td>Multiple per night</td>
<td>May be multiple per night</td>
<td>May be nightly</td>
<td>Less frequent Arousals from delta sleep</td>
<td>May be nightly events Excessive EMG tone during REM</td>
</tr>
<tr>
<td>PSG findings</td>
<td>May find epileptiform activity</td>
<td>Epileptiform activity with extended EEG montage</td>
<td>Epileptiform activity with extended EEG montage</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Abbreviations: EEG, electroencephalography; EMG, electromyography; PSG, polysomnography; NREM, nonrapid eye movement; REM, rapid eye movement.*
considered, but we have also seen brief seizures evoke apparent sleepwalking and confusional arousal events. These events are difficult to capture in the laboratory setting. However, the nonstereotypical behavior may be the strongest differentiating feature, separating these events from epileptic seizures.

REM sleep-related parasomnias may also confound the diagnosis of nocturnal events. REM sleep behavior disorder (RBD) is more common in the senior population, paralleling the increase in the prevalence of epilepsy (97). For most patients with RBD, the behavior with each event is variable. Patients have clear recall of the dream content that typically matches the behavior. Patients may have several events in one night, which more commonly occur in the second half of the sleep period. Dream enactment is not always RBD. REM sleep-related seizures can also mimic RBD (97). The key distinguishing feature to these epileptic events is the stereotypical nature of the dreams and behavior (98,99).

Seizures have stereotypic behavior that occurs with each event. This stereotypic behavior is the key feature for identifying nocturnal events as seizures. The clinician must obtain a detailed description of several events to determine if stereotypic behavior is present. The stereotypic behavior may be relatively brief at the beginning of the event and can be missed by the witness. Thus, the clinician may need further documentation of the events. Families may elect to record the behavioral events using video recording devices at home. Some technologically savvy families may bring recordings to their clinical visit. Other patients may require further evaluation such as a polysomnography with extended electroencephalography (EEG) montage or continuous video-EEG recording with extended sleep parameters (93). This recording should include greater electroencephalographic coverage of the frontal and temporal head region and must be reviewed at the 10-sec/page display as opposed to the typical 30-sec/page display (Figs. 1A and B). The great display allows the reviewer to discriminate epileptiform activity from other background activity. By either recording mechanism, the clinician should consider the possibility of other parasomnia behaviors.

The International Classification of Sleep Disorders 2 has defined the key features of sleep-related epilepsies (100). By this definition, sleep-related epilepsies are characterized by at least 70% of the seizures occurring during sleep. Patients should have at least two of the following: abrupt awakenings, generalized tonic-clonic movements, facial twitching, automatisms, urinary incontinence, tongue biting, or postictal confusion or lethargy. As noted above, the diagnosis of sleep-related epilepsy is supported by electroencephalographic findings of epileptiform activity. Some idiopathic epilepsies are characteristically associated with sleep. Benign childhood epilepsy with centrotemporal spikes is associated with nocturnal events, usually occurring within the first hour after sleep onset (Figs. 1A and B). Patients may have facial tonic posturing or jerking that spreads to involve the ipsilateral body. Patients may awake with the episodes, and have drooling, posturing, and inability to speak. These individuals have a classical electroencephalographic finding of spikes between the central and temporal leads and associated with bifrontal positivity (101). These spikes are more prominent in sleep and easier to identify with an extended EEG montage, including the temporal regions. Early onset benign childhood epilepsy with occipital paroxysms may also have a nocturnal pattern. These events are associated with vomiting, hemi-clonic movements of the face and extremities, or episodes of blindness or visual hallucinations. The EEG shows high amplitude sharp and slow wave complexes in the occipital and posterior temporal region (102).
Nocturnal paroxysmal dystonia is also a form of nocturnal epilepsy (103,104). The disorder is characterized by repeated dystonic or dyskinetic movements, involving a single extremity or more extremities and the neck, paroxysmal arousals, and nocturnal wandering. Patients may vocalize and frequently can recall the total event. The events occur from NREM sleep and demonstrate in two major forms: short duration (15–60 seconds) and long duration (up to 60 minutes). Patients may have multiple spells per night or may have clusters of spells with relatively
quiescent periods. The EEG may show little change with the events, but patients frequently respond to medication. Berkovic et al. (105–107) have described inherited forms of this disorder, Autosomal Dominant Nocturnal Frontal Lobe Epilepsy (ADNFLE). For this rare type of epilepsy, a positive family history can be difficult to obtain, since the spells may not be recognized by or acknowledged to other family members. About one in four of these individuals will have daytime seizures. The Australian form of ADNFLE has been linked to chromosome 20q 13.2. An abnormality of the neuronal nicotinic acetylcholine receptor 4 subunit has been found in association with this disorder, yet augmentation of acetylcholine does not appear to alter the frequency or intensity of the seizures. A Norwegian kindred has been linked to chromosome 8 in the M2 domain of CHRNA4 gene.

Bizarre nocturnal events can be a manifestation of symptomatic epilepsies. Pedley and Guilleminault described six individuals with nocturnal walking associated with screaming and violent automatisms that responded to phenytoin or carbamazepine. Three individuals had epileptiform activity in the right temporal region and one had generalized epileptiform activity on routine EEG recording (108). Other case reports have demonstrated nocturnal wandering as symptomatic of seizures from either temporal lobe (109,110). Seizures emerging from the supplementary sensorimotor regions usually evoke a bilateral asymmetric tonic posturing. One classical position is of flexion of one elbow, extension of the other with head turned coined “fencing posturing” by Penfield and Jasper (111). These unusual behaviors are clearly within the spectrum. Although many times these disorders are difficult to differentiate, Derry has developed a questionnaire to distinguish parasomnia from nocturnal seizures. This questionnaire utilizes age of onset, duration of event, clustering, time of night, and stereotypy. Although further work is needed to verify this tool, the tool does highlight some distinguishing features (112).

Seizure activity during the night may also represent a manifestation of an underlying neurological disorder. Landau Kleffner syndrome and Continuous Spike and Wave during Slow Wave Sleep (CSWS) are two rare disorders classified as progressive epileptic encephalopathies (113). Current debate centers around these disorders as distinct or two components of a single disorder spectrum. Landau Kleffner syndrome is characterized by acquired aphasia and frequent epileptiform discharges in the temporal, parietal, central, and occipital regions. These discharges are typically present in wakefulness and are activated by NREM sleep. Children with this disorder develop verbal auditory agnosia, a rapid reduction in speech and behavioral disturbances. Although seizures can occur, they are not a required feature. Generally, the disorder is considered self-limited and may stabilize during the later teen years. Similarly, CSWS is associated with frequent focal and generalized seizures, progressive cognitive selective or global decline, motor impairment, and generalized and multifocal- epileptiform discharges in at least 85% of the time in sleep on recordings occurring for at least one month. This disorder typically leads to more dramatic cognitive decline. Lennox Gastaut syndrome is the most extreme of the progressive epileptic encephalopathies and may have sleep state-dependent EEG findings. Typically, it starts in infancy and may have a devastating outcome. The EEG findings may be more pronounced during wakefulness or sleep and include a high amplitude disorganized background with multifocal epileptiform discharges. Although a consensus is lacking for defining criteria, these syndromes may represent a spectrum of similar disorders (114).

Beyond distinguishing the type of nocturnal events, the clinician should consider some therapeutic issues. For patients with disorders of arousals, the
clinician needs to limit the other causes of arousals. This means decreasing both the epilepsy related arousals and medication-related disruption. For frequent epileptic-related arousals, improvement in antiepileptic therapy may be helpful in reducing the arousals, especially somnogenic medications. Therapies, that are alert promoting, may increase arousals and have the potential to increase disorders of arousal events. The physician should consider limiting stimulating medications in the evening as well as evaluate the potential of other therapies such as stimulators causing arousals. For patients with RBD and epilepsy, patients may be treated with clonazepam or melatonin. Both of these medications have potential antiseizure properties and have little risk of increasing the seizure frequency.

For nocturnal seizure, we recommend that clinicians consider the use of regular release medication during the sleep period. Ideally this strategy provides a higher drug level during the period of vulnerability and reduces the risk of perceived side effects.

CONCLUSION

The interaction of sleep and epilepsy offers new opportunity to explore issues of diagnosis and therapy. By activation of neuronal networks involved with sleep state determination, we can learn more about the epileptic process. Similarly, the pathophysiological mechanisms in epilepsy represent an opportunity to increase our understanding of sleep. These complex relationships often present challenges for even the most astute clinician. Physicians must take a logical clinical approach to these complex situations to reveal the underlying etiologies that are contributing to the sleep complaints and seizure recurrence. Through this approach, the clinician can direct therapy that will improve the quality of life for the patient.

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Somnambulism or sleepwalking (SW) and sleep terrors (STs) are parasomnias included by the recent International Classification of Sleep Disorders -2 (ICSD-2) (1) among disorders of arousal (DOAs) along with confusional arousals.

Parasomnias are defined as “undesirable physical events or experiences” occurring at sleep onset, within sleep, or during arousal from sleep. This is indeed the case for SW and ST.

The term “disorder of arousal” refers to an early paper by Broughton (2), questioning the physiological mechanisms supporting nocturnal paroxysmal events characterized by incomplete dissociated arousals from sleep. Several mechanisms and theories about different combinations of sleep/wake state dissociations have been proposed later (3,4).

It is not uncommon for patients exhibiting these disorders to have more than one disorder, since they share a common pathogenic substrate (de-arousal with motor or sensory activation), a strong familial predisposition, and common precipitating factors including sleep deprivation. They could also share other sleep disorders and sleep-related conditions [obstructive sleep-apnea syndrome (OSAS), restless legs syndrome (RLS), periodic limb movements of sleep (PLMs), and insufficient sleep syndrome].

They are mostly typical of developmental age (3–13 years), but may also start later in life, posing some problems of differential diagnosis with organic, neurological, or psychiatric disorders. A high rate of violent parasomnias, involving embracing improper behavior, has been recently identified in large epidemiologic surveys (5,6) and some of them qualified as DOA.

Somniloquy or sleep talking has been classified among parasomnias for several years by the previous ICSD-1 (7), but has been coded more conveniently among isolated symptoms, “apparently normal variants and unresolved issues” by ICSD-2, given its high frequency of occurrence in normal sleep or within other parasomnias such as SW and rapid eye movement (REM)-sleep behavior disorder (SBD) or sleep disorders such as OSAS.
arousal), but may go as far as running or driving miles after getting out of bed. Agitation and aggressive behavior occur rarely, only when prompted by people attempting to restrain the subjects by limiting their free movements. Subjects are difficult to awaken and generally confused upon forced awakening. Different grades of amnesia follow in the morning, depending on the time elapsed from the episode. Episodes usually occur during the first third of the night, and many occur from several times per night to a weekly or even monthly frequency, especially when children are outgrowing them. Additional features may include staring with open “glassy” eyes, occasionally routine behaviors such as eating [sleep-related eating disorder (SRED)], involving in sexual intercourse, urinating or, most dramatically, climbing out a window or injuring oneself or others (homicidal behavior).

SW prevalence is high in childhood (17%), peaking by age 12 with no substantial gender difference in childhood. Adult sleep-walkers (4% prevalence) are most often men who usually presented with other DOA previously in life. The incidence of SW and related arousals increase proportionally to the number of affected first grade relatives up to 60% with two parents affected (8). Concordance for monozygotic twins was reported as six times higher than dizygotics (9). Co-occurrence of enuresis and ST is high in SW familiars (10).

Parasomnias including SW seem to decrease during pregnancy (11).

There is a high prevalence of DOA in some neurological disorders. These include benign focal epilepsies of childhood (12), nocturnal frontal lobe epilepsy (13), attention deficit hyperactivity disorder (ADHD) (14), and migraine patients (15). There is no link with other types of headache (16), suggesting a possible implication of the serotonergic system (17). Also, vascular insufficiency, often myocardial infarction, has been linked to SW as well as to cocaine or alcoholic abuse (18). Antiarrhythmic medications and, to a lesser extent, benzodiazepines and tricyclic agents have also been reported as possible triggering factors (19,20). Recently, zolpidem has been specifically involved as a possible inducer of SW episodes in people with SRED (21).

Polygraphic Recordings

Classically, DOA occurs out of SWS (stage 3–4) during the first part of the night (Fig. 1) but, especially in adults, may start out of non-REM (NREM) stage 2.

The actual “arousal” usually consists of hypersynchronous delta waves different from the immediately preceding stage 3 to 4 electroencephalogram (EEG) pattern. It is debatable whether this pattern corresponds to sleep or partial arousal, as it often persists to the end of the episode. Associated heart and respiratory frequency may also increase, signaling an autonomic arousal, more so in ST. EEG polygraphic patterns are less clear and defined in adult onset SW episodes (22); NREM sleep instability has been evoked as a predisposing factor to recurrent SW in prepubertal children (23).

The macrostructure of sleep appears generally preserved, but there is an increase of cyclic alternating pattern, probably related to other associated sleep disorders, in particular OSAS. Recently, Zadra et al. (24) suggested that sleep deprivation (SD) could be a safe precipitating maneuver to increase the yielding power of polysomnographic recordings.

There was in fact no difference between SW episodes recorded on baseline versus recovery sleep. Three patterns of arousal have been described in adults by
type 1 or continuous delta activity, type 2 or delta and theta waves admixed with fast activity, and type 3 low voltage fast frequencies, generally associated with more violent behavior.

According to Zadra (24), overall delta activity during SW precipitating arousals was detected in 48% of behavioral episodes from SWS and in 22% of these recorded in adults from stage 2.

SLEEP TERRORS
Clinical Features and Demographic Aspects
ST consists of brisk arousals from SWS accompanied by a cry or scream with autonomic nervous system activation and behavioral manifestations of intense fear.

Increased heart and respiratory frequency, diaphoresis, mydriasis, and increased muscle tone are typical reported features. The person sits up in bed confused and inconsolable, unaware of external environment and stimuli. Similar to SW characteristics are confusion, retrograde amnesia, occurrence during the first part of the night, and precipitation by spontaneous or other SD-related disorders (Table 1).

TABLE 1 Disorders of Arousal Typical Features

<table>
<thead>
<tr>
<th>Prevalent in childhood</th>
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<tbody>
<tr>
<td>Familial predisposition</td>
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<tr>
<td>First third of the night</td>
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<tr>
<td>Mostly out of slow-wave sleep</td>
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<tr>
<td>Sleep deprivation and sleep disruption precipitating factors</td>
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<tr>
<td>Mostly nonstereotypical, nonaggressive behavior</td>
</tr>
<tr>
<td>Retrograde amnesia</td>
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FIGURE 1 Non-rapid eye movement stage 4. Abrupt somnambulism. 10 mm/sec. The patient sits up in the bed ready to get up. Note the abrupt change in sleep recording morphology. 

Abbreviations: EKG, electrocardiogram; EOG, electroocillogram; EMG, electromyogram; PNG, pneumogram.
There is no sex difference in incidence or prevalence ranges from 1% to 6.5% during childhood and is reported around 2% in adults, falling to 1% in the over 65-year-old group (25).

Genetic factors play a role, as well as psychopathology, but only in the adult population. Epidemiologic studies have found, in fact, a prevalence of bipolar depression and anxiety disorders, and co-occurrence of these disorders needs symptom-specific therapy (26).

A familial pattern of occurrence has been described, although it not as clear-cut as in SW. ST usually peaks at age 12 and tends to resolve spontaneously after adolescence, as for all DOA. Serious or even lethal injuries have been rarely reported. Occasionally, ST, as do all DOA, may overlap in children or young adults with RBD as a less serious syndrome than status dissociatus (27), in the overlap parasomnias disorder.

Sleep Recording
Patterns observed in SW are also seen in ST. Episodes tend to be more spread out across the night and differ in NREM stages including stages 1 and 2, even if the number of episodes in delta sleep is higher (28). Autonomic activation is definitively more pronounced.

Differential Diagnosis of Disorders of Arousal
SW episodes can be confused with nocturnal wandering and nocturnal temporal lobe epilepsy (NTLE), with which they may often co-occur, especially in adults (29). Also, NTLE seizures may be confused with SW or ST episodes (30). Single photon emission computed tomography studies have recently documented a dissociation of metabolic activation that is increased in the anterior cingulate and demodulated in the dorso-lateral-prefrontal-cortex.

ST needs to be differentiated from nightmares that occur out of REM sleep, usually in the last part of the night and are remembered by the subject upon “complete” sudden awakening during the night. RBD is also often associated with violent motor behavior and sleep talking or vocalization, and is similar to SW precipitated by respiratory events in OSAS. RBD is also a parasomnia, typical of REM sleep with dissociated physiological features (loss of muscle atonia and presence of phasic muscle activity co-occurring with desynchronized EEG activity and clusters of REMs). Sundowning in demented patients resembles DOA, but involves chronobiological alterations. Psychiatric or organic confusional states and malingering should also be considered, especially in forensic medicine when patients have been involved in criminal behaviors (31).

Disorders of Arousal Treatment
“First aid” treatment involves providing a safe environment for the SW subject. Precautionary measures include locking windows and doors, choosing to live on the ground floor, and removing all loose objects from the bedroom.

Treatment of all related sleep disorders seen as a possible precipitating factor has also been addressed. In particular continuous positive air pressure (CPAP) has been successful in adult chronic sleepwalkers co-diagnosed with OSAS (32).

Medications have been used in children when disruptive or serious autoinjurious behaviors have occurred. Preferably, benzodiazepines such as Diazepam
2 to 5 mg or Clonazepam 0.5 mg at bedtime have been used (33). Alternatively, trazodone and selective reuptake inhibitors have been successfully employed (34,35). Psychotherapy has been proposed by several authors (36), mostly with undocumented, unencouraging results. Cognitive-behavioral treatment (37) holds more promising results, especially for children. Muscle biofeedback or relaxation training has been useful in 25% of treated adults (38). Hypnosis has proven helpful and safe on a short-term basis with or without psychotherapy (22,38). Treatment may pose some problems in the elderly population, given their specific vulnerability to benzodiazepines and many psychotropic drugs that could, as in elderly, demented patients, induce or worsen confusion at night-time.

Recently, Levetiracetam has been successfully employed to manage sleep disruption in ADHD children with suppression of DOA, besides having a positive effect on RLS, seizures, and interictal EEG abnormalities in the same group (14).

**SOMNILOQUY OR SLEEPTALKING**

Sleeptalking is essentially viewed as a commonly occurring behavior at night-time in normal as well disrupted sleep. It consists of generally brief, infrequent utterances ranging from vocalization to fully elaborated conversational discourse, occurring during REM, NREM, or during arousal. Speech content may reflect sleep or dream mentation, often emotionally loaded. It can be make sense or be nonsensical, and may be precipitated by all factors inducing a temporary arousal (noise, apneic event, and periodic leg movement). It is often associated with atypical sexual behavior during sleep or SRED during confusional arousals or SW episodes. Sleep loss, stress, and psychopathology have all been evoked as possible precipitating factors. Sleep talking is common especially among children; however, the exact prevalence, depending on the frequency of experienced behavior, is difficult to ascertain. In a recent survey, prevalence has been estimated as 4.9% in China (39). Approximately 10% of children of the age three to 10 years would sleep talk on a nightly basis. Co-occurrence with SW and nightmares has been described (40), but not with enuresis. Genetic factors seem to be involved, according to studies in mono and dizygotic twins (41), where co-occurrence with other parasomnias has also been examined. No candidate gene, however, has been so far proposed. Diagnostic work-up is required only when the sleep disorders co-occur, such as OSAS or RBD. No specific treatment exists unless it is part of other sleep disorders. Sleep talking is considered a benign condition potentially resolving spontaneously. No complications are described besides annoyance to the bed partner or undesired disclosure of embarrassing conditions. Sleep talking is not considered as a symptom of psychopathology. Avoidance of stressful conditions and good sleep hygiene (42) may help symptomatic management.

**ENURESIS**

This parasomnia is characterized by recurrent involuntary urination during sleep. It may be classified as primary (80% of all cases) when nocturnal bladder control has never been achieved from infancy or secondary occurring after a period of dryness of at least three months. The reported prevalence varies according to the definition and age groups, with a general prevalence of 8% in healthy children age 7 to 15 years (43) with boys being affected more than girls, and black more than white children. There is a strong familial trait with a suggested incidence of
77% for both, 44% for one enuretic parent. Enuresis is more represented among institutionalized children and highly prevalent, co-morbid, with ADHD (44), OSAS (45), and sickle cell anemia.

Diagnostic work up includes urinalysis and a comprehensive sleep and enuresis history. If symptoms persist after 12 weeks of treatment, further work up will include radiographic and cystoscopic examination, cystometric and sphincter EMG studies. Video-PSG is recommended when snoring or sleep breathing disorders (SBD) are suspected.

Therapeutic options include behavioral techniques such as enuresis alarm (46) variably combined with positive reinforcement and retention control.

Medications include antidepressants (Imipramine 25 mg prior to bedtime), antidiuretics (desmopressine 200–600 mg orally), antispasmodics (tolterodine or oxybutynin) especially in children with detrusor instability, alone or in combination with desmopressin (47). Some success has been reported with either psychotherapy or hypnotherapy.

**CATATHRENA**

This rare disorder also known as “nocturnal groaning” or “expiratory vocalization” refers to an unusual expiratory noise occurring in bursts during NREM sleep stage 2 and especially REM sleep with normal SaO2 and without associated motor phenomena (48). Orem (49) suggests that typical REM bradypnea may play a favoring role through the erratic activation of the internal drive system neurons. Patients are often unaware of it, and the disorder is generally reported by bed partners, representing a potential familial and social source of concern. Differential diagnosis includes stridor, OSAS, snoring, and nocturnal seizures. Symptoms are usually long lasting and may have a familial trait. No specific therapy is advised. CPAP treatment has been explored as an option (50) in a patient with respiratory dysrhythmia, however, atypical for catathrenia.

**SLEEP RELATED EATING DISORDER**

Sleep related eating disorder (SRED) refers to repetitive eating episodes occurring during sleep or during partial arousal from sleep often associated with other sleep related motor disorders such as PLMs, RLS, or SW (51). It may respond to dopamine agonists such as pramipexole (52). Precipitating factors may include sleep deprivation and drugs such as zolpidem (53). An important distinction refers to the nocturnal eating syndrome (NES), nocturnal episodes of binge eating out of wakefulness responding to SSRIs and to topiramate (54) or to compulsive nocturnal behaviors as an extension of daytime binge eating disorders in adults. A disease continuum may be hypothesized. Long-term follow up studies are needed to better elucidate common features and differential diagnosis between the different variants of abnormal eating behaviors.

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Rapid Eye Movement Sleep Behavior Disorder

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INTRODUCTION

The parasomnias can conveniently be divided into two major groups: (i) primary (disorders of the sleep states per se), and (ii) secondary [disorders of other organ systems taking advantage of the sleep period to manifest themselves (nocturnal seizures, or psychogenic dissociative disorders)]. The primary parasomnias may be divided into those arising from nonrapid eye movement (NREM) sleep, from REM sleep, or those not respecting sleep states. The most common and best-studied REM sleep primary parasomnia is the REM sleep behavior disorder (RBD) (1). Although various polysomnographic (PSG) and clinical components of RBD have been identified by European, Japanese, and American investigators since 1966, RBD was not formally recognized and named until 1985 to 1987 (2,3), and it was incorporated within the International Classification of Sleep Disorders in 1990 (4,5).

HISTORY AND BIOLOGICAL BASIS

In 1965, Jouvet and Delorme (6) reported that experimentally induced, bilateral, symmetrical, dorsolateral pontine tegmental lesions in cats resulted in continuous and permanent loss of REM atonia, whereas lesions to other brainstem structures had no effect on REM sleep. These cats displayed de novo “hallucinatory type” behaviors during REM sleep that strongly resembled oneirism (dream-enacting behavior). The oneiric behaviors in these cats always occurred during unequivocal REM sleep, and REM sleep had retained all of its identifying features apart from loss of REM atonia. Thus, the mechanisms responsible for the oneiric behaviors were postulated to originate in the brain and to be dependent upon the internal neural organization of REM sleep. The cat animal model has recently been extended to the rat (7).

The supraspinal mechanisms responsible for REM atonia (8,9) originate in the peri-locus coeruleus (LC)-alpha nucleus in the pons that excite neurons of the nucleus reticularis magnocellularis in the medulla, which then transmit descending inhibitory projections—more powerful than the competing descending excitatory projections—to the spinal alpha motoneurons, resulting in hyperpolarization and thence muscle atonia. Therefore, “REM atonia” results from an active process involving specific neuronal circuitry, and is not the result of passive cessation of muscle tone. During REM sleep, the somatic motor system is shut down at the level of the
spinal motoneurons while being quite activated at higher levels of the neuraxis. Multiple areas of the brainstem may influence muscle tone during REM sleep (10).

Experiments have shown that loss of REM sleep atonia alone is insufficient to generate RBD. Presumably, there must also be disinhibition of motor pattern generators in the mesencephalic locomotor region to result in over-excitation of phasic motor activity with behavioral release during REM sleep (11,12). Recent studies in dogs by Lai and Siegel have revealed a colocalization of the atonia and locomotor systems of REM sleep in the pons, providing an anatomic basis for the simultaneous dysregulation of these two systems in RBD (13).

Neuroimaging studies indicate dopaminergic abnormalities in RBD. Studies of single photon emission computed tomography (SPECT) have found reduced striatal dopamine transporters (14,15), and also decreased striatal dopaminergic innervation has been reported (16). Decreased blood flow in the upper portion of the frontal lobe and pons has been reported (17), as has functional impairment of brainstem neurons (18). Positron emission tomography (PET) and single photon emission computed tomography (SPECT) studies have revealed decreased nigrostriatal dopaminergic projections in patients with multiple system atrophy (MSA) and RBD (19). Decreased blood flow in the upper portion of the frontal lobe and pons has been found in one MRI and SPECT study (20). Impaired cortical activation as determined by electroencephalographic spectral analysis in patients with idiopathic RBD supports the relationship between RBD and neurodegenerative disorders (21).

The overwhelming male predominance of RBD raises the intriguing question of hormonal influences, as suggested in male-aggression studies in both animals and humans (22–24). Another possible explanation for the male predominance is sex differences in brain development and aging (25, 26). There is evidence for a sex difference on the effects of sex steroids on the development of the locus coeruleus in rats (27). Spontaneous cases have occurred in dogs and cats (28).

CLINICAL MANIFESTATIONS

RBD is more common in people older than 50 years of age, but the disorder may begin at any age. Eighty percent to 90% of affected patients are men (29–31). The disorder most frequently presents with the complaint of dramatic, violent, potentially injurious motor activity during sleep. These behaviors include talking, yelling, swearing, grabbing, punching, kicking, jumping, or running out of the bed. Injuries are not uncommon and include ecchymoses, lacerations, or fractures involving the individual or bed partner. The violence of the sleep-related behavior is often discordant with the waking personality. The increased aggressive dream content experienced by patients with RBD is not associated with increased daytime aggressiveness (32). The reported motor activity usually correlates with remembered dream mentation, leading to the patient’s complaint of “acting out my dreams.” Less frequently, the primary complaint is one of sleep interruption. There is evidence that the presentation of RBD is different in males (violent dream-enacting behaviors) than in females (less violent dream-enacting behaviors), skewing the reported male predominance (33). In some cases, bruxism, somniloquy, or periodic limb movements of sleep may be the heralding or primary manifestation of this disorder. The duration of behaviors is brief, and upon awakening from an episode there is usually rapid return of alertness and orientation. Some patients adopt extraordinary measures to prevent injury during sleep: they may
tether themselves to the bed with a rope or belt, sleep in sleeping bags, or sleep on a mattress on the floor in a room devoid of furniture.

**Case Vignette**

A 75-year-old female who reported having dream-enacting behavior since her early 50s, beginning with complex movements and talking during her sleep—often accompanied by very comical dreams. This evolved into more violent dreams involving attacking animals. These behaviors led to the acquisition of a king-sized bed so that her behavior was less disruptive to her husband. She and her family regarded these behaviors as “amusing” until one night, when dreaming she was jumping over a fence in a garden, she threw herself out of bed, denting a door with her head, and sustained a cervical vertebral compression fracture requiring surgical repair. She was on no medications known to trigger RBD, and had no abnormalities on neurological examination. Her sleep study revealed prominent REM sleep without atonia (Fig. 1), associated with very frequent extremity twitching and vocalization.

Due to its association with REM sleep, the timing of the behaviors during the sleep period ranges from 90 minutes after sleep onset to the final awakening in the morning. RBD rarely occurs during daytime naps, as REM sleep during naps is exceptional. Often there is a prodromal period lasting years or decades of progressively more prominent sleep talking, yelling, or limb jerking during sleep. Many patients with RBD report that their dreams have become more vivid and “action-packed” coincident with the onset of the dream-enacting behaviors.

**FIGURE 1** An epoch of rapid eye movement sleep demonstrating dramatic release of both tonic and phasic electromyographic activity during REM sleep in a patient with RBD. This was associated with prominent extremity twitching and vocalization. *Abbreviations:* LOC/ROC, left/right outer canthus; A1/A2, left/right ear; C3/C4, left/right central EEG; O1/O2, left/right occipital EEG; Chin1- submental EMG; Arm, left/right extensor digitorum EMG; LEG, left/right anterior tibialis EMG; ECG, electrocardiogram.
The frequency of the episodes ranges from once every few weeks to multiple nightly episodes (34). Acute transient RBD may last for one night or a few nights and is usually associated with medication use or withdrawal.

Serious injuries, including subdural hematomas may result from dream-enacting behaviors, raising interesting and difficult forensic medicine issues (35–37).

**Acute Rapid Eye Movement Sleep Behavior Disorder**

Acute onset of RBD is almost always induced by medications (tricyclic antidepressants, monoamine oxidase inhibitors, serotonin-specific reuptake inhibitors, bisoprolol, or cholinergic treatment for Alzheimer’s disease) or associated with their withdrawal (alcohol, barbiturate, or meprobamate) (38–41). Caffeine and chocolate abuse has been implicated in causing or unmasking RBD (42). RBD may be triggered by selegiline, prescribed as treatment for Parkinson’s disease and by cholinergic agents, prescribed for patients with Alzheimer’s disease (43–45). Drug-induced [particularly serotonin-specific reuptake inhibitors (SSRI) medication] RBD is becoming increasingly common.

**Chronic Rapid Eye Movement Sleep Behavior Disorder**

The chronic form of RBD is idiopathic in 25% to 60% of occurrences (29,30,46). The remaining cases are associated with various degenerative neurologic disorders (discussed later). All PSG and behavioral features of RBD are indistinguishable across subgroups, irrespective of gender, age, or the presence/absence of a neurological disorder (47). This suggests the presence of a “final common pathway” in RBD that can be accessed by a wide variety of pathologic states.

RBD behaviors occur within REM sleep, often without associated tachycardia, and not during arousals from REM sleep. Complex RBD behaviors are generally aggressive or exploratory and never appetitive (feeding, sexual). There is an almost inextricable link between altered dreams and dream-enacting behaviors, suggesting a mutual pathophysiology: patients do not enact their customary dreams, but rather they enact distinctly altered dreams, usually involving confrontation, aggression, and violence.

**CLINICAL AND LABORATORY EVALUATION**

Laboratory evaluation of injurious or disruptive nocturnal behaviors consists of the following:

1. Clinical sleep–wake interview, with review of physician referral information and past medical records, and with review of a completed, structured, patient questionnaire, covering sleep–wake, medical, psychiatric, and alcohol/substance use history (including family history), and review of systems.
2. Psychiatric and neurologic interviews and examinations.
3. Extensive overnight PSG monitoring with continuous videotaping. A full electroencephalographic montage is employed in addition to conventional physiologic sleep parameters. Monitoring for sleep-disordered breathing is mandatory, as obstructive sleep apnea may masquerade as RBD.
4. Daytime multiple sleep latency testing (MSLT), if there is a complaint or suspicion of daytime sleepiness or fatigue.
5. If RBD is diagnosed, neuropsychometric testing should be performed due to the close relationship between RBD and degenerative neurologic conditions discussed later. Also, a brain imaging study, preferably a magnetic resonance scan, may be indicated, depending on findings elicited from the clinical history and/or neurologic examination.

Minimum diagnostic criteria of RBD (4,48):

1. PSG abnormality during REM sleep: elevated submental electromyographic (EMG) tone and/or excessive phasic submental and/or limb EMG twitching.
2. Documentation of abnormal REM sleep behaviors during PSG studies (prominent limb or truncal jerking, complex, vigorous, or violent behaviors), or a history of injurious or disruptive sleep behaviors.
3. Absence of clinical or EEG evidence of epileptiform activity during REM sleep.

A single night of recording is generally sufficient to establish the diagnosis, because REM sleep polysomnographic abnormalities are usually present even when a behavioral episode does not occur. A polysomnographic scoring system for RBD in neurodegenerative disorders has been developed (49).

PREVALENCE

A recent phone survey of over 4900 individuals between the ages of 15 and 100 years of age indicated an overall prevalence of violent behaviors, in general, during sleep of 2%, one quarter of which were likely due to RBD, giving an overall prevalence of RBD at 0.5% (50). Another survey estimated the prevalence of REM sleep behavior to be 0.38% in elderly individuals (51).

ASSOCIATION WITH OTHER NEUROLOGICAL CONDITIONS

The literature now contains hundreds of cases of RBD (29,52). Increasingly, chronic or “idiopathic” RBD is becoming associated with neurologic disorders, but there is great diversity in category and location. Three pertinent comments are warranted: first, neurodegenerative disorders and narcolepsy are the most common neurologic disorders associated with RBD. Second, the pons is rarely grossly involved, as ascertained by clinical neuroanatomical and neurophysiologic testing, which stands in contrast to the animal model of RBD. Third, a wide variety of neurologic conditions can also manifest “REM sleep without atonia” and/or excessive phasic EMG twitching in REM sleep, as a polysomnographic observation but without the clinical emergence of RBD—in other words, various preclinical forms of RBD can be found in the same neurologic disorders that are associated with RBD, but also in individuals without any apparent neurologic disease (39,48,53–55). Sleep bruxism, in one case, has been reported to be a subclinical manifestation of RBD (56).

Association with Neurodegenerative Disorders

The chronic form of RBD is idiopathic in 25% to 60% of occurrences (29,30,46,57). The remainder are associated with various degenerative neurologic disorders, most notably with the synucleinopathies [Parkinson’s disease (including juvenile Parkinson’s disease)], dementia with Lewy body disease, and MSA (Shy-Drager syndrome, striatonigral degeneration, olivopontocerebellar degeneration) (58,59).
A recent study found that 40% of patients with Parkinson’s disease had either RBD (16%) or polysomnographic evidence of REM sleep without atonia (60), and 90% of patients with MSA had REM sleep without atonia. In another study, all of the 19 patients with MSA had RBD (61). Surveys indicate a very high prevalence of RBD in Parkinson’s disease (up to 47%) and MSA (up to 69%) (62–68). In 27% of patients with both RBD and Parkinson’s disease, the RBD preceded the Parkinson’s disease. There is evidence that Parkinson’s disease and RBD are physiologically and anatomically linked (69). This is supported by the fact that olfactory impairment is common in both (70). The presence of RBD in patients with Parkinson’s disease may be predictive of cognitive impairment (71). RBD is also seen in nonsynucleinopathy-related Parkinson’s disease and in progressive supranuclear palsy (a tauopathy) (72,73). The clinical features of RBD are identical in the idiopathic cases and in those with Parkinson’s disease or MSA (74). Interestingly, there is a striking (77%) male predominance in patients with Parkinson’s disease who display RBD (75).

In one series, more than two-thirds of males initially diagnosed with idiopathic RBD eventually developed symptoms of one of the synucleinopathies (76,77), with the average interval between the onset of REM sleep behavior disorder and the first of the other symptom of the underlying neurodegenerative disease being over 10 years. The fact that the majority of patients with RBD may eventually be found to have an underlying neurodegenerative or medication-induced etiology has led to the suggestion of use of the term “cryptogenic RBD” rather than “idiopathic RBD” (78).

Other reported associations include: mitochondrial encephalomyopathy, normal pressure hydrocephalus, Tourette’s syndrome, Machado-Joseph disease (spinocerebellar ataxia type 3), cerebellopontine angle tumors, group A xeroderma, multiple sclerosis, ischemic or hemorrhagic cerebrovascular disease, brainstem neoplasms, autism, and Guillain-Barré syndrome (79–92).

**Association with Narcolepsy**

Since both RBD and narcolepsy may be considered conditions associated with abnormalities of state boundary control, it would stand to reason that RBD may be a manifestation of narcolepsy, and may be precipitated or worsened by the administration of tricyclic antidepressants or serotonin-specific reuptake inhibitors, prescribed for the symptom of cataplexy (93). One questionnaire survey found that 36% of patients with narcolepsy had symptoms suggestive of RBD (94). RBD-like behaviors have been reported arising from cataplexy in a patient with narcolepsy (95).

**TREATMENT**

The acute form is self-limited following discontinuation of the offending medication or completion of withdrawal. Clonazepam is a remarkably effective treatment in human RBD, in controlling both the behavioral and the dream-disordered components of RBD (47). Treatment is usually immediately effective at a dose of 0.5 to 1.0 mg at bedtime (range: 0.25–4.0 mg). Prompt relapse of RBD occurs whenever the patient fails to take clonazepam on a given night. The mechanism of therapeutic action has been shown by Lapierre and Montplaisir to involve suppression of phasic EMG activity during REM sleep rather than restoration of REM sleep atonia (96). The long-term efficacy and safety of chronic, nightly
clonazepam treatment of RBD and of other parasomnias at this center has recently been reported (97). Underlying obstructive sleep apnea should be ruled out before prescribing clonazepam (98). Adjunctive or alternative treatments, for the few RBD patients who do not respond fully to clonazepam or who develop daytime somnolence from this agent, include the following: desipramine or imipramine, carbamazepine, clonidine, carbidopa/L-dopa, L-tryptophan, or gabapentin (48). Recently, melatonin (in relatively high doses, i.e., 6 to 12 mg at bedtime) (99–101) or pramipexole (102,103) have been reportedly effective.

The treatment of Parkinson’s disease-associated RBD and RBD associated with narcolepsy is the same as for idiopathic RBD (76). Pallidotomy has been effective in one case of RBD associated with Parkinson’s disease, whereas chronic bilateral subthalamic stimulation has not been effective (104–107).

Interestingly, there may be spontaneous improvement in RBD symptoms with progression of the underlying neurodegenerative condition (108).

**VARIATIONS**

**Parasomnia Overlap Syndrome**

A subgroup of RBD patients have been identified with PSG-documented overlapping NREM–REM sleep motor parasomnias consisting of sleepwalking, sleep terrors, and RBD (109). Two other “overlap” parasomnia cases have been reported (110,111). These cases demonstrate motor–behavioral dyscontrol extending across NREM and REM sleep.

**Status Dissociatus**

This is the most extreme form of RBD, and appears to represent the complete breakdown of state-determining boundaries (112,113). Clinically, these patients appear to be either awake or “asleep”; however, their “sleep” is very atypical, characterized by frequent muscle twitching, vocalization, and reports of dream-like mentation upon spontaneous or forced awakening. Polygraphically, there are no features of either conventional REM or NREM sleep. Rather, there is the simultaneous admixture of elements of wakefulness, REM sleep and NREM sleep. “Sleep” is often perceived as “normal” and restorative, despite the nearly continuous motor and verbal behaviors and absence of PSG-defined REM or NREM sleep. Conditions associated with status dissociatus include protracted withdrawal from alcohol abuse, narcolepsy, olivopontocerebellar degeneration, prior open heart surgery, or following brainstem surgery (61,112). The abnormal motor and verbal nocturnal behaviors of status dissociatus may respond to treatment with clonazepam.

**Agrypnia Excitata**

This recently described condition is characterized by generalized overactivity associated with loss of slow-wave sleep, mental oneiricism (inability to initiate and maintain sleep with wakeful dreaming), and marked motor and autonomic sympathetic activation seen in such diverse conditions as delirium tremens, Morvan’s fibrillary chorea, and fatal familial insomnia (81,114,115). Oneiric dementia is likely a related condition (116). Oneiric symptoms reminiscent of RBD in these conditions should lead to closer scrutiny of sleep in other neurologic disorders (80,114–117).
DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes sleepwalking, sleep terrors, nocturnal seizures, psychogenic dissociative states, post-traumatic stress disorder, nocturnal panic disorder, delirium, and malingering. Confusional arousals with behaviors that may mimic RBD can occur with nocturnal seizures, obstructive sleep apnea, sleep-related gastroesophageal reflux, or periodic limb movement disorder (118–120). Previously undiagnosed RBD occurring in a patient in the intensive care unit may be particularly difficult to diagnose (121). A recently described additional “overlap” syndrome of RBD behaviors arising from light NREM sleep raises the question of disinhibition of motor pattern generators as an explanation for RBD behaviors arising from either REM or NREM sleep (73). This broad differential diagnosis mandates formal sleep studies in suspected RBD.

SUMMARY AND DIRECTIONS FOR THE FUTURE

RBD is a fascinating experiment in nature predicted by animal studies. Initially felt to be a medical curiosity, over time, the majority of individuals with RBD will eventually develop additional signs and symptoms of a number of neurodegenerative disorders, notably one of the synucleinopathies—often after a prolonged interval. This relationship should encourage continued close collaboration between clinical and basic science sleep medicine.

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Part VII: Sleep Apneas

Obstructive and Nonobstructive Sleep Apnea: The Neurological Perspective

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INTRODUCTION

Disorders of breathing during sleep constitute an important health problem with significant morbidity and excessive mortality (1–3). Common consequences of sleep-disordered breathing (SDB) vary from nocturnal hypoxemia, sleep fragmentation, impaired daytime vigilance or excessive daytime sleepiness (EDS), cognitive dysfunction (4–7) to increased morbidity and mortality (8) from complications secondary to arterial and/or pulmonary hypertension, arrhythmias, congestive heart failure, stroke, and motor vehicle and industrial accidents (7,9–11).

The American Academy of Sleep Medicine (AASM) has published criteria for the classification of sleep-related respiratory events (12,13). According to these, an apnea is defined as a complete cessation of respiratory flow for at least 10 seconds; a hypopnea is the 30% or more reduction in respiratory flow associated with a drop in oxygen saturation of more than 4%. Obstructive type of apnea/hypopnea is an obstructive respiratory event characterized by partial or complete occlusion in the upper airways along with ongoing respiratory effort. In contrast, central type of apnea/hypopnea is a respiratory event, which is characterized by a reduction or complete cessation of the respiratory effort and drop in oxygen saturation with open upper airways. Mixed events are a combination of both, usually a central apnea followed by an obstructive component as inspiration resumes. In addition, intermittent to heavy, chronic snoring and the upper airway resistance syndrome (UARS), as featured by repetitive EEG arousals related to respiratory efforts and by the increasing negative swings in pressure, represent the other manifestations of SDB (2). The UARS was first described in 1993 as a clinical entity by Guilleminault et al. (14). The new international classification of sleep disorders (ICSD 2nd edition) places UARS in the Obstructive Sleep Apnea section (12). Respiratory effort-related events are defined as an increase in upper airway resistance caused by a reduction in airflow less than 30%, which ends in arousal. The severity of SDB is defined by the number of events per hour sleep. It can be defined on the basis of tabulation of apnea and hypopnea [apnea-hypopnea index (AHI)], as mild (5–15 events/hr), moderate (15–30 events/hr), or severe [the obstructive sleep apnea syndrome (OSAS)]. If “events” include breathing disturbances that are not included in apnea and hypopnea, that is, with abnormal breathing without clear impact on oxygen saturation, or clear, visually recognizable EEG arousal, a respiratory disturbance index (RDI) can be tabulated. It includes, in addition to AHI, other events. Sometimes, AHI and RDI have been erroneously equated.

Classically, breathing disorders during sleep are divided into two categories: (i) disorders of upper airway, (ii) disorders of diaphragmatic and/or other inspiratory muscle dysfunction. Disorders with abnormalities located in the upper airway
can lead to obstructive, central, or mixed respiratory events. Disorders with abnormalities involving the inspiratory muscles can also rarely lead to these three types of respiratory events. Neurological disorders may secondarily result in respiratory problems, the manifestations of which are sometimes complicated by the underlying condition. A better knowledge of disorders of breathing during sleep is therefore crucial in early diagnosis and treatment of respiratory dysfunction, as well as for the management of the underlying condition.

UPPER AIRWAY OBSTRUCTION DURING SLEEP

The disorders of upper airway obstruction include OSAS, the pure obstructive sleep hypopnea syndrome (which is very closely related to OSAS and may be based on monitoring differences), and the UARS. It has been mentioned that these disorders represent different degrees of severity along the spectrum of the same clinical breathing disorder. Actually, the differentiation of these three syndromes is closely related to the technical capabilities of the monitoring equipment used, and the view that it only relates to a different severity is a simplistic view of the question.

PREVALENCE

Sleep-related breathing disorders are highly prevalent among adult population with a prevalence of habitual snoring as 28% to 44% in adult women and men, respectively (15). The OSAS is the most common type of SDB with an incidence of about 35% in patients referred to the sleep laboratory because of socially disturbing snoring and/or EDS (16). However, prevalence studies for OSAS are limited, and there is no similar data on UARS. The Wisconsin sleep cohort study of white-collar workers revealed the prevalence of OSAS as 9% in women and 24% in men aged between 30 and 60 years (15). This data has been extrapolated to the general population to yield a prevalence of 2% for women and 4% for men (15), but this prevalence is recognized as low today. It also concerns Caucasians, and the prevalence in blacks, and far east Asians has been mentioned to be higher, despite the fact that data are mostly lacking. In comparison with neurological disorders, for every 100,000 individuals in the United States, there are 3000 OSAS patients, 2000 migraine patients, 650 epilepsy patients, 250 dementia patients, 200 patients with Parkinson’s disease, 60 multiple sclerosis patients, 40 narcolepsy patients, and 20 patients with polyneuropathy (17). There is a tendency to always associate SDB with a problem in the upper airway, and this is a mistake. There are many disorders that may lead to abnormal inspiratory muscle problems. There is the very complicated problem of obesity, where subjects with android type obesity present a combination of enlarged neck circumference and abdominal obesity, leading to upper airway problems and a chest bellows syndrome resulting in reduction of lung volume, a status always worse during REM sleep due to the supine position and to the REM sleep atonia impacting on the respiratory accessory muscles. There is little knowledge on the prevalence of these inspiratory disorders during sleep or the combined problem seen with obesity, despite the fact that obesity is considered an epidemic in the United States and other industrialized countries and may involve up to 50% of the general adult population.
PATHOPHYSIOLOGY

We have to dissociate primary involvement of the upper airway, primary involvement of the inspiratory muscles and combination of both impairments. The terminology “SDB” is thus a poor labeling of problems.

Upper Airway Problem

It has been proposed there is a pathophysiological continuum that ranges from intermittent snoring to OSAS, that is, partial or complete upper airway occlusion is present (1). This is probably a limited view of the question. In the recent past it has become obvious that there are two different local neurological conditions even in what has been labeled an isolated upper airway problem. They are as follows.

1. Presence of good sensory in-put from upper airway sensors and appropriate conduction of motor commands to the upper airway dilators.
2. Presence of local lesions (involving local sensory and probably local motor pathways) that do not allow appropriate contraction of dilator muscles in a timely manner and that lead to a reduction of the upper airway size with increased risk of upper airway narrowing and collapse related to the changes in diaphragmatic efforts.

The very first step may be related to an anatomical narrowing located in the upper airway, that is, from the tip of the nose to the hyoid bone.

In the first situation, subjects may present with UARS or chronic snoring. In the latter condition, subjects will present with obstructive hypopnea and apnea, and opening of the upper airway will have to call upon different sensors, some slower in response during sleep, such as chemo-sensors (18–27). Passage from absence of local neurological lesion to presence of lesion may be seen in the same individual, but subjects may be presenting the first situation without evidence of evolution to the local neurological lesion phase. Clinical presentation and consequences seem very different, and one condition may be reversible, whereas the other one may leave permanent local dysfunctions potentially responsible for a different presentation.

The presence of abnormal local sensory input has been supported during sleep by clinical neurophysiological and histological studies and also by (18–27) demonstration of the presence of abnormal evoked potentials with experimental upper airway occlusion during NREM sleep (28,29). The presence of a local neuropathy, present in obstructive apnea–hypopnea syndrome, may explain a slow progressive evolution demonstrated over time in certain obstructive sleep apnea (OSA) patients even if appropriately treated with nasal continuous positive airway pressure (CPAP) (30).

In summary, the presence/absence of this local neuropathy seems to be the main element dissociating OSAS from UARS, with their different clinical presentations. However, many unknowns still exist, such as how much of a neuropathy is needed to see the development of OSAS, when does the syndrome become an irreversible problem, and what are the components that lead to this local neuropathy. Suspicion that the vibratory effect of snoring and local microtrauma related to abnormal transpharyngeal pressure, edema, and inflammatory local conditions are involved is strong, but the interaction between these different factors is unknown, as is the speed of development of local irreversible lesions.
**Location of Airway Collapse**

For years emphasis has been placed on the location of airway collapse, as it was thought the exact localization of collapse site was essential for appropriate treatment as it is subject to vary (31,32). However, this indicates again only a poor understanding of the pathophysiology behind the development of obstructive sleep apnea, as mentioned earlier. The understanding of upper airway anatomy is probably the most important during the phase without important local lesions of upper airway sensors, as anomalies may be treated and may avoid evolution toward local neuropathy and, as such to date, presence of permanent local neurological impairment.

Airway anatomy has an important effect on airway patency (33,34). Although nasal narrowing seems to play a clear role in the development of pharyngeal narrowing, little attention has been given to the description of nasal impairment instead; most studies have focused on the pharynx. Normal pharyngeal structures in a small bony compartment or increased amount of soft tissue, such as tonsils or adenoids in a normal-sized bony compartment, will result in upper airway narrowing (35,36).

The intraluminal negative pressure generated by the diaphragm during inspiration and the extraluminal pressure from soft tissue and bony structures surrounding the airway constitute the two primary forces to reduce the pharyngeal upper airway area (37). Thus, negative pressure generated by the diaphragm during each inspiration diminishes the airway size depending on the compliance of the airway walls. These collapsing forces are counteracted by pharyngeal dilator muscle activation, especially genioglossus, tensor veli palatini muscles in the pharyngeal area (37) (other muscles in the nose and the upper larynx are also involved, but most studies to date have focused on the pharyngeal region). Some of the physio-pathological investigations have looked at the effect of sleep on these pharyngeal muscles: serotonergic and noradrenergic neurons modulating arousal have a tonic excitatory influence on upper airway motoneurons, such as the hypoglossal nerve (38,39). However, during sleep, the control of these muscles changes in a way that these responses become less effective or slower. Several additional factors, including vascular perfusion, the posture of the individual (supine vs. lateral), airway secretions, and tissue microstructure, are also important factors in pharyngeal upper airway obstruction (37). The genioglossus muscle also becomes hypotonic, contributing to the airway obstruction in OSAS patients in the supine position (40,41). The pathophysiology based on studies looking at the pharynx and not integrating the problem of abnormal breathing during sleep in a developmental perspective (i.e., effect of development of the upper airway over age and interaction between nasal breathing and cranio-facial, maxillo-mandibular development) is very limited in scope.

**Decrease in Inspiratory Effort**

The pathophysiology behind the development of partial reduction or complete elimination of diaphragmatic effort during sleep is multiple. It can be related to neurologic impairments involving the sensory-motor loop controlling the diaphragm and other accessory inspiratory muscles, or the neuromuscular junction or the muscles themselves. This very large group of disorders may involve many health problems from congenital central alveolar hypoventilation syndrome (CCHS) to the near physiologic periodic breathing seen in humans sleeping in high altitude.
It may also be related to abnormally slow passage of information of the ventilatory status to appropriate receptors due to circulatory deficiencies, such as cardiac failure, to endocrine problems with specific secondary impact on the central nervous system or muscles; it may be related to ventilatory problems due to reduction in lung volume due to intrinsic lung problems or chest bellows impairment, usually greatly worsened by the physiologic REM sleep muscle atonia, as seen in abdominal obesity. To equate decrease in respiratory efforts only to primary neurological disorders involving the central nervous system command of inspiration is thus erroneous.

An interesting demonstration is the appearance of “central” apnea in patients with upper airway narrowing during sleep, that may be seen with incomplete resolution of upper airway obstruction related to too low titration with nasal CPAP, or in opposition the nasal CPAP-induced central apnea when a too high nasal CPAP titration or inappropriate auto-calibrated CPAP equipment setting has occurred, not allowing the normal inspiratory–expiratory switch. This occurrence of central (or better called diaphragmatic) events is often considered as a difficult diagnostic dilemma when performing nasal CPAP titration during sleep. This should not be so, as the pathophysiology behind appearance of the central apnea during incomplete treatment of upper airway obstruction has been well investigated, and is related to the normal switch of the ventilatory controls from wakefulness to sleep and during sleep and particularly the changes related to the changes in these controls at sleep onset. One should first pay attention to where in the respiratory cycle do the diaphragmatic apnea occur. Often it is during expiration, and one should consider the event as a long expiratory pause and not really an “apnea”. Skatrud and Dempsey (42) have demonstrated that it relates to sleep physiology. Due to the nonspecific stimuli, which plays a major role in the inspiratory–expiratory alternation with anticipation of the changes in blood gases, chemosensitivity plays little role in normal subjects during quiet wakefulness. But with sleep onset, subjects become more dependent on chemosensitivity and this dependence peaks during stages 3–4 NREM sleep. With sleep onset the normal chemosensitive response for CO2 (or acid ions) is set at 38 torr; while during sleep normal individuals have a normal CO2 setting at 40 torr due to disappearance of the nonspecific respiratory stimuli. If for any reason a subject wakes up, respiratory rate increases slightly. Depending upon how well one modulates breathing, a drop in blood CO2 will occur due to moderate hyperventilation related to the arousal. This leads to a reduction of PaCO2, and the magnitude of this reduction will impact on the stability of breathing if sleep re-occurs within a short period.

Hyperventilation means that the PaCO2, particularly in slim individuals, can easily drop down to 36 torr, and sometimes 35 torr. As mentioned during wakefulness, nonspecific stimuli keep our PaCO2 at 38 torr and if a sufficient awake time occurs there will a normalization of the PaCO2 at that level. With sleep onset there is always a degree of breathing instability. As well summarized by Dempsey et al. (43), breathing instability will be dependent of at least two types of gains: a controller gain defined by the slope of the ventilatory response to changes in PaCO2 (both above and below eupnea) and what has been called a plant gain related to the magnitude of the reduction of PaCO2 as mentioned earlier. Sleep onset is normally associated with many changes, but more particularly with an abrupt increase in airway resistance (with a short lived overshoot).
It has been shown that increasing the CO₂ reserve has a stabilizing effect on breathing, but transient arousals lead to abrupt reduction in airway resistance and hyperventilation related to the overshoot induced by the abrupt drop in airway resistance (44,45). This change results in greater reduction in PaCO₂. Falling asleep leads again to an increase in upper airway resistance and PaCO₂ increase.

Normally, the stabilization of breathing occurs rapidly after the sleep-onset-related changes, particularly if sleep becomes better established and if a short awakening does not disturb the normal sleep stabilization. Upper airway resistance decreases after the initial overshoot; however, staying above the one measured during wakefulness, and PaCO₂ stabilizes at 40 torr. Several drugs (46,47), such as acetazolamide or almitrine, have been tried to increase the respiratory drive and reduce the plant gain, increasing the stability of breathing, particularly at sleep onset, and acetazolamide has been used on a chronic basis to fight the repetitive central apneas related to these repetitive sleep onset phenomena, and the central apnea seen at high altitude during sleep.

Residual instability of breathing has also been demonstrated with nasal CPAP as indicated earlier. Recently, Thomas et al. (48) have shown that the adjunction of low concentration of carbon dioxide was effective in eliminating central and mixed—with large central component—residual apneas seen despite what looks like an appropriate nasal CPAP titration.

The persistence of central apneas during sleep is generally recognized as related to an enhanced controller or plant gain. These increases mean an increased loop gain as pathophysiologic component.

If good physiologic studies and manipulations have been performed to investigate increase in “loop gain” in subjects with abnormal airway resistance during sleep, investigation of electroencephalographic (EEG) changes related to these abnormal increases in loop gain are mostly nonexistent. Chervin et al. (49) as well as Lopes and Guilleminault (50) have shown, using different techniques, that the EEG patterns change in an important way with abnormal breathing during sleep: the “transient arousal,” that is, cortical EEG changes are present more frequently than often scored using standard sleep scoring techniques, and are clearly associated with the instability of breathing that leads to the repetitive central apneas.

One must also remember that nasal CPAP has different roles and potentially can have a destabilizing influence on breathing pattern with increase ventilatory response to chemostimulation and other ventilatory stimuli leading to transitory ventilatory overshoot and reduce eucapnic CO₂, particularly with a poorly responding upper airway due to neurogenic lesions.

The Nasal CPAP may have also an impact on cardiac output and left ventricular ejection fraction (51), leading to different changes, including impact on baroreceptors that have also an impact on chemosensitivity and control of ventilation. Finally, the change of speed of flow in the upper airway and inability to quickly adjust to this mechanical related change and abnormal local sensations due to lesioned upper airway receptors may also have a role in the destabilization of breathing.

Pathophysiologic studies indicate that abnormal breathing events are related to both ventilatory factors and sleep—wake factors, and that an abnormal narrowing of the upper airway—even more so if small—can lead to a diaphragmatic apnea, and an abnormal control of an upper airway muscle due to a neurological lesion can lead to an obstructive event.
OBSTRUCTIVE SLEEP APNEA SYNDROME

Clinical Features

Symptoms

Snoring and EDS are two major symptoms of OSAS. Snoring of variable severity is very common and may be the presenting complaint. The bed partners may encounter newly occurring snoring or worsening over time. In contrast, snoring may be absent, especially in patients with abnormally narrow upper airways, short soft palate, and predominant narrowing located behind the tongue. Sometimes, bed partner may also report witnessed apneic episodes.

Sleep fragmentation with frequent arousals and the inability to achieve or maintain slow wave sleep lead to nonrestorative sleep and EDS. Patients are rarely aware of frequent awakenings and the perception of such disturbed sleep may lead them to complain about not feeling refreshed in the morning or insomnia (52). If sleep fragmentation occurs during sleep stages of 3 or 4, sleepwalking or night terrors may accompany the clinical picture. If fragmentation is in rapid eye movement (REM) sleep, repetitive unpleasant dreams with themes of drowning, choking may occur. EDS may be mild or severe, depending on the severity of the obstruction. Despite many attempts no good correlation has been shown between the presence of EDS and sleep/wake scoring using international criteria. A better correlation has been seen when short EEG arousals (53) have been scored. In the recent past, Chervin et al. (49) have shown, using a complex algorithm based on computerized analysis of the sleep EEG, that a much better correlation could be obtained between EEG disturbances and EDS. These patients frequently report falling asleep during the day, which can be a cause of driving or industrial accidents. Nocturia and enuresis, especially in children, are commonly reported by patients. Bruxism, sometimes associated with biting of buccal mucosa or tongue, dry mouth, drooling, may be encountered in OSAS patients, which indicate the mouth-breathing during the sleep. Some patients may awaken with tachycardia or heartburn as a symptom of gastroesophageal reflux.

Other commonly reported daytime symptoms include morning headaches and moodiness, impaired memory and concentration, decreased sexual drive, and erectile dysfunction.

Symptoms of OSAS may be exacerbated by weight gain, nighttime alcohol consumption, use of central nervous system depressants, sleep deprivation, and chronic nasal congestion as seen with environmental allergies.

SIGNS

A complete physical examination is essential in OSAS patients with particular attention to the body mass index (BMI), neck circumference, and cranio-facial-maxillo-mandibular and naso-pharyngeal examination.

Evaluation should consider body habitus: presence of weight change, and distribution of fat, looking at the presence of abdominal obesity and size of neck circumference, a better measurement, as far as upper airway is concerned, than BMI. Comparison of hip–waist ratio may be a useful measurement; CT scan of abdomen with cut performed at the umbilicus has been used to determine abdominal fat distribution.

Because craniofacial features are involved in support of upper airway, anatomical evaluation of the region is important. Clinical scales, such as scale
standardizing size of tonsils or position of the uvula compared to the base of tongue (such as the Mallampatti scale), may be helpful.

The evaluation will appreciate the size of the nares, presence of asymmetry and narrowing of external valves, deficiency of internal valves, and deviated septum. In the pharynx, position of soft palate (low lying), size of uvula (large, elongated), and the presence of excess pharyngeal soft tissues will be checked. Evaluation of maxilla will search for narrow nose, narrow and high arched hard palate. Presence of retrognathia, sometimes only indicated by abnormal overjet (antero-posterior distance between upper and lower teeth) or a small triangular chin with steep mandibular plane will indicate involvement of the mandible.

History of early in life (<25 years) extraction of wisdom teeths due to impaction, important orthodontic treatment in teen-age with (erroneous) teeth extraction by overzealous orthodontists unaware of OSA, will suggest presence of small maxilla and/or mandible and anatomical risks for abnormal breathing during sleep (54).

Temporomandibular joint clicks, laxity, tenderness, or crepitus may be also indicative of the jaw falling back posteriorly during the sleep, further obstructing the airway.

The clinical evaluation should appreciate presence of consequences of OSA, particularly on the cardiovascular system. Blood pressure problems should be systematically investigated, as well as associated presence of cardiac arrhythmias, coronary artery disease and cerebrovascular disease, as should also be signs of gastroesophageal (GE) reflux. The role of OSAS in the development of the metabolic syndrome is controversial. It seems that if patients are not overweight (with an upper limit of normal BMI at 25 kg/m²), metabolic risks are not above the general population risk. However, to date, many patients present a combination of OSA—a polysomnographic pattern—and high BMI. The abnormal BMI can be responsible for the development of the OSA due to the upper airway fatty infiltration. The metabolic changes associated with obesity are well-known, and it has been shown now that increase in C-reactive protein and other metabolic factors, including insulin resistance, are significantly increased only with association with abnormal weight. The potential worsening role of repetitive OSA is unclear.

Sleep fragmentation may have an independent impact on metabolic variables, particularly secretion of leptin, grelin, leptin resistance and insulin resistance, or abnormal levels of inflammatory variables, such as tumor necrotic factor-alpha (TNF-α) and interleukin-6. Although the role of sleep fragmentation has been shown well in experimental manipulation of sleep (55–57), there is still controversy on the degree of sleep fragmentation occurring in OSA patients, despite the fact that some patients have it during night. This mechanism of sleep fragmentation secondary to the abnormal breathing may be more important in leading to metabolic changes in OSAS than the direct impact of apneic events (i.e., hypoxemia and abnormal efforts).

SECONDARY OBSTRUCTIVE SLEEP APNEA SYNDROME

Upper airway obstruction during sleep may be related to specific causes that have to be eliminated, such as tumors of the upper airway. Endocrine disorders, more particularly acromegaly with macroglossia, hypertrophy of para and retropharyngeal soft tissue and involvement of craniofacial skeleton; hypothyroidism, including myxedema, with macroglossia, Cushing syndrome (2,3,58,59). Metabolic
syndromes with autonomic neuropathy, such as diabetes mellitus (DM) (60,61), may also lead to secondary OSA.

Neurological syndromes can also lead to secondary OSA, particularly those impairing contraction of the XII nerve (vascular, tumoral, and degenerative syndromes).

Wallenberg syndrome may be associated with OSA; multiple system atrophy (MSA) with frequent involvement of vocal cords (62–65), and neurodegenerative syndromes, such as Leigh syndrome (66,67), may present with OSA symptomatology. Parkinson’s syndrome is associated in at least 20% of the cases with OSA, one reason been presence in some cases of nocturnal akinesia of upper airway muscles (68).

**Diagnostic Test**

The diagnosis of OSAS is definitively established by nocturnal polysomnography (PSG). It is important to keep in mind two facts: (i) increasing the length of the test or the number of variables monitored decreases the erroneous findings and (ii) there is a balance between the number and the degree of invasiveness of variables monitored and the amount of sleep achieved.

In clinically obvious cases, fewer monitored parameters may be sufficient to identify the severity of OSAS, based on the severity and frequency of hypopneic/apneic events, severity of oxygen desaturations, and the presence of any cardiac arrhythmias. Such monitoring can even be achieved with ambulatory equipments using cardiorespiratory monitors, but severity of sleep fragmentation will not be available. This may become an issue if question on metabolic impact of the syndrome is raised.

A full polysomnogram will bring many more information. Despite performed for financial gain, split night studies should be avoided as they never give good answer on diagnostic and rarely obtain appropriate nasal CPAP calibration. One negative factor has been the short sleep time given for both appropriate diagnosis and treatment. The other factor is the distribution of REM sleep during the second half of the night, a time when calibration of nasal CPAP will occur in a split night protocol; that is, a calibration performed without long period of NREM sleep and absence of determination of nasal CPAP pressure with sleep with involvement of respiratory accessory muscles and greater chance of having some residual narrowing of the upper airway related to the greater transpharyngeal pressure than during REM sleep.

The choice of ambulatory versus polysomnography testing should be based on clinical assessment and the likelihood of OSAS. If other associated sleep disorders, such as periodic limb movement syndrome or other syndromes, are also suspected in addition to OSAS, full PSG in sleep laboratory settings should be mandatory.

The following channel should be monitored, independently of the suspected SDB: electroencephalography (C3/A2, C4/A1, Fp1/A2, O1-O2) eye movements, chin and anterior tibialis electromyography, electrocardiography (EKG) (I lead) and position airflow. Respiration should be monitored with nasal cannula-pressure transducer system, mouth thermistor, respiratory effort can be monitored with respiratory inductive plethysmography or at least with both chest and abdomen piezoelectric bands, neck microphone and pulse oximetry; an index of respiratory effort (esophageal pressure-Pes-) is a useful adjunction in many cases and allows
good recognition of UARS. Video monitoring is a mandatory component of the recording for security reason during the monitoring and to evaluate behavior and movements during sleep.

UPPER AIRWAY RESISTANCE SYNDROME

UARS was first recognized in children in 1982 (69). The term UARS, however, was not used until adult cases were reported in 1993 (14). It is defined based on polysomnographic findings with an AHI < 5 events/hr, absence of apnea, SaO₂ > 92% and association with clinical complaint. A full polysomnogram is necessary to recognize UARS.

Clinical Symptoms
Although some of the symptoms in UARS overlap with those in OSAS, recent studies found some important differences (70). Chronic insomnia tends to be much more common in patients with UARS than with OSAS. Many UARS patients report maintenance insomnia characterized by frequent nocturnal awakenings and difficulty falling back to sleep. But sleep onset insomnia is also present which is thought to be due to “conditioning” as a consequence of frequent sleep disruptions (71). Adult patients with UARS are also more likely to complain of fatigue rather than sleepiness. They may have difficulty to get up in the morning and may shift their sleep schedule evolving toward a delayed sleep phase disorder. Other presentations include parasomnias with sleepwalking and sleep terrors (72), myalgia, depression, and anxiety. Gold et al. (73) emphasized that UARS patients have complaints more related to functional somatic syndromes such as headaches, sleep-onset insomnia, and irritable bowel syndrome. Not infrequently, UARS is misinterpreted as chronic fatigue syndrome, fibromyalgia, or as psychiatric disorders, such as attention deficit disorder/attention deficit hyperactivity disorder (ADD/ADHD) (74) or depressive disorders. A clinical case report of UARS has also presented symptomatology mimicking nocturnal asthma (75). Symptoms related to chronic nasal allergies are often seen. The clinical interview reveals the presence of lightheadedness with abrupt positional changes, sometime more pronounced at awakenings. History of fainting mostly during teen age may be also elicited. Between 1/5 and 1/4 will report presence of cold hand and/or cold feet and sometime other signs of mild signs associated with vagal hyperactivity. The other reported health problems are more related to the most common cause of UARS, that is, small maxilla and/or mandible.

Signs
The clinical examination will show low blood pressure in about one-fourth of subjects, often associated with moderate worsening with orthostatic maneuvers (76,77). Indications of anatomic narrowing of the upper airway have to be evaluated.

Polysomnography
Polysomnography reveals an AHI < 5, absence of apnea, oxygen saturation > 92%, and presence of respiratory-related respiratory arousals (RERAs) as well as other nonapnea/hypopnea respiratory events. Although inductive respiratory plethysmography (78), pneumotachograph, and most commonly nasal cannula/pressure transducer have been tried to measure subtle respiratory alterations (79,80),
measurement of esophageal pressure (Pes) remains the gold standard for detecting respiratory abnormalities. The use of a pediatric feeding catheter instead of an esophageal balloon has made the procedure better tolerable in both adults (79) and children (81). The nasal cannula/pressure transducer is more sensitive than thermistors in picking up respiratory changes, and has been used to detect RERAs. In addition to the above nasal cannula/pressure transducer system, respiratory channels, mouth thermistor (mandatory to recognize mouth breathing with nasal obstruction), thoracic and abdominal piezoelectric bands or inductive respiratory plethysmography, neck microphone and Pes are important to allow proper diagnosis. Calibration of different channels, particularly Pes, before beginning and at end of monitoring is mandatory. The other polysomnographic (PSG) channels have to be all present in these cases, more particularly several EEG leads that will allow to monitor not only C3–A2 and C4–A1, but also frontal and occipital derivations, that will help in the investigation of presence of American Sleep Disorders Association (1992) arousals of 3 seconds or more duration and calculation of cyclic alternating pattern (CAP) during NREM sleep (53).

Analysis of PSG will not only recognize hypopnea as classically defined, but it will determine the presence of “flow limitation” based on the analysis of the nasal cannula curve. Flow limitation will appear as “flattening” of the normal bell shape curve of the normal breath with drop in the amplitude of the curve by 2% to 29% compared to the immediately preceding normal breaths. The nasal cannula/pressure transducer is more sensitive than thermistors in picking up respiratory changes and detecting RERAs. However, it has not been demonstrated to have sensitivity comparable with Pes measurement. Three abnormal forms of Pes tracings have been described (82,83). First, Pes crescendo is a progressively increased negative peak inspiratory pressure in each breath which terminates with an alpha-wave EEG arousal or a burst of delta wave. This is not associated with drop in oxygen saturation of 3% as used for definition of hypopnea. The second form is a “sustained continuous respiratory effort”, wherein the Pes tracing shows a relatively stable and persistent negative peak inspiratory pressure, which is more than the baseline and nonobstructed breaths. This lasts longer than four breaths. The third form is Pes reversal, wherein there is an abrupt drop in respiratory effort indicated by a less negative peak inspiratory pressure after a sequence of increased respiratory efforts independent of the EEG pattern seen. This indicates the end of an abnormal breathing sequence, independently of the EEG pattern.

Recent studies also confirm that UARS patients may have more alpha EEG frequency time (82,84) and more RERAs (84) during sleep than patients with OSAHS. Scoring of CAP is another novel approach in evaluating quality of sleep in UARS. A higher frequency of CAP is noted in UARS compared to age and gender matched controls (50,85). The comparison of the sleep EEG of UARS, OSAHS and normal control subjects using power spectrum analysis show a higher amount of high theta and low alpha powers (i.e., 7–9 Hz bandwidth) during NREM sleep, and more delta powers during REM-sleep compared with OSAHS and normal subjects (86). The new analytic approach design by Chervin et al. (87) that quantifies the so-called respiratory cycle-related electroencephalographic changes breath-by-breath, and correlates delta, theta, and alpha EEG powers with respiratory cycle variations may allow detection of more subtle sleep EEG changes related to abnormal respiratory efforts.

Investigation of UARS patient with low blood pressure (76), and studies of heart rate variability using fast Fourier transformation (88), have shown that
UARS subjects present an active vagal tone compared to sympathetic tone during sleep. In contrast, a hyperactivity of the sympathetic tone has been well shown in OSAS patients. In UARS, the inhibition of sympathetic tone during sleep related to the abnormal inspiratory effort associated with increased airway resistance, and liberation of the vagal tone left alone as the autonomic regulator during sleep would be responsible for the observation of mild orthostatism and vagal dominance during sleep and sometime during wake.

CENTRAL (DIAPHRAGMATIC) APNEA AND HYPOPNEAS

**Inspiratory Muscle Dysfunction During Sleep Due to Neurologic Lesions**

Inspiratory muscle dysfunction leads to central respiratory events, either central hypopneas (decrease in muscle contractions for more than 10 seconds) or central apneas (absent muscle contractions for more than 10 seconds). Central sleep apnea syndrome is less common with an incidence of 4% in a population referred to a sleep laboratory (89). Central causes are less frequent, including idiopathic, vascular, degenerative, neoplastic or paraneoplastic processes (90,91). The diagnosis of central sleep apnea is made by the demonstration of intermittent absence of respiratory effort and airflow during sleep, which is associated with sleep arousals or oxygen desaturations. Such muscle dysfunction may follow lesions of the peripheral or central nervous system, and may involve the sensory, the integrative and executive, or the motor component of the nervous pathway (52).

**The Sensory Component**

Central sleep apnea may be of several forms. The central congenital hypoventilation syndrome (CCHS) (Ondine’s curse) is a rare disorder characterized by alveolar hypoventilation, repetitive central apneas, and CO₂ retention during sleep (92). This disorder is usually detected during the first few weeks of life and should be differentiated from neuromuscular, cardiac, and pulmonary diseases (93). It is less marked in REM sleep, and in older infants with a milder form of disease, hypoventilation is exclusively seen during stages of 3 and 4 NREM sleep. In some cases, hypercapnia may also be present while awake, and repetitive cries and agitation normalize the CO₂ levels via the associated tachypnea. No structural brain lesion has been related to CCHS, but functional magnetic resonance imaging (MRI) studies showed the lack of activation of brain stem regions responsible for hypercapnia (94). On the basis of this observation, the primary defect in CCHS is thought to be a dysfunction of central chemoreceptors. This abnormality may also partly explain the frequently observed central hypopnea/apneas during the sleep, and the accompanying hypercapnia as measured by transcutaneous electrodes. In addition to the blunted or absent ventilatory response to hypercapnia as well as hypoxemia, lack of heart rate variability and diminished papillary responses are also reported in these patients, suggesting the presence of a more generalized syndrome of autonomic dysfunction. Supporting this notion is the encounter of a higher incidence of ganglioblastoma and Hirschprung’s disease in CCHS patients. In fact, the presence of one should prompt a search for the other disorder.

Ondine’s curse produced by lesions of structures in the pons and medulla involved in respiration and their tracts has been reported through a variety of causes (95). Lesions of the reticulospinal pathway as in bulbar poliomyelitis (96),
brainstem infarction (97,98), cervical cordotomy for control of intractable pain (99,100), or Leber’s hereditary optic neuropathy in association with brain stem lesions (101) will impair central autonomic ventilatory control, and end in loss of vagal and chemotactic input to the CO₂ receptors in the medulla (102).

Several other syndromes are associated with familial or acquired autonomic dysfunction along with central sleep hypopnea/apnea, again with a prominence in non-REM sleep (65,103). These include familial dysautonomia (Riley-Day syndrome), insulin-dependent diabetes mellitus (DM), chronic uremia, Shy-Drager syndrome, Alexander disease, and chronic neuropathies such as Charcot-Marie-Tooth disease or hereditary sensorial axonal neuropathy type II (61,104–107). Alterations in either peripheral or central chemosensitivity have been increasingly shown in DM patients. However, a decrease in peripheral CO₂ chemosensitivity may prevent adult non-obese diabetics with autonomic neuropathy and postural hypotension from experiencing post-hyperventilatory central sleep apnea despite an increased hypercapnic central drive (108).

Central apnea and periodic breathing is also reported in acromegalic patients (109). An increase in central chemosensitivity to hypercapnia related to the higher serum levels of growth hormone and insulin growth factor-I, has been suggested as a leading mechanism.

**The Integrative and Executive Component**

Acquired central hypoventilation syndromes are often present during wakefulness and worsen during sleep, particularly in NREM stages. Acquired central hypoventilation during sleep is classically secondary to bilateral posterior medullary lesions (110–112), due to cerebrovascular accidents, epidural or subdural hematomas (113), intracranial abscess, encephalitis, tumors, syringomyelia, or any other process affecting this particular area such degenerative and metabolic disease, such as mitochondrial encephalopathies or Leigh disease (67,114–116).

Sometimes no underlying etiology can be found. Such patients are often overweight and the syndrome occurs during an acute lung infection or on a trip to high altitudes. It is suspected that these patients presented an unrecognized upper airway SDB with repetitive sleep fragmentation. Sleep fragmentation lead to blunting of chemosensitivity, perhaps associated with a genetic predisposition for low chemosensitivity response. An abrupt challenge such as acute ventilatory impairment due to infection, lower oxygen content than usual, such as high altitude trip, leads to CO₂ retention during sleep due to the abnormal chemoreceptor response related to the sleep fragmentation.

Although not studied well, the high incidence of SDB in Alzheimer’s disease has been hypothesized to be related to degeneration of the specific brain areas associated with ventilatory control (117,118). In degenerative disease such as multiple system atrophy (MSA) or Parkinson’s disease (PD), on the other hand, central sleep apnea is not reported but preservation of brachiomotor neurons of nucleus ambiguous has been suggested to explain the absence if this phenomenon (119).

**The Motor Component**

Neuromuscular and chest wall disorders constituting disorders of motor component respiratory dysfunction are the most common neurological causes of central hypopnea/apnea. These include chest wall deformities, scoliosis, kyphosis, following a thoracoplasty, other spinal disorders such as ankylosing spondylitis, muscular dystrophies, such as Duchenne muscular dystrophy, myotonic
dystrophies, following poliomyelitis, motor neuron disease [amyotrophic lateral sclerosis (ALS)], myasthenia gravis, paraneoplastic syndrome or myositis. (120–123). Chronic neuropathies such as hereditary motor and sensory neuropathy may also result in distal muscle weakness with atrophy (124). Moreover, restrictive lung disease and respiratory muscle failure are common findings in many advanced neuromuscular disorders.

Hypercapnic ventilatory failure is quite common in thoracic wall disorders, with physiological features of particularly a restrictive ventilatory defect and decreased compliance of the chest wall (125). Hypercapnia first appears in sleep and during activities such as exercise. The respiratory drive is intrinsically normal but there exist mechanical abnormalities. The increased work of breathing reduced respiratory muscle activity and hypercapnia becomes prominent in REM sleep, and involves other sleep stages over time with increased respiratory muscle fatigue (126,127).

Central alveolar hypoventilation is a common cause of sudden death during sleep in ALS patients with increasingly repetitive and prolonged hypopnea/apneas, cardiac arrhythmias, and arrest during sleep (128). Absent or markedly reduced hemi-diaphragm function has been shown to be further reduced in REM sleep. This leads to complaint of somnolence due to severe sleep fragmentation (129).

In patients with a long history of poliomyelitis, particularly longer than 15 years, nocturnal central alveolar hypoventilation is frequently encountered. This is particularly true in patients with initial bulbar involvement, even if initially with good recovery of respiratory function. In these patients, longest apneic events occur in REM sleep due to the combined effects of the REM-sleep related atonia and pathological phrenic nerve output due to medullary impairment. Being more prominent in REM sleep, varying degrees of hypercapnia and reduced tidal volumes are observed.

Hereditary motor-sensory neuropathies, unilateral lower motor lesions, or phrenic nerve roots or trunk lesions can be associated with repetitive central hypopnea/apneas. Acute inflammatory demyelinating polineuropathy may lead to respiratory dysfunction mainly via involving the phrenic nerve causing diaphragmatic weakness. Other factors may also include involvement of other supportive respiratory muscles such as intercostal or abdominal muscles. Patients with myasthenia gravis commonly experience REM-sleep related diaphragmatic weakness as monitored by trans-diaphragmatic pressure measurements, breathing abnormalities, hypercapnia, and acute respiratory failure. These abnormalities are seen in undiagnosed patients or in patients with inappropriate treatments: Because these patients already have generalized myasthenia through out the day, not having slow releasing preparations given at bedtime exacerbate their symptoms during sleep, especially during the longer REM periods in early morning with the reappearance of muscle weakness (130). Lambert-Eaton myasthenic syndrome associated with neoplastic diseases also frequently cause respiratory dysfunction, but usually again in undiagnosed cases. Although rare, respiratory failure even with need of ventilatory assistance may also occur in botulism.

Respiratory muscle dysfunction is usually the initial symptom of myopathies that affect predominantly proximal muscle groups. Myopathies are associated with a decrease in tidal volume, which worsens in REM sleep due to the physiologic muscle atonia (131). The longest apnea periods are noted during the phasic REM sleep segment, indicated by presence of phasic rapid eye movements. Thick-filament myopathy, acute necrotizing myopathy, maltase deficiency, myosin
deficiency myopathy, or cachectic myopathy may also be associated with respiratory problems. Maltase deficiency is a particular case: as diaphragmatic impairment is prominent, REM sleep disorder may be the first indication of the problem, and may translate only by a complaint of chronic unexplained fatigue during the daytime.

Myotonic dystrophies may also first present with sleep related symptoms such as sleep fragmentation, insomnia, and daytime sleepiness (132). Although PSG may not reveal many abnormalities in these patients, the use of esophageal manometry may increase the sensitivity of PSG. The respiratory muscle involvement may occur in all types of muscular dystrophies, mainly by both inspiratory and expiratory muscle weakness. In addition, some other factors such as the involvement of paraspinal muscles and secondary kyphoscoliosis may contribute preexisting respiratory dysfunction. Isolated muscular dystrophy of the diaphragm resulting in diaphragmatic weakness has also been reported (133). Inflammatory myopathies, respiratory steroid myopathy, or use of neuromuscular blocking agents may also involve respiratory muscles that may decompensate during REM sleep.

THE NONNEUROLOGIC CENTRAL SLEEP APNEA

Central sleep apnea events may be seen when performing polysomnography during nasal CPAP calibration. Chemosensitivity plays little role in normal subjects during quiet wakefulness, but with sleep onset, respiration becomes more dependent on chemosensitivity and this dependence peaks during stages 3–4 NREM sleep. With sleep onset the normal chemosensitive response for CO2 (or acid ions) is set at 38 torr, whereas during sleep PaCO2 is at 40 torr due to disappearance of nonspecific respiratory stimuli. If for any reason arousal occurs, increase in respiratory rate is seen with a drop in PaCO2 due to moderate hyperventilation related to the arousal. This leads to a reduction in PaCO2, and the magnitude of this reduction will impact the stability of breathing if sleep quickly recurs (43–45). Sleep onset is associated with an abrupt increase in airway resistance (with an overshoot), and an increase in PaCO2. It has been shown that increasing the CO2 reserve has a stabilizing effect on breathing, but transient arousals lead to abrupt reduction in airway resistance, and reduction in PaCO2, with induction of instability of breathing. This instability will be dependent of two types of "gains": a controller gain defined by the slope of the ventilatory response to a change in PaCO2 (both above and below eucapnia) and what as been called a plant gain related to the magnitude of reduction of PaCO2. Enhancement of one of these gains will lead to repetitive central apnea. The fact that OSA patients have local neurological lesions related most probably to snoring, add to the instability of breathing. Often a small increase in pressure will decrease the sleep instability and eliminate the central apnea. Sometime it persists and adjunction of acetazolamide or low concentration of CO2 will eliminate the central apnea that have persisted. Finally, nasal CPAP may have an impact on cardiac output and left ventricle ejection fraction leading to different changes including impact on baroceptors that have also an effect on chemo sensitivity and control of ventilation, on the top of inducing a phase—circulatory—delay in transport of information to the carotid glomus.

Most of the nonneurologic central apneas are in fact related to either a gain problem or a phase delay (circulatory) problem, and both can be present. This mechanism is often mentioned to explain the repetitive central apnea seen with
cardiac failure- often called “Cheyne-Stoking” as the pattern is slightly different from the classic description of Cheyne-Stokes respiration. Cardiac failure and kidney failure are frequently associated with this breathing pattern. And it may be worsened by treatment with nasal CPAP that will have an impact on atrial filling. At the extreme particularly in severe cardiac failure usage of nasal CPAP may lead to abrupt death related to this atrium impairment. It has also been shown that nasal CPAP may have a beneficiary effect on cardiac failure and abnormal breathing during sleep. A nasal CPAP calibration performed in the laboratory is highly recommended. Presence of increased dyspnea with nasal CPAP titration should interrupt the test. Bilevel may be better tolerated, but even with bilevel enhancement of dyspnea during sleep with risk of death, may be seen with nasal bilevel.

TREATMENT
Upper-Airway Obstruction
In planning the treatment strategies for OSAS, the severity of the disease and associated medical conditions should be first clarified. Generally, patients require combination therapies. First of all, predisposing factors should be addressed, including weight loss, exercise, sleep hygiene, treating nasal obstruction, avoiding sedatives, caffeine and alcohol, and smoking. Then the underlying etiologies, if any, should be appropriately treated.

The standard treatment for especially moderate to severe OSAS is application of nasal CPAP (134), which is a well-established effective treatment modality for OSAS. It applies pressure via the nasal mask to the upper airway, increase the intraluminal airway pressure, and keep the airway open throughout the night. Nasal CPAP is used with an airtight mask over the nose during sleep, which has to be carefully calibrated specifically for each patient. On the other hand, it has some drawbacks as claustrophobia, rhinitis, air leakage, local skin reactions, problems with appearance and intimacy between bed partners, and the inconvenience during traveling with the machine, which cause a major decrease in compliance, especially in young patients. CPAP has also been shown to be very effective in patients with underlying medical conditions such as ALS, congestive heart failure, or acromegaly (2,135,136).

Oral appliances that reposition the jaw or tongue may be tried in patients with mild to moderate apnea in less obese patients, who are intolerant to CPAP. Although no definitive prediction is available, patients with obstruction predominantly behind the base of tongue may be a better candidate for oral appliances. The use of these devices may fall out of mouth during sleep, may worsen the temporomandibular joint dislocations with or without pain, and may end in incomplete control of breathing problems.

Although there is no consensus concerning the indications for surgical interventions to treat obstructive SDB (31), better surgical candidates are those whose lifestyle precludes other treatments or have failed or could not tolerate CPAP. Surgery includes bypassing the upper airway or modifying the soft-tissue or bone/skeletal surgeries to prevent collapse and obstruction. Although long-term outcome results are not yet known, surgical treatment is an option for patients with OSAS. Uvulopalatopharyngoplasty, radiofrequency thermotherapy of the inferior turbinates, or soft palate, hyoidthyroidpexia and multilevel surgeries are shown to be effective in controlling OSAS symptoms (31). Although these types of surgeries may be a supportive rather than curative in adults, especially those
more severe than mild OSAS, these form the mainstay surgical options in pediatric patients. Newer skeletal techniques include various osteotomies for tongue advancement, and maxillomandibular advancement procedures, either alone or combined with uvulo—palato pharyngoplasty (UPPP) to improve the outcome (137). This procedure is performed under general anesthesia and the outcome is strictly dependent on the experience of the surgeon.

Pediatric mandibular distraction osteogenesis is efficiently used for patients with micrognathia and retrognathia or in patients with mandibular deficiency (138,139).

Treatment for upper airway obstruction is therefore very much debated and personal preference will affect the choice of treatment, and will also depend on other factors including severity of the disease, age of the patients, patient preferences, and the availability of well-trained surgeons.

INSPIRATORY MUSCLE DYSFUNCTION

The optimal treatment of the underlying diseases constitute the main treatment of central apneas. Treatment strategies may aim to assist the patients’ ventilation or even replace the patients’ ventilatory capabilities, in particularly advanced cases. In case of hypoventilation syndromes in sleep with no significant deterioration during awake states, bilevel positive airway pressure is the mainstay treatment for idiopathic, or even secondary cases when it is not always possible to eradicate the underlying condition (134). Usually with the progression of the underlying disease, common in neurological degenerative disorders, nasal intermittent positive ventilation may be tried. The last option, however, is tracheostomy with initial nocturnal and eventually continuous mechanical ventilation.

In a small group of patients with significant daytime deterioration and even worsening of breathing symptoms during sleep, diaphragmatic pacing is reserved. Although experience with this modality is not as common as others, good results are reported in the literature in patients with quadriplegia and central hypoventilation syndrome (140).

CONCLUSION

Disorders of obstructive and central sleep apnea present both a diagnostic and therapeutic challenge. The same neurological diseases may lead to both central and obstructive sleep apnea. Additionally, a central apnea may be related to upper airway impairment, a muscle disorder, or a cardiac failure as example; and central apnea does not systematically mean neurological problem. As treatment is often effective, it is important to affirm diagnosis and to recognize the underlying pathology. Continuous improvements in treatment modalities, such as noninvasive nasal ventilation and newer surgical techniques allow the neurologist to improve the quality of life of many patients and decrease mortality and morbidity of sleep related breathing disorders.

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INTRODUCTION

Scarcely 30 years ago, sleep apnea was not found in textbooks of medicine. Today sleep apnea is a household term that conjures popular ideas of suffocation, stroke, and death in sleep. Sudden death or injury as a direct result of sleep apnea is a very rare occurrence and yet sleep apnea is a very common disorder. Some studies indicate that as many as 2% of women and 4% of men (1) may be afflicted with the disorder, intensely enough to warrant medical attention. The increasing recognition of sleep apnea has become a promoter of sleep medicine and has significantly contributed to the dramatic expansion of the discipline of sleep in all its aspects, including development of sleep centers and laboratories, corporate increase, accreditation of hundreds of centers, certification of thousands of individuals, and financial growth. Although sleep is a function of the brain, specialists in breathing have felt compelled to become involved in all medical aspects of the disorder, from clinical diagnosis and treatment to basic research. In many instances, sleep apnea is part of the spectrum of a series of body alterations that requires a holistic approach to better serve patients. Sleep apnea is frequently linked to obesity, a worldwide epidemic (2), and both are linked to cardiovascular and cerebrovascular risk. Obesity is a predisposing factor for obstructive sleep apnea. Other predisposing factors are structural abnormalities of the oropharynx, maxillomandibular malformations, tonsillar hypertrophy, and palatal height. Some endocrinologic disorders, including acromegaly and hypothyroidism, and some congenital anomalies, such as Down’s syndrome, predispose to sleep apnea. Smoking, alcohol consumption, and sedative ingestion worsen the condition.

The immediate mechanism underlying obstructive sleep apnea is the narrowing of the upper airway during sleep. Upper airway patency depends partially on the activity and tone of the pharyngeal dilator muscles, an activity that diminishes in rapid eye movement (REM) sleep. Patients would die in their sleep were it not for the arousal response that terminates the apnea. The interplay between respiratory drive, oropharyngeal dilator muscle activity, arousal threshold, stage of sleep, and anatomical structure determines the presence and severity of apneas. Thus, the source of the problem needs to be sought in the brain where the impulses to breathe or not to breathe originate, where the arousal threshold is set, and where the stage of sleep is programmed. The pathophysiology of sleep apnea has remained at an impasse for more than a decade. Like the source of the river Nile, the origins of sleep apnea lie upstream in the brain and not in the peripheral lungs. Not until researchers become seriously engaged in the investigation of the neurology of sleep-related breathing will the stalemate be overcome.
According to the new classification in ICSD-2 (3), sleep apnea is part of the broad category of sleep-related breathing disorders that includes central sleep apnea syndromes, obstructive sleep apnea syndromes, sleep-related hypoventilation/hypoxemic syndromes, sleep-related hypoventilation/hypoxemia due to medical conditions, and other unspecified sleep-related breathing disorders. In this chapter, the main topic of discussion will be obstructive sleep apnea of adults, which will be referred to by the generic term sleep apnea. Where necessary, differences between central and obstructive sleep apnea are distinguished.

Obstructive sleep apnea is characterized by repetitive episodes of complete or partial upper airway obstruction during sleep (ICSD-2). In consequence, there is often reduction in blood oxygen saturation. Arousals terminate the event. Apneas are defined as respiratory pauses lasting 10 seconds or more. Most apneas are obstructive events resulting from transient occlusion of the upper airway during the inspiratory effort. In general, 10% of apnea events are nonobstructive and result from a central inhibition of the respiratory process lasting 10 seconds or more. Mixed apneas combine nonobstructive and obstructive mechanisms in a single event. Hypopneas are reductions in respiratory effort or airflow of 30% or more, accompanied by a drop in oxyhemoglobin saturation of 4% or more, with duration of 10 seconds or more. Some laboratories define hypopneas by a reduction in respiratory effort or airflow of 50% or more; other centers require an arousal terminating the event to consider it a hypopnea. Most laboratories use an apnea-hypopnea index (AHI) of five or more episodes per hour of sleep as the cutoff index to diagnose the condition. The term sleep apnea syndrome has been used to incorporate the constellation of clinical manifestations that include sleep apnea and excessive daytime somnolence.

Episodes of apnea or hypopnea are more frequent in stages 1, 2, and REM. Typically, snoring is reported by inconvenienced bed partners who usually narrate descriptions of struggle to breathe, gasping for air, and restlessness. Excessive sleepiness is a major component of the sleep apnea syndrome, and is likely related to the numerous arousals that disturb the quality of nocturnal sleep. Quality of life is also adversely affected and medical complications may ensue.

SNORING

Most adults, particularly men, snore past the age of 45 years. Soft, intermittent snoring is probably inconsequential from a clinical perspective. However, pathologic snoring, defined as the habitual, harsh and loud vibratory sound produced by the respiratory effort in the sleeping individual, is frequently a marker of obstructive sleep apnea disorder. Only habitual, sustained, intensely loud snoring that is disturbing to others should be of importance to the clinician. Habitual snoring has been associated with arterial hypertension (4), ischemic heart disease (5), and stroke (6). Epidemiologic studies have suggested that habitual snoring is a risk factor for brain infarction (7) independent of confounding factors, such as hypertension, ischemic heart disease, obesity, and age. The act of snoring implies great effort and force in the process of breathing. It is generally associated with profound negative intrathoracic pressures that alter the hemodynamic function of the heart and significantly contribute to the risk of vascular disease. The association of snoring with obstructive sleep apnea reinforces its weight as a risk factor for vascular complications.
SLEEP APNEA AND HYPERTENSION

Systemic blood pressure increases transiently during the recovery phase from apnea. Elevations reaching 200/100 mmHg and lasting a few seconds have been recorded at the termination of apneas, particularly in REM sleep. The phenomenon has been attributed to the arousal that terminates the apnea event. The arousal includes a constellation of cardiovascular, respiratory, and somatic muscle phenomena together with activation of the electrocorticogram. Transient arousals are only identified in polysomnographic recordings and are characterized by an abrupt shift in electroencephalogram (EEG) frequency lasting three seconds or more, usually associated with electromyogram (EMG) amplitude increase, increased heart rate, or respiration change (8). Microneurography, a technique that evaluates autonomic discharges in nerves, has shown surges in sympathetic activity in association with arousals, explaining the occurrence of blood pressure elevations and acceleration of the heart rate.

Two ascending activating systems, a ventral cholinergic and a serotonergic ascending system, both interacting with other regional neurotransmitter processes contribute to electrocortical activation. Although pain and noise are the arousal triggers “par excellence,” a number of arousal processes interact with the general system, including cerebellar mechanisms, which respond to extreme cardiovascular challenges, and limbic structures, which respond to hypoxia, hypercarbia, and dyspnea (9). The amygdala has major projections to ascending arousal systems. Some arousal-activating systems bypass the thalamus and reach the cortex directly. Cholinergic, serotonergic, dopamine, histamine, and noradrenergic systems can activate the cortex and should be considered part of the general network of arousal responses. Recently, the hypocretin system has been included in the arousal mechanism. Prolonged apnea and profound blood pressure changes during sleep can provoke autonomic or somatic responses with cortical activation. Repeated bouts of hypertension night after night in patients with untreated sleep apnea may eventually lead to sustained hypertension.

Although suspected for a long time, convincing evidence of an association between sleep apnea and sustained systemic hypertension, defined as a resting systolic blood pressure of 140 mmHg and a diastolic pressure of 90 mmHg or more, has become available only within the last few years. The large community-based Sleep Heart Health Study (10) showed a dose–response relationship between sleep apnea and hypertension. The study was conducted between 1995 and 1998 and included a total of 6132 subjects. The AHI and other measures of disturbed sleep, including arousal index and percentage of sleep time below 90% oxygen saturation, were obtained by unattended home polysomnography. The odds ratio for the development of hypertension was 1.37 (CI = 1.03–1.83), when comparing the highest category of AHI (>30/hr) with the lowest category of AHI (<1.5/hr), even after adjustment for confounding variables that included obesity and neck circumference. The adjusted odds of hypertension increased steadily with AHI values of 15 to 20/hr and higher. For very high AHI values, the odds ratios were two or higher. A similar relation was obtained using oxygen saturation measurements of 90% or less as the reference parameter. The strength of the association between sleep apnea and hypertension was diminished when controlling for body-mass index, suggesting that sleep apnea may be one of the intermediary mechanisms between obesity and hypertension.
In the Wisconsin sleep cohort study (11), the authors analyzed data on sleep apnea and blood pressure in 709 subjects. Conventional polysomnography was done at baseline, and patients were followed for four years; in 184 cases the duration of follow-up was eight years. The results indicated a dose–response association between sleep apnea at baseline and the presence of hypertension four and eight years later, after adjusting for confounding factors. The odds ratio for developing hypertension at four years for subjects with a baseline AHI of 5 to 14.9/hr was 2.03 (CI = 1.29–3.17), whereas for subjects with AHI of 15/hr or more the odds ratio was 2.89 (CI = 1.46–5.64).

In a study of 2677 adult patients Lavie et al. (12) showed that each additional apneic event per hour of sleep increased the odds of hypertension by 1%, whereas each 10% decrease in nocturnal oxygen saturation increased the odds by 13%.

The mechanical activity of the diaphragm, the only functional respiratory muscle in REM sleep, is severely challenged in morbidly obese patients with globular abdomens. These patients exhibit the most profound oxygen desaturations in REM stage in association with apnea events and arousals (13). The correlation between abdominal obesity, REM sleep-related apnea events, and desaturations may explain the observed epidemiological link between abdominal obesity, hypertension (14), and vascular risk.

The prevalence of sleep apnea was found to be particularly high in patients with drug-resistant hypertension, defined as a clinic blood pressure of 140/90 mmHg or more, while taking a combination of three or more antihypertensive drugs, titrated to maximally recommended doses (83% of 24 men and 17 women studied) (15). The blood pressure profiles in patients with sleep apnea showed higher diastolic blood pressure and no nocturnal dipping (16).

**SLEEP APNEA DISORDER AND CARDIOVASCULAR DISEASE**

Sleep apnea precipitates arrhythmias that are clinically significant when there is concomitant cardiac or respiratory comorbidity (17). In patients with advanced sleep apnea tachy-bradyarrhythmias appear when the oxyhemoglobin saturation falls below 65% (Fig. 1). Atrio-ventricular block, which has been reported with asystole lasting up to nine seconds during phasic REM sleep in otherwise asymptomatic healthy young adults (18), is of particular concern in patients with sleep apnea (19,20).

Atrial fibrillation is another cardiac complication observed in patients with sleep apnea (21,22). A recent study (23) has shown a strong association between obstructive sleep apnea and atrial fibrillation (odds ratio 2.19; CI: 1.40–3.42), which was even higher than in high-risk patients with multiple other cardiovascular diseases. Sleep apnea with hypoxemia increases the risk of atrial fibrillation 2.8-fold (24).

The incidence of cardiovascular disease in patients with obstructive sleep apnea (36.7%) is increased independently of confounding factors, including age, body-mass index, diastolic blood pressure, and smoking (25). Central sleep apnea and Cheyne-Stokes respirations are commonly observed in patients with congestive heart failure and may be a consequence of heart failure (26).

The presence of patent foramen ovale was studied (27) using Doppler technique in 78 consecutive patients with sleep apnea and the results were compared with those obtained in age-matched controls. Twenty-seven percent of sleep apnea patients and 15% of control subjects had patent foramen ovale. The
authors concluded that the prevalence of patent foramen ovale is statistically higher ($P < 0.05$) in patients with sleep-disordered breathing. It has been suggested that in patients with obstructive sleep apnea, the foramen ovale shunt may be open from right to left during brief Valsalva episodes at the termination of sleep apneas, increasing the risk of stroke due to paradoxical embolization.

SLEEP APNEA AND CIRCULATING VASCULAR RISK FACTORS

Circulating pro-inflammatory risk factors have been found in patients with sleep apnea. The study of circulating pro-inflammatory factors opens a window of opportunity to investigate primary and secondary stroke prevention in patients with sleep apnea. Elevated fibrinogen content in blood as well as increased C-reactive protein, interleukin-6, and plasminogen activator inhibitor have been noted in patients with sleep apnea (28). Homocysteine appears not to be unusually elevated in patients with sleep apnea (29). The well-recognized association between sleep apnea and the metabolic syndrome (obesity, hypertension, dyslipidemia, and insulin resistance) confounds partially the studies linking sleep apnea with risk markers for stroke.
Endothelial dysfunction and platelet activation have also been observed in patients with sleep apnea (30). In addition, a number of activated coagulation factors (factors XIA and VIIa, factors VII, VIII, XII, fibrinogen, von Willebrand factor antigen, and soluble P-selectin) are increased in patients with sleep apnea and remain high despite chronic nCPAP treatment (31).

**SLEEP APNEA AND CEREBRAL BLOOD FLOW VELOCITY**

Transcranial Doppler techniques have shown that during episodes of apnea, significant reductions in middle cerebral artery blood flow velocity correlate with the duration of the apnea rather than with the depth of oxyhemoglobin desaturation (32,33). Profound thoracic negative pressures during obstructive apneas may cause a reduction of cerebral blood flow. In central apnea events, there is decrease in cerebral blood flow velocity during apnea and increase after apnea termination. Intracranial hemodynamic changes occurring repeatedly night after night may contribute to raising the risk of stroke and may trigger irreversible ischemic changes in patients with poor hemodynamic reserve, particularly in borderzone areas and terminal artery territories. Preliminary studies of auditory event-related potential in patients with sleep apnea (34) found no improvement in abnormal P3 wave latencies after treatment of sleep apnea, suggesting permanent structural changes in the white matter of the hemispheres, likely as a result of ischemia. Hemodynamic changes have also been observed in a patient with sleep apnea and intracranial arterial stenosis (35).

**SLEEP APNEA AND SMALL VESSEL DISEASE**

Patients with multi-infarct dementia have a higher prevalence of sleep apnea disorder than patients with Alzheimer’s disease or control individuals of similar age (36). Also, there are reports of an association between sleep apnea and lacunar strokes (37). Leukoaraiosis or white matter disease is more prevalent in patients who have acute stroke and sleep apnea. In a computed tomography (CT) scan study of the brain of 78 patients with acute stroke (38), white matter disease severity correlated with level of AHI \( (P < 0.05) \) in sleep studies performed 7 to 14 days after the stroke. The authors suggested that either white matter is more vulnerable to hypoxia and blood pressure variability associated with sleep-disordered breathing, or that white matter disease exacerbates sleep-disordered breathing following stroke.

**SLEEP APNEA AS A RISK FACTOR FOR STROKE**

The concept of sleep apnea as a risk factor for primary and secondary stroke was suspected based on the confirmed causation or aggravation of systemic hypertension and heart disease, which in turn are risk factors for stroke. Other conditions were included in the roster of risk factors, such as impaired vascular endothelial function, accelerated atherogenesis, prothrombotic coagulation shifts, proinflammatory states, and increased platelet aggregation. But it was not until recently that direct evidence of the link between sleep apnea and vascular events, including stroke, was uncovered.

In the study by Marin et al. (39), the effect of obstructive sleep apnea as a cardiovascular risk factor and the potential protective effect of its treatment with
continuous positive airway pressure (CPAP) were investigated. The authors compared incidence of fatal and nonfatal cardiovascular events in simple snorers, patients with untreated obstructive sleep apnea, patients treated with CPAP, and healthy men. The presence and severity of the disorder was determined with full polysomnography. Participants were followed-up for a mean of 10.1 years (SD 1.6) and CPAP compliance was checked with a built-in meter. Endpoints were fatal myocardial infarction or stroke, and nonfatal cardiovascular events (nonfatal myocardial infarction, nonfatal stroke, coronary artery bypass surgery, and percutaneous transluminal coronary angiography). Multivariate analysis, adjusted for potential confounders, showed that untreated severe obstructive sleep apnea significantly increased the risk of fatal (odds ratio 2.87, 95% CI: 1.17–7.51) and nonfatal (3.17, 1.12–7.51) cardiovascular events compared with healthy participants, and suggested that CPAP treatment reduced the risk.

The risk of stroke or death of any cause in patients with sleep apnea was expressed by a hazards ratio of 2.24 (95% CI: 1.30–3.86) in the work by Yaggi et al. (40). In this study the mean AHI of patients enrolled with the syndrome was 35 respiratory events per hour, a level of moderate severity only. In an unadjusted analysis, the authors found that obstructive sleep apnea was significantly associated with stroke or death from any cause even after adjustment for age, sex, race, smoking status, alcohol-consumption status, body-mass index, and the presence or absence of diabetes mellitus, hyperlipidemia, atrial fibrillation, and hypertension. The trend analysis showed that increased severity of sleep apnea at baseline was associated with an increased risk of stroke and death.

Patients with sleep apnea have a higher incidence of sudden death from cardiac causes during sleep (41), whereas in the general population without obstructive sleep apnea there is a nadir of sudden death from cardiac causes during the same period of time. The marked nadir of sudden death of cardiac causes in persons without sleep apnea during sleep probably reflects the decreased sympathetic activity and decreased incidence of cardiac dysrhythmias. In the study by Gami et al. (41), from midnight to 6 a.m., sudden death from cardiac causes occurred in 46% of persons with obstructive sleep apnea compared to 16% of the general population. The AHI correlated directly with the relative risk of sudden death from cardiac causes from midnight to 6 a.m. (2.57; 95% CI: 1.87–3.52) and was 40% higher in patients with severe obstructive sleep apnea as compared to those with mild or moderate severity. The authors were unable to verify whether patients had been using continuous positive airway therapy prior to the occurrence of sudden death.

**EFFECT OF TREATMENT ON STROKE RISK**

The treatment of sleep apnea has shifted from the early tracheotomies to the modern application of noninvasive CPAP ventilation, bi-level positive airway pressure and more recently, automatic control of airway pressure delivery with auto-CPAP devices. A variety of surgical interventions and prosthetic oral devices aid in the treatment of mild forms of sleep apnea. Despite increased recognition in the past decade, it is estimated that more than 80% of men and more than 90% of women with moderate to severe sleep apnea remain undiagnosed.

In an early study (42), 198 patients with obstructive sleep apnea were divided into two groups: group A received tracheotomy, and group B, a recommendation to reduce weight. Seven years later, 15 patients had suffered a myocardial infarction or
Efficient treatment of obstructive sleep apnea with noninvasive ventilation reduces the cardiovascular risk. Some authors have found that long-term treatment of patients with nCPAP has a normalizing effect on circulating vascular risk factors, notably elevated fibrinogen levels and increased platelet aggregation (43). Total cholesterol may decrease with long-term treatment of sleep apnea with nCPAP (44). The results of another study (45) showed that treatment with CPAP decreased systolic blood pressure and improved left ventricular systolic function, suggesting that sleep apnea disorder has an adverse effect in heart failure.

Several studies have shown that continued treatment of sleep apnea with noninvasive ventilation reduces systemic hypertension and, by inference, the risk of vascular complications. Evidence of a favorable effect was provided by a study of ambulatory blood pressure measurements after therapeutic and subtherapeutic nasal CPAP ventilation (46). In this study, therapeutic n-CPAP reduced mean arterial ambulatory blood pressure by 2.5 mmHg, a benefit seen in both systolic and diastolic blood pressure. Patients with moderate or severe sleep apnea had a mean reduction of 3.3 mmHg in ambulatory blood pressure several weeks later. In another study (47), effective nCPAP treatment in patients with moderate or severe sleep apnea led to a 10 mmHg drop in mean arterial blood pressure.

Mild sleep apnea and snoring respond favorably to the application of mandibular advancement splints (MAS) or airway patency devices. The effect of oral appliance therapy on ambulatory blood pressure was investigated in 61 patients with obstructive sleep apnea diagnosed with polysomnography (AHI 10 or more). Patients showed a 50% reduction in mean AHI with MAS compared with control subjects and a significant improvement in both minimum oxygen saturation and arousal index. There was a significant reduction with the MAS in mean 24-hour diastolic blood pressure (1.8 ± 0.5 mmHg) compared with the control (P = 0.001), but not in 24-hour systolic blood pressure. Blood-pressure variables in the awake state were reduced with the MAS by an estimated mean of 3.3 mmHg for systolic blood pressure (P = 0.003) and 3.4 mmHg for diastolic blood pressure (P < 0.0001). There was no significant difference in blood pressure measured during sleep. The authors concluded that oral appliance therapy for obstructive sleep apnea over four weeks results in a reduction in blood pressure, similar to that reported with CPAP therapy (48).

**ACUTE STROKE AND SLEEP APNEA**

Alteration of the sleep–wake rhythm is common in the days that follow a large hemispheric stroke and is manifested by agitation during the night and lethargy during the day, which may be misinterpreted as a sign of neurological deterioration. The early presence of normal sleep cycles and generation of REM sleep are good prognostic signs. Vascular injury to the respiratory centers in the lateral medullary syndrome may precipitate sleep apnea (49). Other patterns of respiratory dysfunction noted with infratentorial lesions include apneusis or apnea during sustained inspiration, nonobstructive, obstructive, and mixed apneas, and failure of automatic breathing (Ondine’s curse) (50). Sleep apnea is commonly found with hemispheric strokes, particularly if dysphagia (51) and dysarthria are present. In bilateral hemispheric lesions, Cheyne-Stokes respiration may be observed. During the first 24 hours following stroke, sleep apnea appears in 62%
of patients with acute hemispheric lesions (52). In a polysomnographic study of patients nine days post-stroke or post-TIA (53), the authors found an AHI of 10 or more in 62.5% of subjects as opposed to 12.5% of controls. These results indicate that sleep apnea is common in the acute stages of stroke but also suggest that sleep apnea may precede the onset of stroke, since TIA patients have a similar prevalence. In a subsequent study (54), the author found that sleep apnea is common, particularly in elderly male stroke patients with diabetes, nighttime stroke onset, and microangiopathy as cause of stroke; sleep apnea improves after the acute phase, is associated with increased post stroke mortality, and can be treated with CPAP in a small percentage of patients. Unfortunately, the majority of stroke patients with sleep apnea reject CPAP treatment (55).

CIRCADIAN VARIATIONS

In NREM sleep, sympathetic activity decreases while parasympathetic activity tends to predominate, accounting for a reduction of heart rate, blood pressure, cardiac output, peripheral vascular resistance, and respiratory frequency. Nocturnal blood pressure dipping is a normal phenomenon that when violated may increase the risk of stroke (56). REM sleep is characterized by variability in the activity of both the sympathetic and parasympathetic systems, with phasic oscillations and surges that result in a net increased parasympathetic tone and decreased sympathetic influence. During REM sleep, heart rate and arterial blood pressure are variable, while cerebral cortical and spinal blood flows increase.

Plasma catecholamine levels rise from 6 a.m. to noon. During the same time, heart rate and blood pressure increase. Fibrinolytic activity diminishes in the mornings (57), while platelet aggregability increases (58). These phenomena have been linked to augmented vascular morbidity during the morning hours.

In the study by Gami et al. (41), from midnight to 6 a.m., sudden death from cardiac causes occurred in 46% of persons with obstructive sleep apnea compared to 16% of the general population. The study suggests that sleep apnea and circadian factors interplay to increase vascular vulnerability during the night.

STROKE REHABILITATION AND SLEEP

The prevalence of sleep apnea is high during the rehabilitation period of stroke. In an overnight study using continuous computerized oxymetry and polysomnography in selected cases (59), the authors found that 19% of patients had more than 100 desaturation events on the night of recording. Patients with 10 episodes or more of desaturation per hour of sleep had significantly lower Barthel Index scores on discharge and at 3 and 12 months post-stroke. Mortality was associated with oxymetry variables indicating increased percentage of time spent below 90% saturation. The study suggested that oxymetry values compatible with sleep apnea in patients in rehabilitation from stroke had worse functional outcome and higher mortality rates. Using overnight polysomnography, Mohsenin et al. (60) studied patients within one year post-stroke and found that patients had a respiratory disturbance index of 52 ± 10 events per hour when compared with 3 ± 1 in controls ($P < 0.05$). Other studies have pointed out repeatedly that patients post-stroke have a high prevalence of sleep apnea [71% (61), 77% (62)] and that optimal rehabilitation potential is obstructed by reduced motivation and decreased cognitive capacity, while survival may be compromised by an increasing risk of stroke and
death. The application of noninvasive positive airway pressure ventilation offers to patients with sleep apnea a window of opportunity to increase the rehabilitation potential post-stroke. CPAP compliance after stroke was investigated by Palombini and Guilleminault (55). Initial evaluation and regular follow-up of the home trial of auto-CPAP was carried out post-stroke for eight weeks. Of 32 patients with minimum cognitive criteria for enrollment, seven patients (22%) used nasal CPAP for eight weeks. Subject dropout was related to difficulties with CPAP usage, facial weakness, motor impairment and discomfort with usage of full-face mask. The majority of sleep apnea stroke patients rejected CPAP treatment. The authors concluded that better education and support of patients and families and special training sessions in rehabilitation services will be needed to improve compliance.

FINAL COMMENTS

Sleep apnea is a contributing factor for the development of systemic hypertension and thus becomes a surrogate risk factor for myocardial infarction and stroke. In addition, patients with advanced sleep apnea have cardiovascular and cerebrovascular hemodynamic alterations that augment the risk of stroke in sleep. Circadian variations may modulate the risk. Sleep apnea is also more frequent following stroke, and may reduce the potential for neurological and functional recovery, possibly increasing mortality. Sleep apnea can be treated successfully. Its diagnosis and management should be pursued vigorously both before and after stroke (63). Developing evidence of structural brain changes in patients with advanced sleep apnea suggests the desirability of an early diagnosis and therapeutic intervention.

REFERENCES


INTRODUCTION
The older patient population is growing very fast around the world, including the United States. In the year 2000, 34 million Americans were older than 65 years. By the year 2025, this number is expected to double and reach 62 million (1). This anticipated increase is expected to have profound medical, economic, and psychological consequences. Older adults are often dissatisfied with the quality of their sleep (2). Almost half of seniors over age 65 who live at home are not happy with their sleep, and nearly two-thirds of those residing in nursing home facilities suffer from sleep disorders (3). Sleep disorders increase with age, and clinicians need to become familiar with the age-related sleep changes and recognize the sleep disorders, which are likely to impact this patient population.

SLEEP DISTURBANCES IN THE ELDERLY
Sleep disturbances in elderly patients may be caused by a primary sleep disorder, such as sleep apnea, periodic leg movements, and restless legs syndrome (RLS), or may arise secondary to medical problems, psychiatric conditions, polypharmacy, or psychosocial factors (4). Conversely, when sleep disorders become chronic, they may exacerbate coexisting medical and psychiatric illnesses. Chronic sleep disorders are often associated with excessive daytime sleepiness (EDS) and may result in disturbed cognition, impaired intellect, confusion, and psychomotor retardation, which may be misinterpreted as dementia. Sleep disturbances may also increase the risk of injury, compromise the quality of life, and create social and economic burdens for caregivers.

AGE-RELATED CHANGES IN SLEEP ARCHITECTURE
Age-related sleep architectural changes are predictable and consist of sleep fragmentation, reduced sleep efficiency, decreased quality of sleep, as well as a decrement in the amplitude of delta waves which comprise slow-wave sleep (SWS) (4). Older adults spend more time in the lighter stages of sleep, have a reduction in the amount of SWS, and experience increased fragmentations of the entire sleep cycle (5). The latency to the first rapid eye movement (REM) period tends to decrease, and the percentage of REM sleep may also decrease as a result of an overall reduction in nocturnal sleep time. Older patients often take longer to initiate sleep, have a reduced total sleep time, experience more frequent awakenings, early morning awakening, and may be more likely to nap during the day (6,7).
The prevalence of napping in the elderly ranges from 25% to 80% (8,9). The tendency to nap during the day has been previously documented by studies implementing the multiple sleep latency tests (MSLT) to evaluate sleep propensity. When given the opportunity, seniors have a tendency to fall asleep during the day faster than younger patients (7,10). The propensity to experience EDS suggests that older adults are not obtaining sufficient sleep at night. This is interpreted to mean that the ability to sleep is altered rather than the need for sleep (11).

SLEEP DISTURBANCES IN PATIENTS WITH NEURODEGENERATIVE DISEASES

Estimates report that as many as 4% of patients older than 65 years have dementia. Alzheimer’s disease (AD) is the most important and common cause of dementia, accounting for approximately 70% of all cases of dementia (2). This is followed by Dementia with Lewy bodies (DLB), which is currently considered the second most common irreversible cause of dementia, accounting for approximately 20% to 25% of cases. The relationship of DLB to Parkinson’s disease—another disorder with Lewy bodies—is still evolving and is currently not clearly defined. The discussion that follows summarizes the current available data on sleep disturbances associated with AD.

Sleep disturbances in neurodegenerative diseases include insomnia, hypersomnia, circadian rhythm disturbances, excessive motor activity at night, nocturnal agitation and wandering, and abnormal nocturnal behaviors (12). Many of these symptoms have multiple underlying causes and underlying pathophysiologies. Patients with dementia are at risk for additional sleep disturbances such as obstructive sleep apnea (OSA) and periodic limb movement disorder of sleep (PLMS), which occur at higher incidence with aging. Many of these sleep disruptions can cause considerable caregiver burden and may put the patient at increased risk for institutionalization within nursing home facilities (13,14).

PATHOGENESIS OF SLEEP DISTURBANCE IN DEMENTIA

Sleep disturbances in dementia may be due to both direct and indirect mechanisms (12,15). Direct mechanisms are related to neuroanatomic pathways involved in sleep physiology and neurochemistry. For example, in AD, degeneration of the neurons of the suprachiasmatic nucleus (SCN) and may be responsible for circadian rhythm abnormalities, sundowning syndrome, and other sleep–wake-schedule disturbances (12,15). Degeneration of cholinergic neurons in the nucleus basalis of Meynert, the pedunculopontine tegmental and laterodorsal tegmental nuclei, and noradrenergic neurons of the brainstem may be responsible for decreased REM sleep in AD patients (12,15). Degeneration of brainstem respiratory neurons and the supramedullary respiratory pathways may cause sleep-disordered breathing and other respiratory dysrhythmias in sleep in AD (12,15). Figure 1 describes the common sleep disturbances and possible underlying pathophysiology in patients with AD. Indirect mechanisms include medication-related side effects, underlying psychiatric diagnosis such as mood disorders, increasing incidence of PLMS in elderly AD patients, and age-related alterations in sleep. Other indirect mechanisms include general medical diseases affecting the cardiovascular and respiratory systems and environmental factors such as insufficient or dim light and
excessive environmental noise in nursing homes or other long-term-care institutions.

**DIAGNOSTIC APPROACHES TO SLEEP DISTURBANCES IN DEMENTIA**

**Clinical Assessment**

The first and most important step in the management of sleep disturbances of patients with dementia is a detailed inventory of sleep complaints. The history should consist of present and past sleep history, family history, medication and substance use (such as caffeine, nicotine, and alcohol), and information about underlying medical or psychiatric disorders. The history should also be specifically directed at possible respiratory disturbances during sleep. It is important to perform a physical examination for the diagnosis of the primary or associated medical conditions, including neurological disorders that may be responsible for the sleep disturbances.

**Laboratory Assessment**

Laboratory investigations should be undertaken to diagnose the nature of the sleep disturbance and the primary neurological disorder. Overnight polysomnography (PSG) and the MSLT are the two most important laboratory tests for the diagnosis of sleep disturbances. Sometimes, pulmonary-function tests (PFT) are needed to address the question of sleep-related respiratory disturbances specifically in the setting of underlying respiratory disease. Specific PSG montages [including multiple limb electrodes and EEG (electroencephalography)] may be helpful in the evaluation of potential parasomnias and nocturnal seizures.
SLEEP TESTS
Polysomnography
Polysomnography should be performed in patients suspected of sleep-related respiratory disorders (4,11,16,17). Unfortunately, the diagnosis and treatment of sleep disturbances may be difficult in neurodegenerative diseases, with severe functional impairment given uncertainties in the clinical history obtained from the patient. All-night PSG is critical in the assessment of the severity of sleep-disordered breathing, and in documenting the consequences on the sleep architecture. Sleep itself may adversely affect the breathing and the primary neurological disorder; conversely, primary neurological disorders may adversely affect sleep. Overnight PSG should include simultaneous recordings of multiple channels of EEG, electromyography (EMG), electrooculogram (EOG), electrocardiogram (EKG), respiratory monitoring (to detect both abdominal and thoracic effort and airflow), and continuous recording of oxygen saturation by pulse oxymetry. In suspected cases of upper airway resistance syndrome (UARS), which can sometimes be encountered in extrapyramidal disorders, measurement of the esophageal pressure manometry is important and can be accomplished by inserting an esophageal pressure monitor (PES) (18). Comprehensive EEG monitoring is also helpful in the context of neurodegenerative disorders to further characterize sleep architectural disturbances and when focal or diffuse cerebral lesions and epileptiform activities are suspected (19,20).

Multiple Sleep Latency Test
When patients with neurodegenerative diseases present with pathological sleepiness, the MSLT can be helpful in documenting the extent of sleepiness. The MSLT has been standardized and consists of four or five daytime recordings of EEG, EMG, and electro-oculogram at 2-hour intervals, each nap lasting for a maximum of 20 minutes (21). The MSLT measures, the mean sleep latency (time to the first epoch of any sleep stage for the clinical purpose), as well as the presence of sleep-onset REM periods (SOREMP), and provides a measurement of REM sleep latency (time from sleep onset to the first REM sleep). A mean sleep latency of less than five minutes is consistent with pathologic excessive sleepiness. Sleep-onset REM periods in two or more of the four or five recordings during MSLT is suggestive of narcolepsy. Abnormalities of REM-sleep regulatory mechanisms and circadian rhythm sleep disturbances may also lead to REM-sleep abnormalities during the MSLT.

Additional Laboratory Tests
Multi-channel, continuous-video-PSG monitoring may be helpful when abnormal motor activities are encountered in patients with multiple system atrophy (MSA), olivopontocerebellar atrophy (OPCA), Parkinson disease (PD), and AD. Actigraphy, a recently developed technique that uses a motion detector to record activities during sleep and waking (35), may be useful in the diagnosis of circadian rhythm sleep disorders in patients with neurodegenerative diseases. Pulmonary function tests (PFTs), which assess lung volumes, gas distribution and transfer, arterial blood gases, and chemical control of breathing may be employed to evaluate intrinsic bronchopulmonary disease, which may affect sleep-related breathing disorders.
Description and Treatment
Treatment of the sleep disturbances in patients with underlying dementias should begin with the treatment of the primary underlying condition. The goal of therapy is to improve the quality of life. The general measures are directed at reducing the risk factors that may exacerbate the sleep disruption. An attempt should be made to reduce or eliminate medications that could potentially disrupt sleep. Associated conditions such as depression, anxiety, or pain need to be treated with appropriate medications. The patients should be encouraged to develop good sleep habits, maintain a regular sleep-wake cycle, and refrain from taking extensive daytime naps. Substances which may disrupt sleep, such as caffeine, alcohol, and nicotine, should be prohibited. Patients should be encouraged to exercise during the day, but not too close to the evening hours. Table 1 describes the fundamental therapy of sleep hygiene in patients with dementia.

TYPES OF SLEEP DISTURBANCES
Insomnia
Sleep changes in aging often compound sleep changes related to the primary insomnia itself. Insomnia complaints may include difficulty in initiating and maintaining sleep and early-morning awakening. Untreated insomnia can cause an insufficient amount of sleep, and poor sleep resulting in hypersomnolence, irritability, disruption in concentration, and depression, sometimes mistaken for dementia itself (15,22). Insomnia may be complicated by agents prescribed for the specific management of underlying neurodegenerative diseases. The medications used to treat these disturbances can worsen sleep disordered breathing and daytime symptoms (23).

Targeted pharmacotherapy for AD can precipitate insomnia. A prime example is Tacrine (a cholinesterase inhibitor), first marketed for the management of cognitive dysfunction in AD. Tacrine is notorious for causing insomnia. Another

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Suggestions to Improve Sleep Disturbance in Dementia</th>
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<tbody>
<tr>
<td>Treat and manage underlying mood disorders</td>
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<td>Restrict time in bed to sleep</td>
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<tr>
<td>Avoid activities such as reading and watching television in bed</td>
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<tr>
<td>Keep a regular sleep-wake schedule. Get up and go to sleep at consistent times each day</td>
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<tr>
<td>Schedule regular exercise every early in the evening, preferably outside the living environment</td>
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<tr>
<td>Avoid excessive and unplanned napping during the day</td>
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<tr>
<td>Avoid the intake of caffeine-containing beverages and alcohol, especially in the evening</td>
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<tr>
<td>A light snack at bedtime may be helpful</td>
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<tr>
<td>Avoid excessive liquid intake at bedtime</td>
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<tr>
<td>Limit excessive environmental noise and partially insulate the bedroom against sounds that disturb sleep</td>
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<tr>
<td>If insomnia occurs, encourage quiet activity outside the bedroom, returning to bed only when sleepy</td>
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<tr>
<td>If total sleep time is reduced, do not make up for lost sleep by extending sleep</td>
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<tr>
<td>Participate in usual daily activities, no matter how little sleep was obtained the previous night</td>
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<tr>
<td>Foster a safe living environment. Sharp objects and obstacles in bedroom should be removed doors should have locks or alarms</td>
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<tr>
<td>Keep a nightlight on in the bathroom or stairs to reduce falls</td>
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<tr>
<td>Educate caregiver for documenting and reporting snoring or unusual motor activities at night</td>
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<tr>
<td>Sleep problems in the patient can translate into poor sleep in the caregiver: obtain assistance for supervision at nighttime, if needed</td>
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</table>
cholinesterase inhibitor, Donepezil, can produce insomnia when taken before bedtime. Donepezil induces insomnia and nausea, and the manufacturer suggests that it be prescribed at bedtime to minimize the development of nausea. Many practitioners, however, choose to prescribe it in the morning with breakfast, as nausea tends to be less common and not severe, but the insomnia is often problematic.

Patients with AD and other forms of dementia commonly suffer from mood disturbances, which cause insomnia (24,25). Insomnia is also a common and an unpleasant side effect of antidepressant therapy. In patients with AD, cholinergic blockade with tricyclic antidepressants should be avoided, and the practitioner is advised to carefully entertain the risk-to-benefit ratio of utilizing these agents.

Pharmacotherapy of Insomnia
Specific pharmacotherapy for sleep disturbances in neurodegenerative diseases is not particularly effective. In patients with insomnia, a trial with short-to-intermediate-acting benzodiazepines (e.g., Temazepam) or zolpidem (Ambien) may be tried for a short period. For nocturnal wanderings or agitation and sundowning, a trial with small doses (0.5–1 mg) of haloperidol may be instituted.

Hypersomnia
Hypersomnia is a common problem in patients with dementia resulting from inadequate sleep, sleep fragmentation due to primary sleep disturbances such as OSA, and circadian rhythm disturbances. Patients with hypersomnia may fall asleep at inappropriate times and situations (4,5). These patients may also have additional complaints of daytime fatigue, lack of concentration, impaired motor skills and cognition, and may not show any improvement despite adequate sleep time. Some patients may be at additional risk for sleep-related respiratory disturbances and loud snoring during sleep, as well as periodic leg movements (12).

Unfortunately, data regarding the incidence and prevalence of hypersomnia in dementia is unknown. Data is available, however, in a cohort consisting of elderly patients residing in nursing homes in whom low dose methylphenidate (≤5 mg) has been shown to improve alertness (26). Currently, the exact neurochemistry and neurophysiology of hypersomnia in dementing conditions remains a mystery.

Circadian Rhythm Disturbances
Circadian rhythm disturbances (CRD) are commonly seen in institutionalized elderly patients and in patients with neurodegenerative disorders (27–29). Factors that may disturb the circadian regulation of sleep in dementia can be divided into direct and indirect. The symptoms of insomnia and hypersomnia can reflect a primary circadian dysrhythmia. In this clinical setting, patients tend to sleep more during the day and be active more during the night. This increased motor activity at night is the major contributing factor to significant caregiver distress. Direct mechanisms thought to contribute to CRD in patients with AD and other dementing conditions are related to degenerative changes that take place in the SCN of the hypothalamus and related to decreased melatonin production in the pineal gland (30–33). Indirect mechanisms include medications prescribed for those patients that cause nocturnal confusion, or “sundowning.” Patients with AD are commonly affected by an irregular sleep-wake rhythm (ISWR), which is characterized by lack of discernable sleep-wake circadian rhythm. Instead of having a major sleep period, sleep is fragmented into three or more
periods during the 24-hour day, with the longest sleep period occurring between 2 and 6 am. Patients with AD have a high prevalence of this disorder, in which the etiology may be related to changes in the hypothalamus and the SCN (34). Patients with associated neurologic disorders, mental retardation, and brain injury are also commonly affected (34,35).

Important factors which may contribute to ISWR may include weak external entraining stimuli such as reduced exposure to environmental light and diminished daytime activity, which is especially common in institutionalized patients. Patients with ISWR may present with insomnia, hypersomnia, or needing frequent naps throughout the day. The disorder also affects the sleep quality of the caregiver. The diagnosis of the ISWR is made by reviewing the patient’s sleep log or actigraphy, confirming the lack of periodic circadian rhythmicity. A history of isolation or reclusion can often aid in the diagnosis. Other sleep or psychiatric disorders that can cause fragmented sleep must be excluded. On the differential diagnosis of ISWR are factors related to poor sleep hygiene or voluntary maintenance of irregular sleep schedules. Figure 2 outlines potential factors responsible for circadian rhythm disruptions in dementia.

Management of Circadian Rhythm Disturbances
Management of circadian rhythm sleep disorders including the irregular sleep-wake type is aimed at consolidating the sleep-wake cycle with the potential use of melatonin and phototherapy. Melatonin, when given at bedtime, may improve sleep continuity and increase total sleep time in dementia. For institutionalized patients, increased daytime social interactions, and light exposure have been
shown to help consolidate and improve nighttime sleep (36,37). Other strategies aimed at consolidating sleep include scheduled physical activity and minimizing nighttime light and noise (38,39). Combination therapy of vitamin B12, bright light, chronotherapy, and hypnotics produced a 45% success rate in one cohort of patients suffering from AD (40). Treatment with melatonin failed to improve sleep in one large multicenter study in AD based on actigraphy-derived measurement of sleep time (41).

A recently multicenter, randomized, double-blind, and placebo-controlled clinical trial funded by the National Institutes of Health at 31 AD centers in the US demonstrated no beneficial effects of melatonin 2.5 or 10.0 mg on sleep disturbance in a well-characterized, large AD population \( n = 157 \) (41,42). The data relied on actigraphically-derived measures of sleep, and is considered the definitive test of this hormone at this time. On the contrary, light-therapy or phototherapy has proven efficacious in the management of CRD in patients with dementia. However, the optimal timing and duration of phototherapy and illumination intensity have not yet been determined (43,44).

A practical approach to the management of ISWR is to begin with behavioral and environmental strategies. These include bright light exposure and structured social and physical activities, and avoidance of naps during the day. During the sleep period, the environment should be conducive to sleep and should consist of minimal noise, a darkened room, and a comfortable room temperature. The use of hypnotic or sedating psychoactive medications should be used with caution in elderly patients with dementia. Time exposure to bright light in the morning may be helpful in some patients. Evening bright light pulses may ameliorate sleep-wake cycle disturbances in some patients with AD (44). Ancoli-Israel reported that when light exposure is increased throughout the day and evening, it produced a beneficial effect on sleep and on circadian rhythms in patients with dementia. It would behoove nursing homes, therefore, to consider increasing ambient light in multipurpose rooms where patients often spend much of their days to help improve sleep quality (45). Another observation from the same group, evaluating the effect of bright light therapy on agitated behavior in a large sample of patients with severe AD revealed that light was associated with improved caregivers’ ratings, but had little effect on observational ratings of agitation (46). The authors hypothesized that while the SCN of patients with severe AD is more likely to be degenerated, and the circadian activity rhythms deteriorate as AD progresses, it is still possible that patients with less damaged SCNs, or patients with mild-to-moderate AD, might benefit from light treatment even more than those with severe AD (46). Figure 3 attempts to outline potential therapy for circadian rhythm sleep disorders in patients with dementia.

**Sundowning**

Sundowning refers to agitation in dementia patients that has specific temporal exacerbation during the early evening or nocturnal hours (47,48). When poorly controlled, sundowning may lead to eventual institutionalization of the patient and thus it is critical to make an early diagnosis and prescribe appropriate management (14,49). Unfortunately, the use of the term, “sundowning” is often loosely used and ambiguous describing nocturnal agitation without specifically connoting a precise pathophysiologic mechanism or diagnosis. “Sundowning syndrome” describes a combination of nocturnal confusion, hyperactivity, delirium, disorganized
thinking, wandering, restlessness, impaired attention, agitation, insomnia, hypersomnia, hallucinations, anger, delusions, anxiety, and illusions (48,50). Sundowning implies a predilection for the abnormal behavior to evolve or to occur during the evening or the night, although caregivers and nursing home staff describe the escalation of symptoms toward the late afternoon or evening, there is actually little data to support that this indeed occurs (51). Sundowning may very likely have several different underlying pathophysiologic mechanisms. It is suggested that rather than using the term “sundowning” health-care providers should use more descriptive terms when communicating among themselves, and when approaching family member. Examples may include terms such as the patient showed “agitation and physically aggressive behavior” or “wandering and pacing.”

Specific therapy for sundowning is targeted at uncovering the underlying causes. Often, the clinical history and diagnostic testing do not provide a clear answer, and therapy may take the approach of treating by trial and error. When specific pharmacological therapy is contemplated it is suggested to start at low doses and increase slowly. The integration of psychosocial support including education, and respite care can be very helpful. Several modalities have been suggested to ameliorate various features of the “sundowning” syndrome. Data evaluating the use of antipsychotic agents and benzodiazepines have demonstrated improvements in sleep or nocturnal behavior, but lacked real-time behavioral observations as relevant outcomes (47). Agents such as the antipsychotics often have adverse effects including sedation, confusion, orthostatic hypotension, and parkinsonism, which are often clinically significant in elderly patients with dementia (47). The “high potency” antipsychotics (for example, haloperidol) are associated with an increased risk of producing extrapyramidal side-effects, whereas the “low potency” agents (e.g., thioridazine, chlorpromazine), have more sedating,

FIGURE 3  Treatment of circadian rhythm disturbances in alzheimer’s dementia: Light exposure can be beneficial for both advanced sleep phase syndrome as well as irregular sleep-wake schedule disorder. Solid gray bars indicate actual sleep time. Broken lines indicate desired sleep period.
anticholinergic, and orthostatic hypotensive properties (47). Clozapine is a unique antipsychotic agent that is specific to the dopamine D4 receptor and thus may improve the psychiatric manifestations of sundowning without causing significant extrapyramidal side-effects. Melatonin, if used in physiologic doses and at appropriate times, can be helpful for those suffering from insomnia or circadian rhythm disorders (52). One study described a role for oral melatonin (2 mg) for sleep initiation and maintenance in melatonin-deficient non-demented elderly insomniacs (53). Behaviorally, the sleep-promoting effects of melatonin are also distinctly different from those of the traditional hypnotics and are not associated with alterations in sleep architecture (54). However, at high doses (over 0.3 mg), melatonin may cause side effects and disrupt the delicate mechanism of the circadian system, dissociating mutually dependent circadian body rhythms (52). A misleading labeling of the hormone melatonin, as a “food supplement” and the notorious lack of quality control over melatonin preparations on the market, unfortunately continue to be of serious concern (52).

Obstructive Sleep Apnea
The hypothesis of a causal relationship between OSA and dementia has been intriguing. The link has been suspected since many patients with sleep apnea suffer from mental decline and the evidence of higher prevalence of sleep apnea in some dementia patients. At this point, however, the association continues to be somewhat speculative and a subject of controversy (55–64). Obstructive sleep apnea is one of the most important and frequent sleep disorders in elderly patients with dementia since it adversely affects almost every organ system and diminishes quality of life. OSA is characterized by repetitive airway obstructions causing daytime sleepiness, snoring, and impaired cognition. Several studies have noted a higher prevalence of sleep disordered breathing in patients with AD when compared to controlled groups, (65,66) whereas others have not (63). Furthermore, anecdotal reports of dementia like symptoms associated with sleep apnea led to the speculation that there should be a causal relationship between sleep disordered breathing and AD (67). In AD, sleep apnea could be a consequence of cell loss in the brainstem respiratory center. Conversely neuronal degradation in AD could be hastened by nightly insults of intermittent cerebral hypoxemia related to the underlying sleep apnea. In AD however, sleep apnea occurs more frequently than in nondemented older subjects, and its severity is correlated with the degree of cognitive impairment (64).

The diagnosis of OSA in the elderly patient with dementia may be delayed. Unlike younger patients with OSA, the elderly often present with atypical clinical presentation, and the frequency of sleep related complaints are often mistakenly considered to be part of the dementia or inherent to the normal aging process. From a technical standpoint, it is sometimes more challenging to perform PSG in the elderly, especially in those who have an underlying dementia (2). Difficulties in establishing the diagnosis of OSA in the elderly also stems from the lack of established data and the lack of uniform distribution of the apnea-hypopnea index (AHI), in many of the studies done so far.

Consequences of Obstructive Sleep Apnea Patients with Dementia
Typical symptoms of sleep apnea in patients with dementia include disturbances in concentration, memory problems, and neurocognitive decline. Some have related
these impairments to the hypoxemia that accompany the cessation of airflow in sleep apnea (68–70). Chronic hypoxic episodes in patients with OSA have been associated with moderate to severe neuropsychological impairment. Accordingly, speculation and research have focused on relationships between sleep apnea and dementia. A significant proportion of patients with AD have apnea index greater than 10 when compared to controls or patients with depression, and the predominant type of apnea was obstructive. Similar findings were reported by Reynolds et al. (71) in a controlled study, in which 43% of patients with Alzheimer's dementia had an apnea index of greater than 5 versus 4.3 of controls.

Using the Mattis Dementia Rating Scale (DRS) and the Geriatric Depression Scale, Ancoli-Israel et al. (72) determined that sleep apnea was significantly correlated with all subscales on the dementia rating scale. Particular items reflecting attention, initiation and perseveration, conceptualization, and memory tasks on the DRS distinguished between those with and without severe sleep apnea (72). The authors hypothesized that although causality could not be inferred from these associations, sleep apnea may indeed cause deficits in brain function, possibly due to global effects rather than affecting particular cortical or subcortical structure (72).

One of the key genotypic markers for AD is the Apolipoprotein E epsilon4 (APOE4) allele. A recent discovery that sleep-disordered breathing is associated with the APOE4 allele in the general population has sparked an interest in this topic, since OSA is characterized by multiple genetic vulnerabilities (62,73). In individuals under age 65, the APOE epsilon 4 allele was more significantly associated with increased risk of OSA (74). However, other studies did not replicate the results due to different genetic populations and different age-cohorts (75,76).

**Sleep-Disordered Breathing**

Comprehensive discussion of therapy for sleep apnea is discussed elsewhere in this textbook. In patients with dementia, treatment of OSA may help ameliorate the neurocognitive disturbances, hypersomnolence, and quality of life and may optimize therapies for other chronic conditions such as hypertension.

The objectives of treatment of sleep-disordered breathing (SDB) in neurodegenerative diseases are to improve the quality of life and prevent life-threatening cardiac arrhythmias and congestive cardiac failure. The quality of life may be improved by preventing repeated nocturnal arousals, sleep fragmentation, and episodes of hypoxemia associated with sleep apnea. The treatment of SDB in neurodegenerative diseases may be divided into four approaches: general, pharmacological, mechanical, and surgical measures (4,20).

**General Measures**

Patients should avoid substances such as alcohol and sedative-hypnotic medications, which may suppress breathing during sleep, causing further deterioration in SDB. Alcohol may worsen OSA by decreasing pharyngeal airway size and increasing nasal resistance (77). When possible, patients should be encouraged to exercise and loose weight. Patients with underlying supine-related sleep apnea should avoid sleeping in the supine position, which may be facilitated by sewing tennis balls in the back of the pajama shirt (snore-ball technique) or by using specialized wedge-pillows.
Pharmacological Therapy
Pharmacological treatment for OSA has been unsuccessful, and its use, especially in elderly patients may be discouraged due to the higher likelihood of side effects in this patient group ranging from tolerance to serious adverse side effects (68). Mechanism of action of the principle pharmacologic agents include reduction of OSA via respiratory drive stimulation, REM sleep suppression, and stimulation of upper airway muscle tone (78). REM sleep suppressants such as Protriptyline reduce REM sleep (79). REM suppressants may improve OSA during REM sleep since respiratory events during this stage are more severe both in duration and oxygen desaturation. These agents decrease REM stage time and REM sleep apnea duration and produce improvement in oxygenations, which may last beyond six months of treatment (80). Tricyclics may produce cardiovascular complications especially in the elderly, due to their strong anticholinergic side effects.

Mechanical Measures
Nasal continuous positive airway pressure (nCPAP) is currently the most important measure for treatment of OSA in patients with neurodegenerative diseases. Therapy with nCPAP helps to improve the quality of sleep and reduces daytime symptoms of hypersonnia by correcting the sleep disruption caused by OSA and its associated hypoxemia. Unfortunately, in the elderly, treatment of OSA with nCPAP is challenging, as many have diminished compliance with rates ranging from as low as 46% to 80%. (81,82). Neuropsychological analyses have revealed that in patients with OSA, cognitive flexibility, attention, processing speed, and memory all improve with CPAP therapy (4,16,83–85). Compliance with CPAP was also associated with greater improvements in attention, psychomotor speed, executive functioning, and nonverbal delayed recall (86). In the authors’ clinical experience, some of the adherence problems are unique to the elderly and may include problems with dexterity (putting the mask on and off when getting up to use the bathroom) and age related neurocognitive difficulties limiting comprehension when learning how to use and care for the mask leading to non-compliance. Some of these complications can be overcome when the patient’s spouse or caretaker becomes involved and participates in the treatment plan.

Surgical Treatment
Surgery for SDB is targeted at the level of the upper airways preventing their collapse. Extensive and complex surgery such as maxillo–mandibular advancement, whereas sometimes effective in younger patients, carries multiple risks, and should probably be avoided as first line therapy in the elderly. Other than tracheostomy, no surgical measure is practical in patients with neurodegenerative diseases with an unrelenting course. Tracheostomy is probably the only effective measure for emergency treatment of severe respiratory dysfunction and hypoxia in patients with marked laryngeal stridor, as can be seen in laryngeal abductor paralysis in patients with MSA (87,88). In patients with neurodegenerative diseases with a progressive and unfavorable course, a decision for tracheostomy must be weighed carefully.
Central Sleep Apnea
Central sleep apnea (CSA) is known to occur in patients with primary central nervous system and cardiac dysfunction. Part of the etiology may be due to degeneration of central respiratory and autonomic neurons involved in breathing. Disregulation of the brainstem respiratory centers is presumed to be responsible for CSA in the dementia. Continuous and bilevel positive airway pressure therapy, as well as supplemental oxygen, may help improve this condition.

EXCESSIVE MOTOR ACTIVITY DURING SLEEP
Restless Legs Syndrome and Periodic Limb Movement Disorder
RLS is described by patients as a “creeping” uncomfortable sensation in the extremities (89,90), particularly the lower limbs, associated with the urge to kick or move the involved limb. Moving the limb often improves the uncomfortable sensation. Patients may complain of a motor restlessness, difficulties initiating sleep, and multiple nocturnal awakenings (91). This sensation is improved when patients move their legs, but returns when the movement ceases. Patients with RLS often present with sleep initiation insomnia. The RLS may be exacerbated by underlying conditions such as rheumatoid arthritis, peripheral neuropathy, excessive caffeine intake, and iron deficiency. PLMS is a condition characterized by repetitive and continuous leg jerks 0.5 seconds to 5 seconds in duration typically occurring every 20 seconds to 40 seconds during sleep. The diagnosis of PLMS is established when five or more of these movements occur per hour of sleep. Many patients with PLMS may also have coexistent RLS. The nocturnal polysomnogram is often the only reliable way to document periodic limb movements and to establish the diagnosis. The disorder increases in frequency with older age. Ancoli-Israel et al. (92) have reported that 45% of older people may have this condition with no gender predilection. The diagnosis and treatment of RLS is important as it can lead to sleep initiation insomnia in the older person. Most patients with RLS have PLMS, however, the converse is not true. It has been hypothesized that since dopamine agonists and opiates improve the symptoms of RLS and PLMS, related transmitter systems may be involved in the pathogenesis of these conditions.

At present, there are no epidemiologic studies looking at the frequency of RLS in patients with AD and other forms of dementia. Therapy for RLS and PLMS is in the form of dopaminergic agonists such as ropinirole and pramipexole (93). Iron has been implicated to play a central role in the pathophysiology of RLS. Iron deficiency can produce RLS symptoms and its replacement results in clinical improvement. Patients with RLS symptoms should have their ferritin levels checked and those with levels less than 45 to 50 ug/l should begin iron therapy. Many patients with OSA may also suffer from PLMS. It is prudent to determine if OSA and PLMS coexist, since treatment of the underlying PLMS with benzodiazepine may worsen the OSA.

Rapid Eye Movement Sleep Behavior Disorder
REM sleep behavior disorder (RBD) is characterized by pathologic augmentation of skeletal muscle tone during REM sleep. Patients present with unusual, complex, and intense motor activity during a dream sequence. The range of motor activities can vary from a simple limb movement to a very complex quasi-purposeful
movement, suggestive of dream content enactment (94). The potential for self and bed partner injury is high, especially during severe episodes (95). Current hypotheses suggest that the pontine tegmentum is the locus of muscle tone inhibitor system which normally causes muscle atonia during REM sleep (96). The peri-locus ceruleus of the rostral tegmentum of the pons produces activation of the medullary inhibitory zone via the tegmentoreticular tract. In REM sleep behavior disorder (RBD), the brainstem mechanisms generating muscle tone become disrupted. The pathophysiology of RBD in humans is based on the cat model. In the cat model, bilateral pontine lesions result in a persistent absence of REM atonia associated with prominent motor activity during REM sleep, similar to that observed in RBD in humans. The pathophysiology of the idiopathic form of RBD in humans is still not very well understood but may be related to reduction of striatal presynaptic dopamine transporters.

**FIGURE 4** Muscle atonia during REM sleep results from pontine-mediated peri-locus ceruleus inhibition of motor activity. This pontine activity exerts an excitatory influence on medullary centers (magnocellular neurons) via the lateral tegmentoreticular tract. These neuronal groups, in turn, hyperpolarize and the spinal motor neuron postsynaptic membranes via the ventrolateral reticulospinal tract. In REM sleep behavior disorder (RBD), the brainstem mechanisms generating muscle become disrupted. The pathophysiology of RBD in humans is based on the cat model. In the cat model, bilateral pontine lesions result in a persistent absence of REM atonia associated with prominent motor activity during REM sleep, similar to that observed in RBD in humans. The pathophysiology of the idiopathic form of RBD in humans is still not very well understood but may be related to reduction of striatal presynaptic dopamine transporters.

**Abbreviations:** RBD, REM sleep behavior disorder; REM, rapid eye movement. **Source:** From Ref. 114.
commonly affected with RBD. Polysomnographic records of patients with MSA demonstrate that as many as two-thirds reported nocturnal paroxysmal episodes related to dreams suggesting the clinical diagnosis of RBD. The data shows that RBD represents the most common clinical sleep manifestation and polysomnographic finding in patients with MSA. REM-sleep behavior disorder can frequently herald the appearance of other MSA symptoms by years. Polysomnographic investigation consisting with multiple limbs recording and video monitoring is recommended in patients with MSA when these spells are suspected (103,106). Secondary causes of RBD include diseases, which disrupt brainstem centers involved in REM sleep-generated-muscle atonia such as multiple sclerosis, cerebral vascular accidents, and brain stem neoplasm. Twenty-five percent of patients may have a prodrome of subclinical behavioral during sleep. The acute onset of REM sleep behavior disorder is related to drugs such as tricyclic antidepressants (TCA), monoamine oxidase inhibitors (MAOI), selective serotonin-reuptake inhibitors (SSRI), and acute withdrawal of alcohol and barbiturates. Caffeine use has also been recently implicated in causing RBD (101,102,104).

If there is evidence of an abnormal neurological examination, a full neurological workup including a brain MRI and may be also be needed (102,106).

The differential diagnosis of RBD includes sleepwalking, nocturnal seizures, post traumatic stress disorder (PTSD), sleep terrors, nocturnal panic disorders, delirium, sleep related gastroesophageal reflux, PLMS, psychogenic dissociative state, and confusional arousals with sleep apnea. Distinguishing RBD from nocturnal seizures may sometimes be difficult. However, unlike nocturnal seizures, the typical RBD-spell is usually not stereotyped and is often variable (95,102,104,107). Additional laboratory studies may be needed especially if the clinical history remains vague or ambiguous. When the possibility of nocturnal seizures cannot be reliably excluded additional sleep testing may be warranted.

Environmental safety is crucial in every patient with likely RBD. This may include protecting and sleeping environment by removing sharp objects and padding the bed area. Suggested pharmacotherapy for RBD may be in the form of clonazepam (0.25–1 mg p.o Q.H.S), which is effective in 90% of cases (102). There is little evidence of tolerance or abuse with this form of treatment. Caution should be exercised when using it in patients with chronic respiratory diseases or impaired renal function, and it is contraindicated in patients with documented hypersensitivity, severe liver disease, or acute narrow-angle glaucoma. Abrupt discontinuation of clonazepam can precipitate withdrawal symptoms (102). Other agents that can be helpful include imipramine (25 mg p.o Q.H.S), carbamazepine (100 mg, p.o T.I.D.), and levodopa, in cases where RBD is associated with Parkinson’s disease. Recent studies have also demonstrated improvement with the use of melatonin, which is believed to exert its therapeutic effect by restoring REM sleep atonia. One study reported that melatonin was effective in 87% of patients taking 3 to 9 mg at bedtime (108), whereas a later study reported resolution in those taking 6 to 12 mg of melatonin at bedtime (109). As noted earlier in this chapter, the reader is reminded that melatonin, a food supplement, is not approved by the Food and Drug Administration, has poor regulation in terms of pharmacologic preparation. Its uses, especially in elderly patients, should be done with great care as it is vasoactive in laboratory animals and side effects have not been widely studies. Tacrine, Donepezil, and Serzone, drugs used in AD and other dementing disorders may exacerbate RBD. Some antidepressant may potentially increase total REM sleep, which may worsen RBD.
SLEEP DISTURBANCES IN OTHER NEURODEGENERATIVE DISORDERS

Multiple-System Atrophy

MSA is characterized clinically by any combination of autonomic, extrapyramidal, or cerebellar signs and symptoms. Patients with MSA experience degeneration of the pontine tegmentum, nucleus tractus solitarius, nucleus ambiguus, hypoglossal nucleus, reticular formation of the brainstem, and at times, the cervical and thoracic spinal cord. Therefore, the diffuse neurodegenerative process that encompasses these key structures involved in the regulation of the sleep-wake transition and respiratory function in MSA may account for the most frequent sleep disturbances in MSA, SDB, and RBD (110,111). Increasing evidence points to the role of basal ganglia dysfunction in the underlying pathophysiology of RBD in MSA, in fact, a recent study from our center has revealed that decreased nigrostriatal dopaminergic projections may contribute to RBD in MSA (112).

Patients with MSA frequently manifest a variety of sleep-related respiratory disturbances, some of which are life threatening. Above all, a common and serious complication is upper-airway OSA associated with stridor, which is caused by vocal cord abductor paralysis (VCAP) and may lead to sudden death during sleep (113). For this reason, nocturnal stridor in MSA has been considered a poor prognostic feature (88). For the early diagnosis of VCAP, it is critical to perform laryngoscopy during sleep, because VCAP does not appear during wakefulness in the early stage of MSA (87). A PSG study should be obtained to assess the severity of respiratory disturbances; tracheostomy is the most reliable treatment for respiratory disturbances due to VCAP, whereas nCPAP may be a useful treatment for some patients, but absolute compliance is mandatory.

Progressive Supranuclear Palsy

Besides progressive supranuclear oculomotor disturbances, other characteristic signs of progressive supranuclear palsy (PSP) include pseudobulbar paresis, axial rigidity, gait disturbances, and subcortical dementia. Sleep disturbance is universal in PSP (15,114). Insomnia is the most common complaint and is worse than insomnia in Parkinson’s disease or AD. Other sleep disturbances may be related to the well documented immobility in bed and difficulty with transfers, depression, dysphagia, and frequent nocturia seen in PSP. REM-sleep behavior disorder and sleep-disordered breathing are not common in PSP (15,114).

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INTRODUCTION

The autonomic nervous system, through its complex central and peripheral circuits, controls vital involuntary functions of the body such as circulation, respiration, thermoregulation, neuroendocrine secretion, gastrointestinal, and genitourinary functions. There is an intimate relationship between the autonomic nervous system and sleep from anatomical, physiological, and neurochemical points of view. However, in the past it was commonly assumed that autonomic regulation remained unchanged across behavioral states and the concept of a state-dependent regulation of the autonomic nervous system has been addressed only recently. The first to understand the importance of recording autonomic parameters during sleep in clinical medicine were Lugaresi et al. who described the dramatic changes in systemic and pulmonary blood pressure associated with apneas and renewal of breathing in Pickwickian patients (1,2).

SLEEP AND AUTONOMIC NERVOUS SYSTEM INTERACTIONS

Sleep and autonomic nervous system are interdependent on each other by virtue of their common controls, neurobiological substrates and functions. Major confirmation of this is the presence of dynamic and synchronous fluctuations in sleep-phases and autonomic functions.

It is important, for example, to emphasize that the changes in state during sleep are coordinated principally by the pons, basal forebrain areas and other subcortical structures, and the main neurotransmitters involved are norepinephrine, serotonin, and acetylcholine. Experimental lesions and evidence from use of a variety of drugs suggest that serotonin is involved in the induction and maintenance of slow-wave sleep; this in turn appears to affect non-REM sleep because slow-wave sleep is generally a prerequisite for REM sleep, so that an alteration of brain serotonin levels will also affect REM sleep. Behavioral arousal occurs after lesions to the raphe nucleus (serotonergic nucleus) and a gradual reduction of slow-wave and REM sleep is produced by the injection of para-chlorophenylalanine, which depletes the brain of serotonin. Norepinephrine is predominantly involved in the waking mechanism and in the REM sleep suppression system. Acetylcholine is involved in wakefulness, slow-wave sleep, and REM sleep. The injection of acetylcholine into the brainstem is followed by slow-wave sleep but
sometimes REM episodes occur. Atropine abolishes REM sleep. The same neuronal populations that produce and distribute these neurotransmitters constitute the central representation of the sympathetic and parasympathetic nervous system. The central autonomic network, through its ascending and descending connections between hypothalamic-limbic region and the nucleus tractus solitarius in the medulla, orchestrates the sympathetic and parasympathetic divisions of the autonomic nervous system (3). Sleep promoting neurons, which are scattered in the vicinity of the central autonomic network and its connections (e.g., preoptic-anterior hypothalamic region and nucleus tractus solitarius) along with cholinergic “REM-on” and catecholaminergic “REM-off” cells in the ponto-mesencephalic junction and pons, control NREM and REM sleep cycles. Sleep induces profound changes in the functions of the autonomic nervous system, and disorders of the autonomic nervous system adversely affect vital functions during sleep that includes circulation and respiration. The two aminergic neuronal subgroups (locus coeruleus and raphe nuclei) that are most active in wake, become progressively less active in NREM sleep and virtually cease firing in REM sleep. On the other hand, the cholinergic neurons (in the dorsolateral tegmental and pedunculopontine nuclei) are active in both waking and REM sleep. Consequently, in waking both systems are active. In NREM sleep both systems are less active and in REM sleep the cholinergic system acts alone.

Cardiovascular Regulation During Sleep
NREM sleep is characterized by electrocortical synchronization, reduced muscle tone, and stable parasympathetic predominance. In this phase, there is a tonic decrease in arterial pressure and heart rate as a result of a parasympathetic activation and sympathetic inhibition. Hypotension reflects a decrease in cardiac output and in peripheral resistance. A moderate reduction of cardiac output results primarily from a decrease in heart rate, reflecting an increased parasympathetic activity. The decrease in total peripheral resistance is largely due to a reduction in sympathetic vasomotor tone, resulting in skin, muscle, and visceral vasodilation. In normal human subjects, hypotension, and bradycardia during NREM sleep become increasingly more pronounced as sleep progresses from stage 1 to stage 4 (4). Sympathetic nerve activity, as recorded in skeletal muscle and skin nerves, is decreased by more than half from wakefulness to stage 4 of NREM sleep (5). The combination of lower arterial pressure, heart rate, and sympathetic nerve activity indicates that NREM sleep is accompanied by downward resetting and increased sensitivity of the baroreceptor reflex. The increase in baroreceptor reflex gain during NREM sleep contributes to the decreased variability of arterial pressure, typical of this stage (6,7). In NREM sleep, sympathetic activity may be transiently increased by arousal stimuli, coinciding with the appearance of K complexes in the electroencephalogram. This is associated with increased heart rate and respiration.

REM sleep is characterized by electrocortical desynchronization, muscle atonia, and phasic motor autonomic changes. Marked phasic fluctuations of sympathetic and parasympathetic activity and impairment of baroreflex responses and thermoregulation are the hallmarks of this sleep phase. During tonic REM sleep, there is a marked bradycardia and decreased peripheral resistance, resulting in a decrease in arterial pressure below the levels observed in NREM sleep. The decrease in arterial pressure observed during REM sleep is interrupted by large

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transient increases in arterial pressure and in heart rate during bursts of rapid eye movements and muscle twitches; variability of these cardiovascular parameters results from phasic inhibition of parasympathetic activity and phasic increase in sympathetic discharge.

**Respiratory Regulation During Sleep**

Because of the close relationship between the cardiovascular and respiratory systems, the variations of the former during sleep–wake cycle implicate related modifications to the latter. The integration of the cardiorespiratory system during sleep is achieved at several levels in the neuraxis; it is essentially linked to the autonomic nervous system and is important in preserving functional homeostasis during sleep. The respiratory system is essential for oxygen exchange and the cardiovascular system for blood transport.

In NREM sleep, respiration is controlled by an automatic system driven by chemical stimuli. The core of this automatic system is composed of various neuron groups in the medulla; a neural subgroup produces consistent respiratory activity and is relatively insensitive to non-respiratory influences; another subgroup is less in respiratory activity but is affected greatly by NREM sleep and by various non-respiratory influences. Medullary respiratory neurons have a variable behavior in REM sleep and this factor largely accounts for the irregular breathing during this state. It is also known that medullary respiratory activity in REM sleep is influenced by at least one type of phasic REM sleep event (Pontine-Geniculate-Occipital spike waves), a finding clearly indicating non-respiratory and state specific influences on the respiratory system in REM sleep. Some studies, however, show that the central respiratory drive, although erratic, is often increased in REM sleep.

**Thermoregulation During Sleep**

The regulation of body temperature is controlled by the autonomic nervous system, which uses many sources of information to generate specific thermoregulatory responses (e.g., sweating, shivering, and skin vasomotor adjustments). The characteristics of thermoregulatory control vary significantly between sleep phases and wake and with time of the day, being modulated by the circadian system and by sleep control mechanisms. Body temperature is regulated at a lower level during NREM sleep that is characterized by downward resetting of the thermostat, resulting in a reduction of body core temperature and metabolism. Decreases in rectal temperature or increases in skin temperature have been reported routinely at the onset of sleep in adult humans sleeping in neutral or cool environments.

Thermoregulatory responses to changes in peripheral or core body temperature show qualitatively different responses in NREM compared to REM sleep in animal studies; during NREM sleep, thermoregulation mechanisms are operative and the ambient thermal load variations are balanced. This homeothermy is controlled by hypothalamic-preoptic integrative mechanisms that drive the subordinate brainstem and spinal somatic and visceral mechanisms. In contrast, transition from NREM sleep to REM sleep is characterized by a disruption of ongoing thermoregulation. In this phase, there is a marked inhibition of thermoregulation and the changes in body temperature occur passively in relation to the heat environmental load. The result is that the temperature of the body changes according to its thermal inertia, as one would expect in a poikilothermic organism (8,9).
On the other hand, thermal environment and body temperature are important determinants of sleep architecture, and they have a prominent influence on both the amount and distribution of arousal states. Parmeggiani et al. first showed in cats that total sleep time is maximal within the thermoneutral zone and decreases above and below it (10). Moreover, the NREM-sleep to REM-sleep ratio increases as ambient temperature deviates from thermoneutrality. This is due, primarily, to a reduction in the number of epochs of REM sleep. Some studies showed that in a cold environment there is an increase in wake, sleep latency, and movement time, and the decrease in sleep time is due mostly to the decrease of REM sleep and of stage 2 of NREM sleep (11). According to other authors, the decrease of stage 2 NREM sleep, when tested at a cold (21°C) versus neutral (29°C) ambient temperature, is greater than REM variations (12). Warm environments also cause an increased wakefulness, and reduce both REM and NREM sleep during the night. Then, when subjects were exposed to a range of ambient temperatures, it became evident that total sleep time, NREM and REM sleep are maximum at thermoneutrality (29°C) (13).

The environmental temperature effects on sleep are more prominent during the light phase compared with the dark phase of the diurnal cycle; these data emphasize the importance of considering time-of-day on the relationship between temperature and sleep. Moreover, there is an important relationship between the duration of sleep, REM sleep propensity, and body temperature. Body temperature, for example, has a profound effect on the paradoxical sleep cycle. In the "pontine" cat, the normal body temperature is about 39.5°C but if body temperature falls to 30°C, the duration of each paradoxical sleep period is increased from six minutes to about 20 minutes. In humans, the duration of sleep has also been related to changes in body temperature. In addition to the variations in environmental temperature and thermoregulatory responses associated with different stages of sleep and wake, there are daily cycles in the properties of the thermoregulatory system and consequent changes in body temperature that are independent of arousal states; they are under the control of the circadian system, which also influences the organization of vigilance states. In a temporal isolation experiment, subjects slept longer when they went to sleep at or shortly after the peak of the circadian temperature oscillation. All subjects awoke during the rising phase of the temperature cycle and went to bed most frequently shortly after the circadian temperature trough, when alertness was decreased.

An example of the effect of body temperature on sleep comes from studies of fever. In 1968, Karacan et al. (14) reported that fever had specific effects on nocturnal sleep, including an increase in wake and stage 1 of NREM sleep and a dramatic decrease in both REM and stage 4 of NREM sleep. However, subsequent studies on the effects of putative pyrogens on sleep revealed controversial data; in most cases the sleep and temperature effects were temporally displaced and dependent on dose, site and mode of injection, and time of the day (15,16).

Hormonal Secretions During Sleep
With regard to the relationship between sleep, autonomic nervous system, and hormonal secretions it is useful to remind that many biological, physiological, and biochemical rhythms are regulated by the integration of the circadian clock and the sleep wake cycle. In mammals, the suprachiasmatic nucleus of the anterior hypothalamus serves as the central neural pacemaker of the circadian timing system.
and the discovery of its functional role sets the stage for understanding how a central circadian pacemaker can drive the daily fluctuations in a whole array of physiological functions. There is growing evidence that hormones have a mutually regulatory influence on circadian rhythms and sleep–wake cycle. Melatonin levels are highest during night sleep (17); cortisol is low at the time of habitual sleep onset, but then it is high at the habitual morning wake time (18). Urine volume is an example of another variable that exhibits wide fluctuations under constant routine conditions but is also influenced by the sleep–wake state. Sleep opposes the circadian variations of thyroid-stimulating hormone so that its hormone levels reach the highest level just before sleep onset and are suppressed during sleep episodes. Instead, growth hormone, prolactin, and parathyroid hormones show a prominent sleep-related increase. Moreover, ultradian variations in the release of renin are closely related to the NREM–REM sleep cycle; increased relative delta power (S3–S4 stages of NREM sleep) is associated with increased levels of plasma renin activity.

SLEEP DISORDERS WITH AUTONOMIC DYNSFUNCTIONS

Table 1 lists primary sleep disorders, which may have autonomic deficits. Some of these conditions may show mild autonomic changes whereas others may have clinically relevant autonomic nervous system dysfunction. Moreover, there are a large number of neurological and general medical disorders associated with autonomic failure and many of these patients have sleep disturbances. Table 2 lists disorders of primary and secondary autonomic failures, which are associated with sleep dysfunction.

**Fatal Familial Insomnia**

Fatal familial insomnia is a rare prion disease characterized by major sleep and autonomic disturbances. Postmortem brain studies disclosed severe loss of neurons particularly in the anteroventral and dorsomedial thalamic nuclei (19). PET studies have shown that severe thalamic hypometabolism is present at the onset of insomnia and dysautonomia, suggesting that damage to the medial thalamus is the biological cause of symptoms (Fig. 1) (20). The autonomic symptoms are sexual impotence, sphincter impairment, increased tearing, salivation and sweating, and increased core body temperature. Polysomnographic recordings show total absence of sleep patterns, short episodes of REM sleep without muscle atonia associated with enacted-dreams, and a consistent elevation of blood pressure and heart rate (21). Correlation with EEG tracing showed that in those cases in which short episodes of NREM sleep are still present, blood pressure and heart rate fell abruptly displaying a normal state dependent behavior. An imbalanced

<table>
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<th>TABLE 1</th>
<th>Sleep Disorders Associated with Clinically Relevant Autonomic Nervous System Dysfunctions</th>
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<td>Sleep disorders</td>
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*Abbreviation: REM, rapid eye movement.*
autonomic control with preserved parasympathetic activity and a higher background and stimulated sympathetic activity was the conclusion derived from the autonomic tests in fatal familial insomnia patients. Evidences of sympathetic overactivity are the elevated noradrenaline plasma levels at rest which further increase during orthostatic stress, the exaggerated blood-pressure responses to physiologic stimuli (postural changes, Valsalva maneuver, isometric handgrip), the absent blood-pressure response to noradrenaline infusion, the increased heart rate response to atropine, and the diminished depressor and sedative effects of clonidine (22,23).

Obstructive Sleep Apnea Syndrome

There are reports of alterations of both sympathetic and parasympathetic systems in patients with obstructive sleep-apnea syndrome. Most of the studies emphasized the hyperactivity of sympathetic nervous system causing an increased plasma norepinephrine levels and urinary catecholamine secretions. Enhanced muscle sympathetic nervous activity during wakefulness and sleep in patients with obstructive sleep-apnea syndrome has been clearly documented (24,25). The pathogenetic hypothesis is that, tonic activation of excitatory chemoreflex afferents may contribute to increased efferent sympathetic activity to the cardiovascular system.

Studies of heart rate variability using spectral analysis show sympathetic activation (increased low frequency component and increased low frequency/high
frequency components ratio) during sleep apnea (26). The circadian rhythm of heart rate variability show that the mean high frequency component (parasympathetic activity index) is lower and the mean low frequency/high frequency components ratio (sympathetic activity index) is higher in obstructive sleep-apnea syndrome. These findings suggested that sleep disordered breathing influenced heart rate variability not only during sleep but also during wake.

Normotensive awake obstructive sleep-apnea syndrome patients have higher heart rate and norepinephrine plasma levels at rest and a higher blood pressure response to head-up tilt with a significantly lower respiratory arrhythmia and Valsalva ratio, associated with a greater decrease in heart rate induced by cold face test. These data suggest that even in the awake condition a sympathetic overactivity is present and that reflexes dependent on baroreceptor or pulmonary afferents are blunted with normal or increased cardiac vagal efferent activity (27). Moreover, there is evidence of a depression of spontaneous baroreceptor reflex sensitivity during sleep (28). These alterations of circadian autonomic rhythms could determine the increased prevalence of cardio and cerebrovascular disease, which was demonstrated in patients with obstructive sleep-apnea syndrome. Early investigators recognized hypertension as a clinical feature of sleep apnea but until recently the link between sleep apnea and hypertension was uncertain because of the many confounding factors (obesity, age, alcohol ingestion). Nowadays, there are good epidemiological evidences supporting a direct contribution of sleep apnea to hypertension (29). Moreover, in a population of essential hypertensive patients, the nondipper condition appeared to be closely linked to the presence of nocturnal obstructive sleep apnea (30). Many hypotheses have been advanced to explain how sleep apnea leads to daytime blood pressure elevation. According to many

![Graph showing regional cerebral glucose metabolism](Image)

**FIGURE 1** Regional cerebral glucose metabolism was imaged utilizing [18F]-2-fluoro-deoxy-o-glucose (FDG) PET in a patient with familial fatal insomnia (FFI) of 10 months duration. Note the severe thalamic hypometabolism and milder secondary impairment in frontal and cingulate cortices (arrows).

*Source: Photo courtesy of Dr. Perani, HSR Milan.*
authors, the most important causative factors leading to an increased sympathetic activity are the effect of episodic hypoxemia and hypercapnia on chemoreceptors, the modification of the cardiovascular system (including fluid balance) in response to marked fluctuations in intrathoracic pressure during obstructive apneas, the generalized stress derived from sleep disruption (the arousal effect), and other metabolic or endocrine factors. However, the common mechanism shared by hypertension and obstructive sleep-apnea syndrome is the activation of the sympathetic system (31).

A number of cardiac arrhythmias resulting from changes in the autonomic nervous system were associated with obstructive sleep apnea. The most common are brady-tachyarrhythmias (relative bradycardia during obstruction and relative tachycardia on resumption of normal breathing). The other dysrhythmias include sinus bradycardia, sinus pauses lasting for two seconds to 13 seconds, second-degree heart block, ventricular ectopic beats, and ventricular tachycardia. Although ventricular arrhythmias seem to be closely related to the degree of desaturation, the cause of dysrhythmias in patient with obstructive sleep-apnea syndrome remain controversial.

Ondine’s Curse
This term describes a disease characterized by hypoventilation during sleep and by varying degrees of hypoventilation during wake. This is a condition of failure of the autonomic control of breathing. During sleep, the pattern of breathing is often a reduced tidal volume rather than an apnea, but in severely ill patients, the sleep onset is associated with complete central apnea (32). Hypoxic and hypercapnic ventilatory responses are impaired (33). To describe patients without an identified cause of hypoventilation, the term used is primary alveolar hypoventilation or congenital central hypoventilation syndrome. There is an association of congenital central hypoventilation syndrome with ganglioblastoma and Hirschsprung disease (congenital megacolon due to absence of ganglion cells in the myenteric plexus) (34). The term secondary alveolar hypoventilation identifies the same pattern of breathing during sleep but with a clear neural cause (brainstem tumor, brainstem damage from encephalitis, neuropathy affecting the respiratory motor nerves).

Parasomnias
Parasomnias are abnormal movements or behavior intruding into sleep without substantial alteration of the sleep architecture. Some of the parasomnias, particularly sleep terrors and REM sleep behavior disorder, are associated with autonomic dysfunction.

Sleep terror is a parasomnia classified as a disorder of arousal. The clinical onset is generally between five and seven years of age and familial cases are common. Sleep terror or pavor nocturnus arises out of Stage 3 to Stage 4 NREM sleep phases during the first one-third of sleep period. Episodes of sleep terror are characterized by intense autonomic manifestations such as marked tachycardia, tachypnea, excessive sweating, pupillary dilatation, flushing of the skin, and reduced skin resistance. There is a correlation between the amount of prior NREM sleep (S3–S4 phases) and autonomic intensity as measured by the degree of tachycardia (35).
REM sleep behavior disorder is a sleep parasomnia characterized by violent-and dream-enacting behavior during REM sleep, often causing injuries to the patient or bed partner. The polysomnographic examination shows loss of REM sleep-related muscle atonia associated with a variety of abnormal motor activities during sleep. This condition may be either idiopathic or secondary to a neurologic illness; it can precede, by several years, the onset of some degenerative diseases associated with autonomic failure (Parkinson’s disease, multiple system atrophy) (36). Evaluation of cardiac autonomic function showed that autonomic dysfunction could be detected earlier during sleep than during wakefulness. The tonic and phasic heart rate variability, in fact, appear reduced during sleep in patients with REM sleep behavior disorder. Moreover, in these patients tachycardia does not accompany the abnormal movements during REM sleep, indicating an impairment of the sympathetic nervous system (37,38).

**DIAGNOSIS**

The first step is the clinical diagnosis; it should be directed at diagnosing the primary or secondary autonomic failure and its causes as well as assessment of sleep disturbances. It is extremely important to obtain a history, documenting characteristic clinical manifestations of autonomic dysfunction, and the physician’s attention should be directed to the possibility of sleep disorders and particularly sleep-related breathing disorders. The diagnosis of sleep dysfunctions starts from a detailed history of sleep habits, sleep hygiene, and subjective sleep complaints, which often can be obtained only from the bed partner.

Laboratory investigations should be an extension of the history and physical examination. For the assessment of sleep disorders and respiratory dysfunctions during sleep the gold standard is represented by overnight polysomnographic study. This examination should include simultaneous recordings of electroencephalogram, electrooculogram, electromyogram, electrocardiogram, respiratory monitoring (oronasal flow and thoracic and abdominal effort), snoring, oxygen saturation by oximetry, noninvasive continuous monitoring of blood pressure, and rectal temperature. Video-polysomnography may be needed in some patients to diagnose the type of movement disorders referred during sleep.

Choosing how to assess autonomic nervous system function in the awake condition mainly depends on the clinical presentation of the dysfunction. In clinical practice, the main methods of autonomic investigation are based on assessment of cardiovascular function, which can disclose a deficit but also determine its location and severity. These methods are the most commonly used, because they are noninvasive and easy to perform and interpret. A postural fall in arterial pressure over 20 mmHg for systolic and 10 mmHg for diastolic pressure or a less radical drop in arterial pressure accompanied by symptoms demands further investigation in a laboratory for the study of autonomic nervous system function. The head-up tilt test is the postural stimulus most commonly used with concomitant measurement of arterial pressure and heart rate. In some cases, postural hypotension may be initially masked by food intake, physical exercise or a warm environment. Further tests will help to determine the severity of impaired autonomic control of the cardiovascular system. Arterial pressure and heart rate responses to Valsalva maneuver when intrathoracic pressure is increased depend on the integrity of the
whole baroreceptor reflex arch. Stimulation such as the handgrip exercise (35% maximum effort for three to five minutes), the cold-pressor test (immersing the hand in ice-cold water for 90 seconds) and mental arithmetic (serial subtractions of 7 and 17) activate sympathetic vasoconstrictive efferents and raise arterial pressure. Heart rate response during deep breathing (respiratory arrhythmia), Valsalva maneuver, and hyperventilation provide information on the integrity of the cardiac efferent vagal pathways. To assess postprandial orthostatic hypotension, an orthostatic test is performed before and after a standard liquid meal with known quantities of carbohydrates, proteins, and fats. In pure autonomic failure, noradrenaline plasma levels at rest in a supine position are low, suggesting a sympathetic efferent neuropathy. Instead, in multiple system atrophy with autonomic failure, noradrenaline levels at supine rest are within normal limits because the lesion is centrally located. In any case, a reduction or lack of the plasma noradrenaline increase from a lying-down posture to a standing posture is found in both groups of patients due to a shared impairment of the baroreceptor reflex. Nowadays, skin and muscle sympathetic fiber activity can be recorded directly by inserting a microelectrode through the skin into the peroneal and median nerves (microneurography). This method is also useful to clarify the various mechanisms physiopathologically linked to a hyperactive sympathetic system, but is of little clinical use in investigating autonomic failure, when sympathetic activity is progressively reduced. Pharmacological tests will determine the degree of sensitivity of alpha-adrenergic (noradrenaline infusion), beta-adrenergic (isoprenaline infusion), and cardiac muscarinic vascular receptors (atropine infusion). Pressor response to raised plasma noradrenaline levels on infusion of tyramine will indicate the reserves of noradrenaline in the peripheral sympathetic terminal. Measurement of arterial pressure and heart rate circadian rhythm is especially useful to check for the nocturnal supine hypertension (nondipper behavior) characteristic of patients with autonomic failure and hence tailor the timing of treatment.

PROGNOSIS, COMPLICATIONS AND MANAGEMENT

The obstructive sleep-apnea syndrome, particularly if untreated, may lead to serious consequences related to nocturnal hemodynamic alterations and excessive daytime sleepiness. Obstructive sleep-apnea syndrome is an important risk factor for hypertension, cardiac arrhythmias, myocardial infarction, congestive cardiac failure, and stroke. Moreover, reduction of diurnal vigilance may increase the risk of car or work accidents. REM sleep behavior disorder can precede the onset of neurodegenerative disease (multiple system atrophy and Parkinson’s disease) by several years; this is the most important factor for a long-term prognosis.

In primary sleep disorders with autonomic dysfunctions, treatment directed to the primary condition may also correct autonomic symptoms. The most important example is obstructive sleep-apnea syndrome in which autonomic dysfunctions are attenuated by treatment (39,40). There are general measures directed to eliminate or reduce the aggravating factors for sleep-related breathing disorders (reduction of body overweight, avoidance of alcohol, and sedative hypnotic drugs) but nasal continuous positive airway pressure is the most widely utilized and efficacious therapy for obstructive sleep apnea. This treatment eliminates the sleep-related upper airway obstructions, oxygen desaturations, and hemodynamic consequences of apneas.
REFERENCES

INTRODUCTION

There is an intimate relationship between headache disorders and sleep that is complex and difficult to sort out. Both excessive and insufficient sleep may trigger headaches, and patients with headaches may suffer sleep disorders in a mutual relationship with common reinforcements. In a review of sleep and headache syndromes, Sahota and Dexter (1) categorized the relationship as follows: (i) headaches occurring during or after sleep, (ii) sleep-stage-related headaches, (iii) excess, lack, or disruption of sleep causing headaches, (iv) headaches relieved by sleep, (v) headaches associated with sleep disorders, (vi) effect of headaches on sleep, and (vii) dreams and headaches. Migraineurs are more prone to develop parasomnias, and statistically there is a correlation between migraine and narcolepsy. Cluster headaches and paroxysmal hemicranias may exhibit a specific correlation with stages of sleep such as is the case with the cluster variant rapid eye movement (REM)-sleep-locked headache, which appears during REM sleep. Headaches caused by brain tumors have a tendency to appear during sleep, although, owing to the low prevalence of brain tumors, most headaches that occur during sleep have another origin. Headaches on awakening are idiosyncratic and have traditionally been linked with the sleep apnea syndrome, but not all patients with sleep apnea develop headache and not all patients with morning headache have sleep apnea. Patients with chronic headache commonly complain of daytime fatigue and insomnia. Therapeutic modification of sleep deprivation or of a sleep disorder reduces the incidence and intensity of headache.

Historically, Freud (2) was aware of the relationship between headaches and sleep, mentioning “headache-dreams” and giving a psychodynamic interpretation of their occurrence. Headaches on awakening or morning headaches were described as early as 1945 by Bing [cited in Ref. (1)], and more recently Gans (3) wrote about treating migraines with sleep rationing. Dexter and Weitzman (4) reported the relationship between headaches and sleep-stage patterns, and Lance et al. (5) provided a neurophysiological account of the relationship between the nucleus locus coeruleus and mechanisms underlying migraine. The intriguing association between paroxysmal hemicrania and REM sleep (6) has attracted attention to the circadian sleep rhythms and their influence in triggering headaches.

The International Classification of Sleep Disorders-2 (7) recognizes the following headache disorders in association with sleep: classic migraine, migraine with aura, common migraine, migraine without aura, hemiplegic migraine, cluster headache, chronic paroxysmal hemicrania, and hypnic headache. The diagnostic criteria require that the patient complain of headache during sleep or upon awakening from sleep.
EPIDEMIOLOGY

Surveys of headache patients indicate a high prevalence of nocturnal or sleep-related headaches. Paiva et al. (8) reported that 17% of patients attending a headache clinic suffered headaches during the nocturnal period or early in the morning (before final awakening). In the nocturnal headache subgroup, 55% of patients had a specific sleep disorder identifiable by polysomnography in a sleep center.

The prevalence of migraine in the general population is 10% for men and 16% for women (9). Cluster headache, occurring in 0.4% of men and 0.08% of women (10), is predominantly a nocturnal disorder, since 75% of cluster headaches appear between 9 p.m. and 10 a.m. (11), and half of them are associated with REM sleep (12). Headache on awakening occurs in one-third of patients with sleep apnea (13), and although headache is unrelated to severity of obstructive sleep apnea syndrome, patients with sleep apnea had more headaches than control subjects (14).

Children with migraine have a higher incidence of disturbed sleep and parasomnias (15), night terrors, and enuresis (16). As many as 30% of children with migraine report episodes of somnambulism (17). Prolonged deep sleep is a risk factor for development of sleep terrors and somnambulism, as well as for migraine attacks in susceptible patients (18), a phenomenon that suggests shared pathogenetic mechanisms.

In a survey conducted in Germany, patients with narcolepsy reported an abundance of headaches (19). Sixty-eight patients with idiopathic narcolepsy were interviewed for the presence of headaches. Eighty-one percent reported headaches that fit an International Headache Society diagnosis, whereas 54% (64% women, 35% men) had migraine satisfying International Headache Society criteria.

In another study, 56 patients with obstructive sleep apnea syndrome were compared with 50 patients with insomnia (20) to evaluate headache characteristics. The authors reported that in patients with obstructive sleep apnea syndrome and headache, the pattern was most frequently a tension-type form and occurred on awakening in 74% of patients.

In a study of 1283 migraineurs attending a tertiary headache clinic, Kelman and Rains (21) found that migraineurs were 84% female, with a mean age of 37.4 years. Sleep complaints were common and associated with headache in a sizeable proportion of patients. Over half of migraineurs reported difficulty in initiating and maintaining sleep at least occasionally. The short sleep group, who routinely slept six hours per night, exhibited the more severe headache patterns and more sleep-related headache. Sleep complaints occurred with greater frequency among chronic than episodic migraineurs. The authors suggested that normalizing sleep times in the short sleepers might impact headache threshold.

In a study of the prevalence of sleep disorders in children with headaches, the authors found (22) that children with headaches have a significantly higher prevalence of excessive daytime sleepiness, narcolepsy, and insomnia when compared with children without headaches ($P < 0.005$). The study contradicts previous work stating that children with headaches have a higher prevalence of sleep apnea, restlessness, and parasomnias, an association that may be more specific for genuine migraines and not for headaches in general. The authors conclude that pediatricians should inquire about daytime sleepiness, narcolepsy, and insomnia in children with headaches.
HEADACHE SYNDROMES AND SLEEP

Certain types of headaches may be associated with specific stages of sleep and may lead to sleep disruption.

Migraine attacks have been described in association with sleep stages 3, 4, and REM. Sleep-related migraine attacks, similar to daytime episodes, are characterized by unilateral throbbing head pain associated with nausea and vomiting, scotomata, visual-field defects, photophobia, paresthesias, and sometimes hemiparesis or aphasia. Migraines are highly idiosyncratic and not all symptoms are present. Attacks may last from several hours to a few days. Migraine attacks in children under eight years often resolve after an interval of sleep (23). Although migraine headaches may be provoked by sleep, the most common association is sleep following a migraine attack.

In one study (24), migraineurs showed a lower cyclic alternating pattern (CAP) rate in non-REM (NREM) sleep and, in particular, a lower number of A1 phases [low-frequency, high-amplitude electroencephalograph (EEG) bursts] compared with the controls. Migraineurs also showed a lower index of high-frequency EEG arousals during REM sleep. The reduction in CAP rate was interpreted by the authors as a lower level of arousal fluctuation in NREM sleep. They suggested that the reduced arousal index in REM was due to a dysfunction in neural structures involved in both the control of REM sleep and the pathophysiology of migraine, including the hypothalamus and the brainstem.

Cluster headaches occur in 0.4% of men and 0.08% of women (10) and 75% appear predominantly at night between 9 p.m. and 10 a.m. (11). They are characterized by severe unilateral, periorbital, malar, and temporal pain with lacrimation, nasal engorgement, rhinorrhea, sweating forehead, and flushing of the malar area. Attacks last less than two hours and may appear several times daily, sometimes at the same time of the day or night, commencing and terminating abruptly. Situational insomnia of a transient nature in association with cluster headache resolves after the headache syndrome subsides (25). Cluster headaches have been linked with stage REM and sleeping late in the morning, a situation that promotes REM sleep, a possible triggering factor. Spontaneous remissions lasting several months are the norm.

Autonomic dysfunction was suggested in a nine-week actigraphic recording with repeated polysomnography of a patient with cluster headache, evaluating both sleep macrostructure and microstructure (26). During the acute bout, the authors observed an irregular sleep–wake pattern and abnormalities of REM sleep. After the cluster phase, these alterations remitted. The authors concluded that cluster headache was associated, at least in this patient, with sleep dysregulation involving the biological clock and the arousal mechanisms, particularly in REM sleep. They hypothesized that the abnormalities were consistent with posterior hypothalamic dysfunction.

The study of the relationship of the hypothalamus to respiratory physiology and its comorbidity with sleep apnea was undertaken by Nobre et al (27) in 37 patients with episodic cluster headache. The authors investigated whether apneas were more frequent during REM sleep and whether desaturations could be triggers of cluster attacks. They found a greater percentage of obstructive sleep apnea in patients with cluster headache (58.3%) compared to the control group (14.3%) and to the general population (2–4%). The risk increased in patients with a body mass index (BMI) higher than 25 kg/m² and in patients over 40 years
The authors recommended that polysomnography be performed in patients with cluster headache over 40 years of age, particularly if the BMI is higher than 25 kg/m².

**Chronic paroxysmal hemicrania** is characterized by attacks of severe pain associated with conjunctival hyperemia, rhinorrhea, and rarely Horner’s syndrome. Events are shorter than those in cluster headache but more frequent; they may occur predominantly at night, generally at the same hour, and do not remit spontaneously. REM-sleep-locked headache refers to a specific form of paroxysmal hemicrania that shows a close linkage to REM sleep. Chronic paroxysmal hemicrania is considered a variant of cluster headache featuring more frequent attacks of pain of shorter duration. It responds quasi-specifically to the therapeutic administration of indomethacin.

Unilateral headaches characterized by severe, strictly unilateral pain in the territory of the distribution of the trigeminal nerve, associated with autonomic manifestations are also known as trigeminal autonomic cephalalgias (TACs) (28). They include cluster headache, episodic and chronic paroxysmal hemicrania, and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing. Work incapacity may occur during severe attacks, and global disability may prevail if attacks are severe and frequent. In women, attacks may cease after menopause.

**Hypnic headache** is a benign headache disorder initially described in the elderly characterized by regular awakenings from sleep at a constant time of night (29). The headache is diffuse in two-thirds of patients; its intensity varies widely, usually lasts 30 to 60 minutes, and is sometimes associated with a dream. Generally, there is only one attack per night, although more than one episode has also been described. The majority of patients experience the attack during the middle third of the night and report regularity in its occurrence. Less than 10% of patients have associated autonomic symptoms like lacrimation, nasal congestion, or rhinorrhea, and these are usually mild when they occur. Results of laboratory tests including MRI of the head, EEG, and Doppler ultrasound have been invariably normal. Polysomnography has shown occurrence of headache attacks during REM sleep in a few but not all patients. In a series of 19 cases reported by Dodick et al. (30), the mean age of headache onset was 60.5 ± 9 years. Patients were generally awakened between 1 and 3 a.m.; in a few patients, a similar headache occurred during daytime naps as well. In 68% of patients, headaches appeared four nights per week, with resolution within two hours. The number of unilateral hypnic headaches reported has increased (31). In a more recent review of 71 cases (32), the following characteristics were reported: age at onset 63 years, female 63%; duration of attack 67 ± 44 minutes; frequency of attacks 1.2 per 24 hours; moderate intensity of pain: 67%, bilateral pain 61%, diffuse pain 56%. Newly reported cases have expanded the clinical spectrum of the disorder to include unilateral forms (about 40%, half of which are side-locked), forms with a longer duration (up to three hours), and cases with onset in juvenile/adult age (33). The location of pain is frontotemporal in over 40% of cases, headache is throbbing in 38% of cases, dull in 57%, and stabbing in less than 5%. Nausea is reported in 19% of cases; photophobia, phonophobia, or both are present in 6.8%.

The exploding-head syndrome or “snapping of the brain” (34,35) is a peculiar but benign condition occurring mostly in patients over 50 years characterized by abrupt onset of flashing lights and sounds during the night that terrify patients. Pain is not present. Polysomnographic studies have shown that the attacks take place during...
awakenings, without evidence of epileptogenic discharges (36,37). There is one case report of exploding-head syndrome followed by sleep paralysis and migraine (38).

Hemicrania horologica or clock-like hemicrania (39) is a rare disorder with headaches that occur with clock-like precision every 60 minutes, day and night, lasting 15 minutes. Unlike chronic paroxysmal hemicrania, there are no autonomic signs. Hemicrania horologica responds to nonsteroidal anti-inflammatory drugs (NSAIDs) and indomethacin. Attacks also occur during the day, a feature that distinguishes it clearly from hypnic headaches.

Headaches on awakening appear in conjunction with a variety of disorders. Although common in children with brain tumors, they occur in only 5% of adults with brain tumors. In the sleep apnea syndrome, patients complain of diffuse headache in the morning localized to the frontal region, with a frequency that is independent of the severity of the disease (14). The pain is mild to moderate and tends to disappear within 30 minutes after getting out of bed. The following mechanisms have been implicated in headaches on awakening in patients with sleep apnea syndrome: hypoxemia, hypercapnia, altered cerebral blood flow, increased intracranial pressure, excessive neck movements, and sleep disturbance caused by depression. However, the exact mechanism of headache and the relationship between obstructive sleep apnea, headache, and morning headaches in particular remain controversial (40). In patients with sleep apnea syndrome, prolonged afternoon naps may be followed by headache. Morning headaches, although seemingly independent of the severity of sleep apnea syndrome, respond to the successful treatment of the nocturnal respiratory disturbance. Significant improvement of chronic headache is observed in 30% of treated patients (41).

Headaches on awakening are not the exclusive province of the sleep apnea syndrome. Morning headaches are also observed in relation to bruxism, systemic hypertension, depression, muscle-contraction headache, alcohol intoxication, and sinus inflammation. Bruxism, or clenching and grinding of teeth, occurs predominantly in stages 1 and 2 of sleep and sometimes in REM sleep, occasionally leading to headache on awakening. The prevalence is 8% in the adult population (42) and somewhat higher in children (43). Bruxism has been related to psychophysiological stress or may be idiopathic. Both phasic and tonic oromandibular muscle contraction have been observed in bruxism. Headaches are presumably caused by temporomandibular joint stress and muscle contraction.

Chronic insomnia and headaches form the core of the postconcussion syndrome that develops following head trauma in some individuals. Symptoms appear in conjunction with memory deficit, depression, anxiety, and irritability, along with judgment and personality disorder in susceptible patients. Polysomnographic studies immediately following severe head trauma have shown alpha-wave intrusion, increased amount of sleep spindles, decreased REM density, and enhanced muscle tone in REM sleep, whereas individual sleep stages become less distinct. Weeks to months following recovery of consciousness, stages 3 and 4, and REM are decreased along with total sleep time (44). Sleep spindles are reduced and the polysomnogram is punctuated by numerous arousals and awakenings. The postconcussion syndrome appears within hours to days following head trauma and may persist for as long as two years thereafter.

Psychogenic headache occurs after awakening, as suggested by early polysomnographic studies performed by Dexter and Weitzman (4). This observation suggests that polysomnographic evaluation may be useful to differentiate genuine sleep-related headaches and psychogenic headache.
SLEEP DISORDERS AND HEADACHE

Snoring has been associated with headache (odds ratio 1.5, with a 95% confidence interval) independently of other potential confounders, as shown in a study of 3323 middle-aged and elderly men in Denmark (45). Although obstructive sleep apnea could underlie such an association, the lack of nocturnal measurements precluded the evaluation of that hypothesis.

Clenching and grinding of teeth during sleep, or bruxism, occurs predominantly in stage 2 of sleep, although it has also been noted in REM sleep. Hundreds of events occurring during the night may lead to abnormal wear of the teeth, temporomandibular joint disorder, and jaw pain (46). Some patients with bruxism have associated muscle-contraction headaches. Headaches associated with bruxism are presumed to be secondary to the muscle activity or the temporomandibular joint stress. Masseter muscle hypertrophy is seen in patients with chronic sleep bruxism, although daytime bruxism may cause hypertrophy too.

There appears to be an association between somnambulism and migraine headaches. In a controlled study of 100 patients with migraine, Dexter (16) found that 71% of the subjects had pavor nocturnus, 55% somnambulism, and 41% enuresis, indicating a higher incidence than that in control subjects. Other authors (47) have corroborated these associations, in particular with somnambulism.

Insomnia and daytime fatigue are common complaints in patients with chronic headache. A recent study of the prevalence and intensity of fatigue in chronic headache sufferers (48) has shown that these patients feel more tired, especially the women, and do not sleep as well at night, especially the men.

Dreams loaded with anxiety and terror may culminate in migraine, as reported by Levitan (49), who offered a psychodynamic hypothesis to explain the association that fails to satisfy modern concepts of headache mechanism.

ETIOPATHOGENESIS

The cause of migraine, cluster headaches, and chronic paroxysmal hemicrania remains unknown, and the interaction between headaches and sleep is poorly understood. In rare instances, intracranial tumors cause severe headaches that awaken the patient at night. Meningitis causes insomnia because of head pain.

Migraine headaches may be triggered by sleep, but the most common association is for sleep to follow a migraine attack. Current theories of migraine suggest that neural stimuli originating in the hypothalamus or brainstem cause changes in cerebral and extracranial circulation. Stimulation of the noradrenergic locus coeruleus decreases regional cerebral blood flow (5), whereas stimulation of the serotonergic raphe nuclei increases cerebral blood flow (50). The “therapeutic” need for sleep (51) in some patients having an attack of migraine may be related to disorders of serotonin metabolism in migraine but proof is lacking. Calcitonin gene-related peptide elevation in the jugular venous blood of migraineurs during the attack (50) has led to the hypothesis of involvement of the trigeminovascular system that promotes vasodilation and release of calcitonin gene-related peptide and substance P (52).

Serotonin (5-HT) is released from platelets during migraine headaches, and 5-hydroxyindolacetic acid, the main metabolite of serotonin, is excreted in excess in the urine following a migraine attack (53). Sumatriptan, an agonist of the 5-HT1 receptor found in cerebral arteries, where it has an inhibitory effect, aborts
the migraine headache. Methysergide, an antagonist of the 5-HT2 receptor found mainly in temporal arteries, where it has an excitatory effect, also terminates migraines. Serotonin, implicated in mechanisms of non-REM sleep, is a possible neurotransmitter link between migraine and sleep.

Cluster headache shows a remarkable periodicity in its occurrence, suggesting a linkage to the circadian rhythm. The neurovascular hypothesis suggests excitation of autonomic fibers of the greater superficial petrosal nerve that would be responsible not only for lacrimation and conjunctival injection but also for edema of the wall of the internal carotid artery with pain and ipsilateral Horner’s syndrome. The association between migraine attacks, cluster headache, chronic paroxysmal hemicrania, and REM sleep remains unexplained. Cluster headache is the most common and best defined of the TACs. Convincing proposals for pathophysiological mechanisms must explain the trigeminal distribution of the pain, the homolateral autonomic manifestations, and the periodic recurrence of the crises and clusters. In cluster headache, the pain is located periorbitally frontally, implicating nociceptive mechanisms involving the trigeminal nerve; the autonomic manifestations are homolateral to the pain and appear to implicate parasympathetic (lacrimation and rhinorrhea) and sympathetic (ptosis and miosis) systems; and, finally the periodicity of the attacks and seasonal recurrence of the cluster periods suggest involvement of the hypothalamus.

Chronic paroxysmal hemicrania is considered a variant of cluster headache, however, with sufficient individual traits to be listed separately. In this condition, attacks of pain are more frequent but of shorter duration than in typical cluster headache, and the therapeutic response to indomethacin is quasi-specific. There is a case report (54) of a patient with headaches meeting the criteria of chronic paroxysmal hemicrania who was fully responsive to indomethacin administration during the first three months of treatment. Further investigations revealed a macroprolactinoma and headaches stopped after cabergoline treatment. The authors suggested that patients with paroxysmal hemicrania should be investigated for pituitary abnormalities.

Evidence from polysomnographic studies indicates that hypnic headache is a primary REM-sleep-related headache disorder of chronobiological origin. The pathophysiology is still unclear, but available data implicate an abnormality of the circadian clock based on the regularity of events.

DIFFERENTIAL DIAGNOSIS

Migraine and cluster headaches occurring at night need to be differentiated from other acute severe headaches, such as those associated with intracranial brain tumors, ruptured aneurysm, and meningitis. Patients with intracranial tumors may be awakened at night by headache that improves upon getting out of bed. Headaches on awakening, as observed in sleep apnea patients, are also seen in patients with severe hypertension, depression, intracranial tumor, muscle-contraction headache, alcohol intoxication, and craniofacial sinus disease. Causes for concern are first or worst-ever headache, associated neurological symptoms or signs, progressive worsening of headache over days or weeks, intractable nausea or vomiting, fever, lethargy, confusion, and stiff neck. Hypnic headaches differ from cluster headaches and chronic paroxysmal hemicrania in their lack of unilateral pain with autonomic symptoms and the older age of onset.
Neurological consultation, neuroimaging studies, and lumbar puncture are indicated in patients who exhibit causes for concern. The sleep apnea syndrome is investigated with nocturnal polysomnography using the sleep apnea protocol followed by a multiple sleep latency test. Minimal criteria for the diagnosis of sleep apnea syndrome are the presence of five or more episodes of respiratory interruption of more than 10 seconds duration per hour of sleep, variably associated with excessive sleepiness, loud snoring, morning headaches, and dry mouth on awakening. Parasomnias are studied with nocturnal polysomnography that includes a seizure protocol and videotaping. Somnambulism and sleep terrors are generally associated with stages 3 and 4 of sleep. Patients with migraine, cluster headache, and hypnic headache may wake up with an acute attack more frequently during REM sleep than during other stages of sleep, and those with cluster headache may suffer the attack at the same time every night.

The use of polysomnography has been recommended by Paiva et al. (55) in patients complaining of morning and nocturnal headaches. In a study of 25 patients with headache, disturbed sleep was found in 21. The clinical diagnosis was re-assessed after polysomnography in 13 patients on account of the finding of obstructive sleep apnea, periodic limb movements, alpha-delta sleep, and insomnia.

**MANAGEMENT**

Proper sleep hygiene is paramount in the prevention of sleep-related headaches. Patients with migraine, cluster headaches, and chronic paroxysmal hemicrania should be instructed to follow good sleep hygiene and to avoid potential precipitating factors such as sleep deprivation, excessive sleep, stress, trauma, and ingestion of certain idiosyncratic foods, including alcohol.

Migraine attacks that occur more than twice a month or are prolonged and refractory to acute therapy warrant daily administration of preventive therapy. All effective headache medications interact with the serotonergic system and thus will likely have some corollary effect on sleep. Preventive treatment of migraine includes beta-blockers, calcium-channel blockers, serotonin receptor antagonists (methysergide, for a period not to exceed four weeks), 5-HT2 antagonists cyproheptadine and methylergonovine, antidepressants that interact with serotonergic receptors such as tricyclics, monoaminooxidase (MAO) inhibitors, and serotonin re-uptake inhibitors (fluoxetine and sertraline), anticonvulsants, particularly in children with abnormal EEG, and nonsteroidal anti-inflammatory agents (56). Sumatriptan, a 5-HT1-selective agonist, administered via subcutaneous injection (6 mg, may repeat after one hour, limit two injections in 24 hours) is an effective medication for migraine attacks. Other abortive medications include ergotamine derivatives, acetaminophen, corticosteroids, and nonsteroidal anti-inflammatory derivatives. Symptomatic treatment for migraine attacks includes nonsteroidal anti-inflammatory derivatives, mixed barbiturate and analgesics, anti-emetics (promethazine 50 mg), and, in special circumstances of severity, meperidine (50 mg) or codeine sulfate (30 mg).

A report of a 2006 European Federation of Neurologic Societies (EFNS) task force (57) for the drug treatment of migraine recommends for the acute treatment of migraine attacks oral NSAIDs and triptans. The administration should follow the concept of stratified treatment. Before intake of NSAIDs and triptans, oral meclopramide or domperidone is recommended. In very severe attacks, intravenous acetylsalicylic acid or subcutaneous sumatriptan are recommended as drugs of
first choice. Status migrainosus can be treated with steroids. Prophylaxis of migraine may be exercised with beta-blockers (propranolol and metoprolol), flunarizine, valproic acid, and topiramate as drugs of first choice. Drugs of second choice for migraine prophylaxis are amitriptyline, naproxen, petasites, and bisoprolol.

Cluster headaches are prevented by avoiding triggering factors, foremost of which is alcohol consumption. Sleeping late in the morning has been cited as a precipitating factor that should be avoided by patients with cluster headache. Cluster headaches are arrested with ergotamine derivatives at bedtime (1–3 mg sublingual), amitriptyline (150 mg daily), methysergide (6–8 mg daily), prednisone (40 mg daily), and lithium carbonate (initial dose 250 mg). An acute attack may be terminated with inhalation of oxygen. Chronic paroxysmal hemicrania responds specifically to indomethacin (50 mg at bedtime or 25 mg three times a day).

Hypnic headaches respond to the administration of lithium (300–600 mg) at bedtime (29). Dodick et al. (30) reported that successful prophylaxis was achieved by drinking coffee at bedtime, with ergotamine tartrate 0.6 mg, phenobarbital 40 mg, and belladona 0.2 mg at bedtime, with atenolol 25 mg at bedtime, and with aspirin 325 mg and caffeine 40 mg at bedtime. Reassurance and administration of clomipramine are curative in most instances of exploding-head syndrome.

Indomethacin-responsive headache syndromes represent a unique group of primary headache disorders characterized by rapid and full response to indomethacin. The paroxysmal and continuous hemicranias invariably respond in an absolute manner to indomethacin. Hypnic headache recently has been described as another primary headache disorder that may respond to indomethacin (58).

Bruxism is treated with stress management, a mouthguard, or an intra-oral occlusal splint (59). For short-term management, diazepam (5 mg) given at bedtime will reduce the tooth-grinding activity.

The symptoms of postconcussional syndrome may respond to the administration of tricyclic antidepressants. Good to excellent relief of symptoms has also been obtained with the administration of intravenous dihydroergotamine and metoclopramide (60).

Successful treatment of sleep apnea syndrome with nasal CPAP, Bi-PAP, or tracheostomy will eliminate associated headaches on awakening.

Remissions of migraine attacks and cluster headaches are common during pregnancy. Preventive medications should be discontinued during pregnancy. Ergotamine and its derivatives are to be avoided during pregnancy.

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Sleep in Traumatic Brain Injury and Other Acquired Central Nervous System Conditions

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INTRODUCTION

Sleep is an active and integral component of central nervous system (CNS), and may be one of its most important functions. Sleep is generated exclusively by the brain, and the brain is the sole benefactor of sleep: there is little evidence that any other organ system requires or benefits from sleep. All elements of wake/sleep function [the biological clock and the generators of all three states of being wakefulness, nonrapid eye movement (NREM) and rapid eye movement (REM) sleep] reside in the brain. That given, it would be expected that any condition that affects the CNS could possibly result in abnormalities of wake/sleep functioning. The ostensible purpose of this chapter is to review the effects of acquired brain dysfunction on wakefulness and sleep. The true purposes of this chapter are to underscore the fact that there is a massive void of knowledge in this most important area, and to encourage further study—the results of which will add immeasurably to our knowledge of brain function and of the wake/sleep process.

ACQUIRED CENTRAL NERVOUS SYSTEM CONDITIONS AND THEIR EFFECTS ON SLEEP AND WAKEFULNESS

Traumatic Brain Injury

Of the acquired CNS lesions, traumatic brain injury (TBI) is the most (but still very inadequately) studied. TBI may result in substantial abnormalities of sleep/wake function. The importance of this is revealed by the numbers: head trauma results in the hospitalization of 500,000 individuals in the United States annually, and permanent disability in 90,000 with severe, complicated, and often devastating social, medical, and personal consequences (1,2). The prevalence of mild TBI is much greater, affecting approximately 1.5 million individuals (3). Despite the incredible prevalence of TBI, its effects on sleep/wake functioning are mentioned only briefly, if at all, in recent sleep medicine, neurology, or rehabilitation medicine textbooks.

Sleep disorders are extremely prevalent in the general population. A pre-TBI sleep disorder could have been causative of the TBI and, even if not, certainly would be expected to persist following the TBI. Given the role of the CNS wake/sleep functioning, clearly the prevalence of sleep/wake disorders is much higher in the TBI population.

Actigraphy as a means of studying wake/sleep functioning in the TBI population deserves special emphasis. Prolonged sleep/wake diaries completed by the patient or observer may give an at-a-glance overview of wake/sleep patterns not
obviously apparent by clinical history. If the sleep/wake disturbance is bothersome and cannot be diagnosed by history alone, procedures to obtain objective information regarding the quality, quantity, and/or timing of sleep should be performed. Actigraphy is an under-utilized tool for the evaluation of sleep/wake complaints, and may be of particular value in the evaluation of the TBI population. In many cases, analysis of sleep diaries may be insufficient to verify a tentative diagnosis in patients with suspected wake/sleep cycle abnormalities. In such cases, definitive objective data may be obtained by actigraphy, a recently-developed technique to record activity during wake and sleep that supplements the subjective sleep log. An actigraph is a small wrist-mounted device that records activity plotted against time—usually for a number of weeks. There are different models of actigraphs, whose principles are reviewed elsewhere (4,5). When data collection has been completed, the results are transferred into a personal computer, where software displays activity versus time. Figures 1 and 2 show actigraphic reports, and demonstrate how the rest/activity pattern is apparent at a glance. There is direct correlation between the rest/activity recorded by the actigraph and the wake/sleep pattern as determined by polysomnography (PSG) (6,7). Actigraphy is particularly valuable in two settings: (i) confirming or refuting a bizarre or difficult-to-believe sleep/wake complaint (such as, “I only sleep two hours per night” or “I am sleeping 18 hours a day.”); and (ii) in the setting of circadian rhythm abnormalities. Correct diagnosis and proper treatment of such conditions may be impossible without actigraphic information (8).

**Effect of Traumatic Brain Injury on Wake/Sleep function**

**Neuropathology of Traumatic Brain Injury**

The mechanisms of brain injury are very complex. Direct blows to the head are not necessary: severe TBI may occur simply from cranial acceleration/deceleration.

![Typical actigraphic report](image)

**FIGURE 1** Typical actigraphic report. The vertical bars represent activity levels plotted over seven consecutive 24-hour periods, permitting rapid assessment of objective rest/activity patterns, which correlate highly with sleep/wake patterns. The overall wake/sleep pattern appears normal.
injuries. Shearing injuries in direct and indirect TBI produce pathologic changes that are often very diffuse, affecting multiple portions of the CNS, including the brainstem (9). Since sleep/wake generation is dependent upon the proper simultaneously functioning of multiple levels of the nervous system, particularly the brainstem, basal forebrain, and hypothalamus, severe TBI could be expected to involve at least some of the structures involved in sleep/wake declaration and function.

Traumatic Brain Injury-Induced Increased Intracranial Pressure
Intracranial pressure (ICP) normally has circadian or sleep-state determinants, being increased during sleep. The ICP increase noted to occur during REM sleep (10–14) was formerly attributed to sleep-related CO2 retention. The change in ICP is now thought to be related to a diurnal increase in blood volume. The increased ICP during sleep may be further exaggerated in patients whose ICP is already elevated (15–19). Cerebral blood flow, which may be compromised in the

![Single Plot of Data](image)

**FIGURE 2** An expanded display of the 24-hour periods of the actigraphic study shown in Figure 1. It is now readily apparent that although the overall wake/sleep pattern is normal, the timing of the sleep period is very abnormal, with sleep onset not possible until approximately 4 AM. This study confirms a severe delayed sleep phase syndrome, and would be of intense value in the management of a patient in rehabilitation following traumatic brain injury. Actigraphy is the only practical and reliable means of obtaining this clinically invaluable information.
setting of increased ICP, may be monitored by the transcranial Doppler ultrasound technique (20,21). In TBI patients with nocturnal decompensation of ICP, severe bradycardia and systemic arterial hypertension were inaccurate surrogate predictors of the increased ICP (22).

Secondary Central Nervous System Injury in Traumatic Brain Injury
Acute TBI may be associated with apnea and systemic hypotension that may individually result in additional secondary CNS damage, further increasing morbidity and mortality (23). It must be remembered that sleep-disordered breathing (SDB) identified following TBI may have been present prior to the TBI, may have resulted from the neurologic injury, or may be due to associated nonneurologic (cervical spine, thoracic cage, cardio-pulmonary) injuries. It is important to detect and treat obstructive sleep apnea (OSA), because it causes severe sleep fragmentation, sleep-related hypoxia, and/or hypercapnia that may impede recovery from TBI. Another important reason to identify and treat OSA is that there may be marked episodic increases in ICP during the apneic episodes (24–27). This is particularly relevant for those TBI patients who may already have TBI-related increased ICP.

Sleep Studies in Severe Traumatic Brain Injury
There have been numerous reports of the presence or absence of normal polygraphic sleep patterns as an indicator of the extent or severity of brain injury, and as predictors of recovery from TBI (28). Given the fact that multiple levels of the CNS are necessary to generate and orchestrate the sleep/wake cycle, it should follow that the more abnormal the sleep/wake patterns are in a TBI patient, the more extensive the damage to the CNS. Conversely, the more normal the sleep/wake cycle the more likely that the integrity of the CNS has been maintained, and perhaps the better the outcome. Many of the commonly cited studies have been reviewed (29).

Analysis of the existing studies is difficult. The methods of reporting sleep have been variable: subjective report, limited EEG monitoring, and formal polysomnographic recording. There is no objective confirmation of insomnia or excessive daytime sleepiness in studies reporting those complaints. It is difficult to compare these studies, as the selection criteria, methods of monitoring, and outcome measures are quite variable, as was the severity of TBI and interval between TBI and study. By definition there are no behavioral manifestations of sleep/wake cycling in comatose patients, however, electrophysiological evidence of sleep/wake is seen as various stages of NREM sleep reappear, followed by episodes of REM sleep. It may be tentatively concluded that the early appearance of wake/sleep cycling generally, but not uniformly, indicates a better prognosis. The same may be said for the correlation (again, incomplete) between the preservation or reappearance of REM sleep and cognitive recovery. Although it has been suggested that this supports the postulated role of REM sleep in memory, it could just as reasonably indicate that the better the return of brain function, the better the memory.

There have been studies employing neurophysiologic measures other than sleep as prognosticators in TBI. One of the most comprehensive is that of Rae-Grant et al. (30), who found a high correlation between Glasgow outcome score and a number of EEG criteria including sleep spindles and EEG reactivity and variability. EEG reactivity was also found to be prognostically significant in other studies (31–33).
All objective sleep/EEG studies in TBI performed to date have been performed on patients with severe TBI, and the outcome variables have been generally gross. Given the broad spectrum of EEG changes attendant with acute severe TBI and the variable rate of recovery, it is questionable whether further sleep/EEG study of this acute and severely affected population will be fruitful. Although there may be some general predictive value of acute sleep-EEG studies on outcome in severe TBI, the degree of overlap among the various groups provides little, if any, meaningful value in individual cases (34). These studies are very expensive both in terms of time and money. Attention may be better directed at evaluation of wake/sleep functioning in the patient who has recovered sufficiently from TBI to participate in a rehabilitation program.

Despite the importance of nighttime sleep and daytime alertness upon daytime function and performance, studies of psychosocial outcome of severe head injury have made no mention of sleep—either objective or subjective (35). In discharged TBI patients with sleep complaints, neurobehavioral impairments and occupational outcome were worse than in those without sleep complaints (36). Further objective study is obviously of the utmost importance.

Sleep/ Wake Functioning Following Minor Head Injury

The situation is even bleaker in studies of wake/sleep function in minor head injury patients. In one subjective questionnaire study, Levin (37) listed “sleep disturbance” as a subscale of the “emotional disturbance” category. In a questionnaire survey of 75 patients following minor head injury, sleep interruption and impaired sleep quality were reported. The percentage experiencing sleep/wake complaints was not stated, and no objective studies were performed (38). In another study of minor head injury, about 20% of patients reported subjective “dysfunction of sleep and rest” (39). Indicating that minor head injuries may result in long-term wake/sleep sequelae, one (subjective) study of 39 patients with the “postconcussion” syndrome indicated a much higher frequency of long-term wake/sleep complaints (both insomnia and daytime hypersomnia) than in a matched group of noncerebral trauma patients (40). It is likely that insomnia is a much more common complaint following mild head injury than the complaint of hypersomnia (41). One preliminary report of objective PSG study in a group of 15 mild TBI patients found impressive circadian rhythm and sleep architecture abnormalities in all patients (42). One study using polysomnographic and actigraphic data found objective evidence of insomnia persisting three years following minor TBI in adolescents (43). Clearly, larger and more rigorous objective studies are needed.

Regrettably, the objective study of wake/sleep functioning and cycling in those patients who have regained consciousness and who are candidates for rehabilitation has never been addressed. It is clear that insomnia, excessive daytime sleepiness, and shifts in the timing of the wake/sleep cycle are common following TBI, and should be expected to pose severe impediments to rehabilitation programs. There is some clinical (without objective verification) suggestion that the complaint of disturbed sleep and impaired attention during wakefulness may change as the patient progresses (44). These complaints may be confounded or exacerbated by the routines employed on most rehabilitation and chronic care facilities. For instance, the practice of putting patients to bed at the same time, usually very early, is more for the convenience of the staff than in the best interest of the patients (or of respect for their biologic clocks). Imposing such constraints upon a patient’s sleep/wake cycle may result in sleep-onset “insomnia” or early
morning awakenings, leading to unnecessary administration of medication. Such practices could be expected to exacerbate circadian abnormalities.

**Chronopharmacology**

The circadian timing of administration of a wide variety of (and, perhaps all) medications and other therapies such as X-ray irradiation may have profound effects upon their efficacy and toxicity (45–48). There is compelling evidence of the importance of consideration of time of circadian cycle in drug administration in other conditions such as cancer chemotherapy, use of anesthetics and antiepileptic drugs, and steroid administration (49). There have been no studies to date on the circadian considerations of drugs utilized in the setting of TBI. It is likely that chronopharmacologic considerations will prove to be of importance in TBI.

**Sleep Disorders Associated with Traumatic Brain Injury**

**Hypersomnia**

Few objective studies documenting hypersomnia in TBI patients are available. One, using the multiple sleep latency test, found nearly 50% of TBI patients suffered from objective hypersomnia (50). In one study of 10 TBI patients with subjective hypersomnia, eight were found to have SDB and two were felt to have narcolepsy (51). Preliminary studies indicate that cerebrospinal hypocretin-1 levels may be reduced in a large majority of individuals with moderate to severe TBI (52).

**Sleep Apnea**

**SLEEP APNEA IN TRAUMATIC BRAIN INJURY.** OSA is prevalent in the general population, therefore, at least 4% of female and 9% of male patients on the rehabilitation service could be expected to have pre-existing OSA (53). TBI may cause OSA by altering respiratory control systems (54). Furthermore, many patients with TBI have also sustained noncerebral injuries that could predispose to OSA. OSA may result from injury, burns, or surgery to the upper airway (55,56). OSA may also result from simple nasal obstruction (57) or nasal packing used for treatment of upper airway problems commonly seen in conjunction with TBI (58).

**SLEEP APNEA IN SPINAL CORD INJURY.** SDB is particularly prevalent in patients with cervical spinal cord lesions (traumatic or congenital), which may be associated with some degree of loss of central respiratory muscle control (59,60). The prevalence of SDB in this population is clearly under-appreciated. It appears to be greater than in the population-at-large, and there may be no consistent relation between commonly employed supposed predictors of SDB (61,62). In one series, 10 of 22 unselected adult patients with stable spinal cord injury were found to have sleep apnea (63). Another study showed significant SDB in quadriplegic patients in whom there was a low clinical suspicion for SDB (64). Persistence of SDB in patients with traumatic tetraplegia has been documented in a longitudinal study (65). This has obvious therapeutic implications. In addition, many medications frequently administered on rehabilitation services (sedative/hypnotics, myorelaxants, and analgesics) may exacerbate SDB (66). To make matters worse, many patients who are relatively immobile tend to gain weight, a known risk factor for the development of OSA.
SDB is readily diagnosed and easily treated. Regrettably, the diagnosis is often simply not suspected.

**Narcolepsy and Idiopathic Central Nervous System Hypersomnia.** Narcolepsy and idiopathic CNS hypersomnia are two conditions characterized by excessive daytime sleepiness in the absence of sleep deprivation or other identifiable abnormality during sleep such as OSA (67,68). Documented narcolepsy or idiopathic CNS hypersomnia following head injury is very uncommon (69). The lack of documentation relates to the fact that many earlier reports were based upon clinical criteria, and have not utilized objective studies such as formal sleep studies and have not employed HLA typing or CSF hypocretin determinations. Clearly, narcolepsy may, albeit rarely, develop as a consequence of acquired CNS lesions (70). The relationship between narcolepsy and TBI requires systematic study. In some reported cases, narcolepsy was likely a pre-existing condition (71). Others suggest that narcolepsy may be induced by TBI, or that TBI may be a triggering factor in unmasking a genetic predisposition for narcolepsy (72,73). A single case of TBI resulting in cataplexy (without objective studies) has been reported (74). Careful study of 20 patients with objectively evaluated post-traumatic hypersomnia revealed multiple causes, including SDB, nonspecific objective hypersomnia, and two cases with subjective, but not objective, hypersomnia (75). The multiple etiologies identified mandate objective study of the complaint or observation of hypersomnia in TBI. Clearly, there are numerous possible causes of post-TBI hypersomnia that require accurate diagnosis by objective PSG and MSLT, as the treatments are diagnosis-specific. The hypersomnia of narcolepsy and idiopathic CNS hypersomnia usually responds nicely to stimulant medication (76,77).

**Kleine-Levin Syndrome.** The Kleine-Levin syndrome is characterized by recurring hypersomnia lasting days to weeks, occurring at intervals of days to years with intervening normal wake/sleep function and alertness. The classic form is idiopathic, and seen in adolescent males, but may affect both sexes and all age groups. The periodic hypersomnia may be associated with hyperphagia and hypersexuality, and likely represents recurrent hypothalamic dysfunction. Many cases are not associated with hyperphagia or hypersexuality (78). TBI was felt to be etiologic in 9% of 186 cases recently reported (79). A post-traumatic form responsive to lithium has been reported (80).

**Wake/Sleep Cycle Abnormalities**

*General.* The wake/sleep cycle in mammals is determined by the suprachiasmatic nucleus (SCN), entrained by the environmental light/dark cycle. Given the fact that the SCN is a brain structure, it would be expected that TBI affecting the SCN may result in severe abnormalities of the wake/sleep cycle. Although circadian dysrhythmias have most important rehabilitation implications, they have been virtually ignored in TBI research. There are two cases of TBI-associated delayed sleep phase syndrome (81,82). One case of an actigraphically documented TBI-associated hypernyctohemeral syndrome has been reported (83). In one study of severely head-injured patients, Billiard et al. (84) found that in seven of nine there was a reversal of the normal circadian rhythmicity. In another study, a large percentage of comatose TBI patients demonstrated a persistent 24-hour temperature cycle, which was advanced or delayed from the usual wake/sleep cycle by a
number of hours. This study suggested that the biologic clock is resilient, but may become “reset” relative to the environment following TBI (85). Other studies have failed to identify shifts in circadian timing following TBI (86). Chronobiologic abnormalities may be common in TBI patients (42), and identification of cycle abnormalities would be most important, as these disorders could be expected to severely impede rehabilitation, and there are a number of effective treatment options available.

Visual dysfunction may occur in patients with TBI, and when the injury is severe, blindness may ensue. The majority of blinded individuals have abnormal wake/sleep cycles (87,88). Therefore, some patients who have pregeniculate (lesions anterior to the SCN) blindness as a result of a TBI could be expected to develop abnormalities of the wake/sleep cycle.

Circadian Rhythms and Psychiatric Disorders. There is a striking relationship between circadian rhythms and certain psychiatric disorders—particularly seasonal affective disorder, primary depression, and bipolar affective disorder (89–92). Localized brain damage has been implicated in the development of posttraumatic mania (93). Appreciation of this relationship may be relevant in the rehabilitation of TBI patients with major neuropsychological problems—either premorbid or post-traumatic. It is also likely that there is a high incidence of premorbid psychosocial disorders in patients with TBI resulting from high-risk behaviors such as recklessness and alcohol or illicit drug abuse.

Treatment Modalities. Consideration and identification of circadian dysrhythmias in the TBI population is of more than academic interest. Untreated, these disorders may severely interfere with rehabilitation efforts. Importantly, these conditions are diagnosable and treatable (94).

Insomnia
No studies specifically address the association between TBI and insomnia. Insomnia is a symptom of many different conditions, and not a disorder in and of itself. Insomnia is a common complaint following TBI with a reported prevalence of 30% to 70% (95–99). Most studies of insomnia in patients with TBI are based upon subjective questionnaires (100). Insomnia-promoting factors such as pain, anxiety, medications, or adverse sleep environment are present in many TBI patients during the period of rehabilitation. It should also be remembered that persistent insomnia affects 30% of the adult population and, therefore, will be a pre-existing condition in many TBI patients, hardly being expected to improve following TBI. Once the factors contributing to insomnia are identified in a given case, specific effective behavioral and/or pharmacologic therapies may be undertaken (101).

Parasomnias
Parasomnias are undesirable motor or behavioral events that occur exclusively or predominately during the sleeping state. These may result in potentially injurious and violent behaviors, or disruption to caregivers or ward-mates (102,103). They may even present in the hospital/intensive care setting (104). There are many different conditions that may present with such bothersome or injurious sleep-period-related behaviors such as disorders of arousal, REM sleep behavior disorder (RBD), and nocturnal seizures. These conditions are undoubtedly
present in the TBI population, but virtually no systematic studies are available to indicate whether they are more common following TBI than in the population at large. The parasomnias are thoroughly reviewed elsewhere in this volume. There are no studies addressing TBI and disorders of arousal. In some cases, the TBI may have resulted from a pre-existing disorder of arousal that led to the injurious behavior, for example, frenzied sleepwalking, or driving a motor vehicle during a “sleep-driving” episode. It is probable that the REM sleep behavior disorder and nocturnal seizures result from TBI, although there are neither anecdotal nor systematic studies available.

**Psychiatric Conditions**

There are a number of “psychiatric” conditions that may occur predominately during the sleep period. These include nocturnal panic, post-traumatic stress disorder, and psychogenic dissociative states. The current concept that these conditions likely have a psychobiologic basis and may be triggered by emotional or physical trauma indicate that they must occur in the TBI population (105). Virtually no studies are available in this most important area.

**Psychogenic Dissociative States**

No reports of post-traumatic psychogenic dissociative states could be found. It is likely that fugue states may tragically result in TBI. There is a single report of a TBI patient who was not progressing as expected. She was found to have had long-standing, but previously undiagnosed, multiple personality disorder that antedated the TBI. Her lack of improvement had been incorrectly attributed to cognitive defects acquired from the TBI (106). It must be remembered that failure to recover as expected from TBI may be the manifestation of a pre-existing condition.

**Dreaming**

The cessation of dreaming has been reported following TBI. This alteration in oneric (dreaming) activity may be related to impairment of visual memory (107). In one study of 10 patients reporting decreased or absent dreaming following head injury, there was no correlation between the dream-change complaint and amount of time spent in REM sleep (108). This may reflect the fact that much dream-mentation occurs during NREM sleep (109). Another study questioned the common belief that dream recall is reduced following severe head injury. It found, rather, a change in the content (more threatening, fewer with sexually manifest content), but not in the overall incidence (110). More studies of larger numbers of subjects are needed.

**Hallucinations**

In many cases, apparent “hallucinations” simply represent the release of dreaming (either REM or NREM) into wakefulness—a manifestation of state-dissociation. Clearly, waking hallucinations do not necessarily indicate major psychiatric disorders (109). Treatment of organic hallucinations with haloperidol is often effective (111).

**Sleep Disorders as a Cause of Traumatic Brain Injury**

Sleep disorders may not only result from TBI, but may actually result in TBI. The true consequence of sleep disorders and sleepiness with particular reference to accidents on the highway and in the workplace is now known, and the figures are
alarming. In the United States alone in 1990, it is estimated that 200,000 motor vehicle accidents were due to falling asleep at the wheel (112). Statistics on motor vehicle accidents clearly indicate that fall-asleep accidents are more prevalent in patients with untreated OSA and narcolepsy (113–116). This undoubtedly holds true for other sleepy populations such as shift-workers and other volitionally sleep-deprived individuals. Frequent falling asleep on the job has been well-documented in night-shift workers (117). This includes sleep episodes occurring in pilots while “at the stick” (118). The potential for TBI in this setting is obvious. Violent parasomnias, particularly sleepwalking, sleep terrors, and RBD have resulted in significant injury, and it is likely that TBI may result (119–121).

Just as in the multiple personality disorder case cited earlier, it must be remembered that any sleep disorder following TBI may have pre-existed and may have, in fact, even caused the TBI. Given the known consequences of sleepiness due to sleep disorders and sleep-deprivation, the American public, employers, and policymakers must consider these conditions as a significant cause of TBI. Sleepiness and sleep disorders can no longer be discounted as a “minor annoyance.”

Sleep Disorders and Traumatic Brain Injury
Summary and Directions for the Future Review of available literature indicates that although much is known about the nature of sleep and wake/sleep cycling, there is striking lack of specific information regarding sleep and sleep/wake disorders in patients (both as cause and consequence) with TBI. Given the huge numbers of TBI patients, and the prevalent and incapacitating nature of sleep/wake disorders, much work needs to be done. Most sleep disorders can be readily diagnosed with effective therapeutic implications. Their identification and treatment in the TBI population will have important and exciting rehabilitation ramifications. There are critical scientific lessons to be learned from this population and, more significantly, there are substantial therapeutic implications.

Central Nervous System Tumors
There have been no systematic studies of wake/sleep function associated with brain or spinal cord tumors. As with TBI, it should be obvious that CNS tumors and their treatment may result in wake/sleep abnormalities. The literature in this area is comprised primarily of anecdotal case reports or very small series.

Postcerebral Irradiation Somnolence
A postcerebral radiation somnolence syndrome, which may be an early indicator of long-term neurological sequellae has been well-described, but few formal sleep studies are available (122–124). As a possible explanation for the commonly observed growth retardation in children following cranial irradiation, there is some evidence that there is a reduced amount of growth hormone released during sleep, but not upon the sleep-related timing of the release (125,126).

Circadian Dysrhythmias
Tumors involving the hypothalamic or pineal region or their environs should be expected to result in circadian dysrhythmias. For instance, craniopharyngiomas may result in severe sleep maintenance insomnia and daytime hypersomnia (127). Melatonin replacement in patients with circadian rhythm irregularities due
to abnormalities of melatonin secretion secondary to pineal tumors may restore the
wake/sleep cycle (128).

**Narcolepsy and RBD**
Structural lesions of the CNS may very rarely result in narcolepsy or RBD (70,129).

**Sleep-Disordered Breathing**
OSA may result from CNS tumors (111,130). Central hypoventilation associated
with a paraspinal ganglioneuroblastoma has been reported. The mechanism of
the hypoventilation was unclear (131). Central sleep apnea may be associated
with syringobulbo-myelia associated with a spinal extramedullary tumor (132).
OSA may result from acromegaly (133). The high prevalence of SDB associated
with high cervical spinal cord lesions has been discussed above in the TBI section.

**Periodic Limb Movements of Sleep and Propriospinal Myoclonus**
Spinal cord mass lesions have resulted in periodic leg movements in sleep. The sus-
pected mechanism is disinhibition of spinal cord locomotor pattern generators
(134). Propriospinal myoclonus is a spinalcord mediated movement disorder
which is in the differential diagnosis of restless legs syndrome (RLS), and which
may shed light on the pathophysiology of RLS and periodic limb movement
disorder (135–143). The concept of spinal cord locomotor centers that persist
intact following CNS lesions should be of intense interest—from both a scientific
and rehabilitation standpoint (144).

**Cerebrovascular Disorders**
There appears to be a very high prevalence of clinically significant SDB (both
central and OSA) following cerebrovascular accidents (145). SDB may be a risk
factor for the occurrence of cerebrovascular accidents (CVAs) (146–150). In one of
the large studies of the occurrence of sleep-SDB following CVAs, the prevalence
of SDB was very high (70–95%) (151). There was no correlation with age, body
mass index, pre-CVA history of snoring or hypersomnia, or stroke topography
between subjects with and without SDB (152). This would suggest that in this par-
ticular study population, the SDB was not a predisposing condition. The complex
nature of the relationship between SDB and the development of CVAs and
between SDB caused by CVAs warrants aggressive study, as the identification of
SDB either before or following the appearance of CVAs has important therapeutic
implications (153). Evidence that OSA is an independent risk factor for the develop-
ment of stroke is accumulating, and that treatment of OSA with nasal continuous
positive airway pressure in patients who have already experienced strokes may
prevent the occurrence of subsequent new cerebrovascular events (154). The poten-
tial impediment to rehabilitation of unsuspected and untreated OSA in a stroke
patient is obvious (155).

**Central Nervous System Infections**
There are virtually no studies addressing the acute effects of CNS infections on
wake/sleep function. Scattered studies indicate that some CNS infections may
result in hypersomnia. Although encephalitis lethargica is often considered a con-
dition of the past, having occurred in the 1914 to 1930 pandemic, it should be
remembered that sporadic cases still do occur (156). One fascinating fact is that
in the case of “African sleeping sickness,” there is good evidence that, except in the terminal stages, the primary abnormality is in the wake/sleep cycle. Affected individuals do not sleep more per 24 hours, but, rather, experience a disintegration of the circadian pacemaker function. The brunt of the pathology appears to involve the SCN (157,158).

The widespread neurologic dysfunction following encephalitis of any type would indicate that wake/sleep disorders should be common in this patient population, again, with important therapeutic and rehabilitation implications. Virtually no studies are available.

SUMMARY AND IMPERATIVES FOR FUTURE OPPORTUNITIES

Over the past few decades, much has been learned about wake/sleep function. As amply documented in this chapter, there remains a woeful and massive void of knowledge regarding the effects of most neurologic conditions upon wakefulness and sleep. Inasmuch as one of the most important functions of the brain is the generation of sleep, wakefulness, and consciousness, systematic study of these functions in a wide variety of neurologic conditions should yield invaluable information about both functioning of the CNS and the nature of wakefulness, sleep, and even consciousness (159,160). Recent advances in technology (polysomnography, actigraphy, functional neuroimaging techniques, and sophisticated neurophysiologic monitoring at the cellular level) have provided exciting and powerful tools. In the realm of CNS function (and dysfunction) and wakefulness, sleep, and consciousness, there exist nearly limitless opportunities for the close collaboration of basic sleep and neurophysiology researchers, with their clinical counterparts to advance our knowledge of both normal and abnormal brain function.

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INTRODUCTION

Fatigue is one of the most prominent symptoms in patients with multiple sclerosis. It may take the form of mental tiredness, physical exhaustion, or excessive somnolence. Inappropriate daytime sleepiness and nocturnal sleeplessness, together or independent of each other, are common complaints in multiple sclerosis. The mechanism is multivariate, suggesting causes that range from depression to brain-lesion site, and its investigation is a cost-effective, clinical exercise that may help determine corrective therapy. Descriptions of cases of multiple sclerosis associated with excessive daytime sleepiness, variously termed narcolepsy or drowsiness, have appeared in the neurological literature since the first half of the 20th century (1–3). A specific linkage of multiple sclerosis with narcolepsy was the focus of attention of various studies after a description of cases and reviews that appeared in 1949 (4). Later, cases of narcolepsy–cataplexy and multiple sclerosis (5) and of familial multiple sclerosis with narcolepsy–cataplexy were reported (6), including a citation of the presence of the DR2 histocompatibility antigen in two patients with narcolepsy and multiple sclerosis, which triggered the suggestion of a common inheritance for both conditions (7). Reports of undetectable hypocretin levels in patients with demyelinating plaques observed with magnetic resonance imaging (MRI) in the hypothalamus and symptoms of acute hypersomnia have advanced the understanding of the association (8). Other authors (9,10) have indicated that sleep disturbance is relatively common in multiple sclerosis, and the etiology, multifactorial.

CLINICAL MANIFESTATIONS

Excessive somnolence and inappropriate daytime sleep can occur in patients with multiple sclerosis. In some individuals, excessive daytime sleepiness and sleep attacks appear in conjunction with cataplexy, sleep paralysis, and hypnagogic hallucinations, leading to a diagnosis of narcolepsy. Excessive somnolence and other narcoleptic symptoms may appear before (11) or after (12) the onset of multiple sclerosis, with the age of presentation varying widely. Laboratory confirmation of narcolepsy is lacking in older reports, or, if present, has failed to confirm a diagnosis of narcolepsy (13). The common complaint of chronic fatigue in multiple sclerosis may confound the interpretation of sleep disturbances. In a study of families with concurrent multiple sclerosis and narcolepsy–cataplexy by Ekbom (6), two members had narcolepsy appearing shortly after the onset of multiple sclerosis, and one had narcolepsy as the putative initial symptom of multiple sclerosis. In
Berg and Hanley’s (5) two cases with concurrent diseases, narcolepsy was the initial symptom of multiple sclerosis. Schrader et al. (12) described the case of a woman with definite multiple sclerosis who developed typical symptoms of incapacitating narcolepsy–cataplexy at the age of 56 years, 25 years after the onset of multiple sclerosis. The sleep disorder was confirmed polygraphically, and the authors argued that the unusually late onset of severe narcolepsy–cataplexy strongly favored a causal relationship between both conditions. Younger and colleagues’ (7) two patients had narcolepsy preceding and following, respectively, the onset of multiple sclerosis, and both had presence of the DR2 antigen.

Patients with multiple sclerosis also report difficulty in falling asleep, restless sleep, nonrestorative sleep, and early-morning awakenings more frequently than control subjects (14). In a study of 28 consecutive patients with multiple sclerosis, 15 patients (54%) reported sleep-related problems (15), including difficulty in initiating or maintaining sleep, frequent awakenings due to leg spasms, habitual snoring, and nocturia. Three patients showed episodes of nocturnal oxygen desaturation, and two had sleep apnea syndrome. MRI of the brain showed abnormalities in 20 of 22 cases studied. In another study of 10 patients with definite multiple sclerosis, Wunderlin et al. (16) used limited nocturnal polysomnography, fatigue and sleep questionnaires, and MRI of the brain to investigate whether fatigue was the result of a sleep apnea syndrome. None of the patients with abnormal fatigue or sleep scores had an abnormal sleep apnea index, suggesting that fatigue and sleepiness cannot be explained solely on the basis of sleep respiratory disturbances.

**ETIOLOGY AND PATHOGENESIS**

The association between multiple sclerosis and sleep disturbance is more intimate than expected by chance. In one series (10), the prevalence of nocturnal sleep difficulties assessed by the Minnesota Multiphasic Personality Inventory in patients with mild, definite multiple sclerosis was 25.2%. In another series (13), the prevalence by questionnaire in 70 patients with multiple sclerosis of daytime sleep attacks was 77% and of cataplectic attacks 56%, without a difference between DR2-positive and -negative multiple sclerosis patients. Nine patients in this series were studied using polygraphic evaluation, but no objective evidence of narcolepsy or excessive sleepiness was obtained, indicating a major discordance between sleep symptoms and objective findings.

Patients with narcolepsy exhibit the highest known association with the HLA-DR2 and DQwl antigens, estimated at 95% or above in most series (17–19). The susceptibility to multiple sclerosis is coded by genes at or close to the HLA-DR-DQ subregion (20). The coincidence of genetic susceptibility between multiple sclerosis and narcolepsy converging on the HLA-DR2 histocompatibility antigen has led some authors to postulate a common immunogenetic etiology that remains to be confirmed (7). In a study of DRB5 alleles in Dw2-positive patients with multiple sclerosis or narcolepsy, Fogdell et al. (21) found that the HLA-Dw2 haplotype in multiple sclerosis and narcolepsy patients extends to the DRB5 locus. Rumbach et al. (22) measured daytime sleep latencies in patients with multiple sclerosis and failed to observe a clear difference between DR2-positive patients and controls, suggesting that, by themselves, the genes coding for HLA-DR2 and DQwl are not sufficient to cause an early sleep onset in patients with multiple sclerosis.
The remitting course of sleep attacks (5) and the late onset in life of incapacitating narcolepsy–cataplexy (12) exhibited by some patients with multiple sclerosis have been interpreted as an indication that multiple sclerosis may cause symptomatic narcolepsy. This hypothesis received some impetus with the observation by Castaigne and Escourroule (23) of midbrain plaques in the hypothalamic periventricular region of a patient with sleep attacks and multiple sclerosis. MRI of the brain can exceptionally reveal a plaque of demyelination in the hypothalamic area, as observed in a patient with multiple sclerosis exacerbation who developed acute hypersomnia and had undetectable hypocretin levels in cerebrospinal fluid (CSF) (8).

Rapid eye movement (REM) sleep behavior disorder was the heralding manifestation of multiple sclerosis in one case report. The patient had MRI hyperintensities in the pons and in a periventricular location (24). In another case report, a 51-year-old woman developed nocturnal manifestations suggestive of REM sleep behavior disorder following an acute attack of multiple sclerosis. The patient had no recall of dreams associated with abnormal nocturnal motor behavior. However, the polysomnogram showed REM sleep without atonia. MRI of the brain showed increased T2 signal in the dorsal pons suggestive of demyelination. The nocturnal events responded to the administration of clonazepam at bedtime (25).

The observation of lesions in the supplementary motor area identified by MRI in patients with mild but definite multiple sclerosis led Clark et al. (10) to suggest that the motor lesions triggered periodic limb movements during sleep, resulting in sleep interruptions and depression, a correlation found in 25.2% of patients studied. Spasms or discomfort in the legs have also been cited as a mechanism of frequent arousal in patients with multiple sclerosis (15). Others (9) have found that patients engage more in daytime napping than control subjects (53% vs. 21% of controls), perhaps as a result of nocturnal and early-morning awakenings caused by bladder problems. Intractable hiccups persisting for more than 48 hours and sleep apnea syndrome were associated in two patients with lesions, detected by MRI, in the tegmentum of the medulla (26), suggesting a pathogenetic correlation between anatomical location and clinical manifestations. In the opinion of these authors, development of intractable hiccups should suggest the associated presence of sleep apnea syndrome.

To investigate whether fatigue and sleep disturbance in multiple sclerosis patients might be due to disrupted circadian sleep regulation, Taphoorn et al. (27) performed actigraphy and multiple sleep latency tests in 16 patients with prominent complaints of fatigue and sleep disorder. Sleep latency values were altered in some patients with multiple sclerosis, but actigraphy scores did not differ from control values, failing to provide evidence of circadian rhythm disturbance in patients with multiple sclerosis. Accumulation of cytokines in the CSF of patients with active multiple sclerosis (28) may contribute to sleep changes since these substances intervene in sleep mechanisms.

DIFFERENTIAL DIAGNOSIS AND LABORATORY EVALUATION

Sleep disorders may be suspected by patient testimony, but confirmation in a sleep laboratory is recommended. Nocturnal polysomnography identifies sleep disruption, and daytime multiple latency tests measure daytime sleepiness. Narcolepsy–cataplexy can be diagnosed clinically and should be distinguished
from other sleep disturbances in patients with multiple sclerosis. In genuine narcolepsy–cataplexy, hypocretin levels in CSF are below 110 pg/mL (29). Narcolepsy with or without cataplexy is diagnosed in the sleep laboratory when short-onset REM sleep appears in two or more segments of the multiple sleep latency test and the onset of daytime sleep demonstrates a latency of eight minutes or less (30). Fatigue is a common symptom in multiple sclerosis that may be confused with or contribute to disordered sleep. A variety of underlying physical and emotional factors (bladder problems, spasticity, muscle spasms, periodic leg movements, depression, and anxiety) that converge to disturb nocturnal sleep in patients with multiple sclerosis should be considered. Excessive daytime somnolence in multiple sclerosis may be secondary to nocturnal disruption and nonrestorative sleep perhaps amenable to proper management.

Sleep laboratory evaluations in patients with multiple sclerosis have underscored that sleep disturbance is common and its etiology multifactorial, involving both physical and psychological features (9,31). Polysomnographic studies of patients with definite multiple sclerosis have shown significantly reduced sleep efficiency and more awakenings during sleep (32). Periodic leg movements were found in 36% of patients compared to 8% in controls, and central sleep apnea was found in two patients. In patients with multiple sclerosis and REM sleep behavior disorder, REM sleep without atonia has been observed (25). MRI of the brain shows a greater load of lesions in the cerebellum and brainstem in patients with periodic leg movements.

The diagnostic criteria for multiple sclerosis serve to identify patients with this condition (33). Polysomnography and multiple sleep latency testing are required to distinguish narcolepsy from other causes of excessive daytime sleepiness while identifying possible causes of sleep disruption. Human leukocyte antigen typing demonstrates DR2 positivity in 95% of narcoleptic patients (17,19) and in 50% to 60% of multiple sclerosis patients (34).

**MANAGEMENT**

Sleep disturbance in multiple sclerosis is heterogeneous with physical and emotional features (9). Bladder problems, spasticity, depression (9), periodic limb movements (31), and lesion sites that subserve strategic areas may cause or contribute to sleep disturbance in multiple sclerosis.

Antidepressant medication has been suggested for the treatment of sleep disorders in multiple sclerosis (14), while clonazepam has been advocated for the treatment of REM sleep behavior disorder (25). Amantadine may improve chronic fatigue (31,35). Increased evening wakefulness has been reported by patients with multiple sclerosis treated with selegiline (36). Despite initial reports of efficacy, modafinil has not shown a beneficial effect in patients with multiple sclerosis and chronic fatigue. In a recent double-blind, placebo-controlled, parallel group study of modafinil, administered up to 400 mg/day in 115 patients with multiple sclerosis, there was no improvement of fatigue. The primary outcome variable was the change of the Modified Fatigue Impact Scale (37).

Narcolepsy–cataplexy should be treated conventionally. Anecdotal case reports suggest that symptoms respond to habitual treatment modalities, including methylphenidate to enhance alertness and clomipramine for alleviation of cataplectic attacks. Protryptiline should be used with caution in patients with spinal-cord disease who are prone to develop periodic limb movements.
There is one report of resolution of sleep paralysis in a patient with multiple sclerosis using transcranial electromagnetic field therapy (38). The patient was a 40-year-old woman with remitting-progressive multiple sclerosis. Episodes of sleep paralysis occurred once a week on awakening in the morning and were enhanced by mental stress, fatigue, sleep deprivation, and exacerbation of multiple sclerosis. Experimental treatment with alternate-current-pulsed applications of picotesla intensity electromagnetic fields of 5 Hz frequency was applied extracerebrally one or two times per week. Three weeks after initiation of treatment, sleep paralysis gradually abated and eventually disappeared and there was improvement in fatigue, memory, and other symptoms related to multiple sclerosis.

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Sleep Disorders and Neuromuscular Disorders

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INTRODUCTION
Changes in the physiology of respiration in sleep increase the risk for the development of sleep-related respiratory alterations and respiratory failure. A variety of sleep-determined changes that converge in the sensory and effector mechanisms of the respiratory system may compromise the already challenged ability to breathe in patients with a neuromuscular disorder. Included under this heading are alterations of the lower motor neuron, the neuromuscular junction, and muscle. Diaphragmatic weakness, chest-wall weakness, restrictive lung disease, weakness of the pharyngeal wall, obesity, and nocturnal hypoventilation of central origin are the principal causes of sleep-related respiratory insufficiency in patients with a neuromuscular disorder.

ANATOMY AND PHYSIOLOGY OF RESPIRATION IN SLEEP
The control of breathing is of paramount importance while an animal or a human being is asleep and unconscious, and thus unable to introduce voluntary variations. During sleep there are powerful mechanisms that control ventilation, and ultimately awaken the sleeping individual should an overpowering impediment occur. The control of breathing is different in non-rapid eye movement (REM) and REM sleep.

The respiratory muscle groups, which include the diaphragm, intercostal muscles, and upper respiratory dilator muscles, receive appropriate signals from a medullary respiratory center. Three types of stimuli modulate the activity of the medullary center: chemical, chest/lung mechanical, and behavioral. Chemical stimuli arise from chemoreceptors that are responsive to PaCO$_2$, PaO$_2$, and pH. PaCO$_2$ receptors are located in the carotid body and medulla and respond to increases in PaCO$_2$ by stimulating a hyperventilatory response. PaO$_2$ receptors located in the carotid body trigger a hyperventilatory response via the glossopharyngeal nerve when the PaO$_2$ descends below 60 mmHg. Very low PaO$_2$ levels depress the respiratory center. Mechanical receptors in the chest-wall and lungs respond to inflation and deflation. Signals are transmitted centrally via the vagus nerve, causing the respirations to become shallow and rapid. Behavioral control of breathing is exerted in the wake state and is involved with functions in which airflow is necessary, such as speaking, singing, crying, and laughing. Supramedullary signals originating in cerebral centers override chemical stimuli.

Both hypoxia and hypercapnia stimulate arousals independently, but when combined, hypoxia increases the sensitivity to arousals caused by PaCO$_2$. Cough is suppressed during sleep and can occur only after an arousal. Laryngeal stimulation during sleep causes reflex apnea that is longer in REM than in non-REM sleep.
Non-REM Sleep
In light non-REM sleep, which includes stage 1 and early stage 2, respirations are dependent on stimuli originating in chemoreceptors responsive to PaCO₂ and PaO₂, but the ventilatory response to hypoxia and to hypercapnia is decreased. Respirations are irregular, with periodic variations in amplitude, and thus the label of periodic breathing is applied by some authors. The wakefulness stimulus is of primary importance in sustaining breathing through changes in chemical stimulation or when obstructions to respiration occur in sleep. Both hypoxia and hypercapnia are arousal stimuli that contribute to the respiratory and sleep-wake instability early on.

For reasons that remain obscure, respiratory stability is achieved, as stage 2 takes firmer control. Breathing becomes regular, both in amplitude and frequency, resulting in decreased minute ventilation that may be the consequence of a decrease in both respiratory rate and tidal volume. Overall, ventilation is lower during non-REM sleep, and this relationship progresses as non-REM sleep deepens. Electromyographic activity increases in intercostal muscles as the ventilatory rate decreases, suggesting increased upper-airway resistance that reflects a partial impediment to airflow. Detailed studies of pharyngeal electromyographic (EMG) activity during non-REM sleep have shown a decrease in activity in dilator muscles that probably contributes importantly to the upper-airway resistance encountered in this stage.

REM Sleep
In REM sleep, respirations become faster and more irregular, with changes in amplitude and rate. The irregularity persists through hypoxia, hypercapnia, and metabolic alkalosis, suggesting a strong neural influence. As in non-REM sleep, there is an overall decrease in ventilation and in responsiveness to chemical stimuli, with minute ventilation being the lowest during phasic REM sleep. Muscle atonia in REM sleep reduces the activity of intercostal muscles without affecting diaphragmatic muscle tone, which may even be increased to compensate for the intercostal loss. Upper-airway resistance is also higher during REM sleep, contributing to a decreased efficiency of the ventilatory effort that leads to mild hypoxemia.

NEUROMUSCULAR DISORDERS AND RESPIRATION
The physiological reduction of muscle tone in non-REM sleep and virtual loss of activity of intercostal muscles with preservation or enhancement of diaphragmatic drive in REM sleep create a unique series of circumstances. In patients with muscular disorders, the challenged ventilatory mechanism may exhibit diverse patterns as a result of the various clinical forms of muscular weakness. Focal deficit of diaphragmatic function, as in acid-maltase deficiency (1), is characterized by REM-sleep-related nocturnal breathlessness and respiratory failure even before limb weakness becomes symptomatic. Some generalized myopathies, such as Duchenne muscular dystrophy, present sleep-disordered breathing only in terminal stages of the disease. In general, patients with diaphragmatic weakness are particularly vulnerable to the development of hypoventilation/hypoxemia in REM sleep. Sleep-related hypoxemia, nocturnal fragmentation of sleep, and decreased daytime function are potentially correctable in patients with muscular...
weakness, so their recognition and characterization become part of the work-up of a patient with a neuromuscular disorder.

Although obstructive sleep apnea is the principal sleep-related abnormality in most patients with a neuromuscular disorder, hypoventilation/hypoxemia may predominate or coexist with sleep apnea. Some respiratory sleep alterations cannot be explained solely on the basis of a mechanical respiratory disorder in some patients with neuromuscular disease. Patients with myotonic dystrophy may have hypersomnolence that is not corrected with ventilatory assistance or that appears without an obvious ventilatory impediment. These patients may have hypersomnolence of central origin that remains poorly understood.

The second edition of ICSD (2) recognizes sleep-related hypoventilation/hypoxemia due to neuromuscular and chest-wall disorders as a distinct entity and makes the differential diagnosis with obstructive sleep apnea that may be secondary to oropharyngeal muscle weakness. ICSD-2 also recognizes that both conditions may coexist. Furthermore, some patients with congenital forms of myopathy may have reduced chemosensitivity of central origin with reduced sleep-related ventilatory drive independent of hypoxemia and hypercapnia, which suggests yet another form of central dysfunction and not a mere blunting of chemosensitivity.

According to ICSD-2 a diagnosis of sleep-related hypoventilation/hypoxemia due to neuromuscular and chest-wall disorder may be entertained when the following happen.

1. A neuromuscular or chest-wall disorder is present and believed to be the primary cause of hypoxemia.
2. Polysomnography or sleeping arterial blood gas determination shows at least one of the following:
   (a) an SpO2 during sleep of <90% for more than five minutes with a nadir of at least 85%;
   (b) more than 30% of total sleep time at an SpO2 of less than 90%; and
   (c) sleeping arterial blood gas with PaCO2 that is abnormally high or disproportionately increased relative to levels during wakefulness.
3. The disorder is not better explained by another current sleep disorder, another medical or neurological disorder, medication use, or substance use disorder.

FACTORS INTERVENING IN SLEEP-DISORDERED BREATHING IN NEUROMUSCULAR DISEASE
The Arousal Response
The arousal response dispels sleep when threats arise and provides a means to restore homeostasis after a system failure during quiescence. Transient arousals are only identified in polysomnographic recordings and are characterized by an abrupt shift in electroencephalography (EEG) frequency lasting three seconds or more usually associated with EMG amplitude increase, increased heart rate, or respiration change (3).

Two ascending activating systems, a ventral cholinergic and a serotonergic ascending system, contribute to electrocortical activation. Although pain and noise are the primary arousal triggers, a number of arousal processes respond to extreme cardiovascular challenges, including hypoxia, hypercarbia, and hypotension (4). The cerebellum and amygdala contribute projections to the ascending
arousal systems. Some arousal activating systems bypass the thalamus and reach the cortex directly. Cholinergic, serotonergic, dopamine, histamine, and noradrenergic systems can activate the cortex and should be considered part of the general network of arousal responses. Recently, the hypocretin system has been included in the arousal mechanism.

Prolonged apnea and profound blood pressure changes during sleep provoke autonomic or somatic responses with cortical activation. Afferent vagally mediated respiratory responses can reach the cerebellum via the inferior olive that gives rise to climbing fibers to the cerebellar fastigial nuclei and Purkinje cells. The fastigial nucleus projects to the medial reticular formation and intralaminar nuclei of the thalamus. Poor maturation of cerebellar systems is associated with developmental breathing disturbances during sleep, including the sudden infant death syndrome (5).

The Gasping Response
Spontaneous recovery from sleep-related apnea or positional asphyxia can occur without cortical arousal as a result of autoresuscitation by hypoxic gasping, a universal response in mammals. The gasping mechanism, a brainstem function causing intermittent, strong inspiration after severe hypoxia, may provide some protection from prolonged apnea for the infant in the first month of life if arousal fails (6). Autoresuscitation serves as a backup mechanism and is considered to be the last operative mechanism used to ensure survival during exposure to severe hypoxia. Partial or complete autoresuscitation by gasping is not uncommon in moribund infants during the first year of life.

Sleep Apnea in Neuromuscular Disease
In a study of 60 adult and pediatric patients with a variety of neuromuscular disorders, Labanowski et al. (7) found a high proportion of sleep-disordered breathing. The authors performed the study in a clinic population at an altitude of 1500 m. They utilized a sleep–wake questionnaire, a disability index, pulmonary-function tests, and an EdenTrace II monitor for one night to measure oxygen saturation, total apneas, hypopneas, and respiratory disturbance index (RDI). They found that 42% of the population had an RDI $> 15$, which is much higher than frequencies observed in general population surveys. The authors failed to find strong predictors of sleep-disordered breathing in the population tested but concluded that, given the high prevalence of respiratory disturbance, screen testing of patients with a neuromuscular disorder is warranted to identify early sleep-disordered breathing.

Diaphragmatic weakness is a major determinant of ventilatory compromise in patients with neuromuscular disease. The diaphragm may be weak in isolation or as part of a generalized muscle involvement. Diaphragmatic muscle weakness becomes specifically manifest during REM sleep (8), when the diaphragm is physiologically the only effective muscle pump. Diaphragmatic muscle weakness becomes apparent during REM sleep, particularly if the patient lies supine. Patients with diaphragmatic paralysis cannot breathe while supine even in the awake state. Individuals with neuromuscular disease and diaphragmatic involvement exhibit the greatest oxygen desaturations in REM sleep, so this stage becomes a test of diaphragmatic muscle function.

Patients with neuromuscular disease may have restrictive lung disorder as a consequence of chest-wall muscle weakness. Contributing factors (9) are scoliosis, a
common occurrence in patients with neuromuscular disease, and/or pulmonary microatelectases that result from chronic hypoventilation, repeated episodes of aspiration, and retained secretions. Mechanical alteration of the spine causes a disadvantage of intercostal muscles and diaphragmatic function that is translated into a less efficient inspiratory mechanism. These changes may lead to perfusion of non-ventilated lung, a phenomenon that contributes to hypoxemia.

Inspiratory upper-airway resistance and obstructive sleep apnea may affect patients with neuromuscular disorders, causing an additional burden on sleep-related ventilation. These conditions may develop as a result of weakness of pharyngeal muscle dilators, leading to increased upper-airway resistance and a tendency to collapse of the pharyngeal wall. The alteration is further aggravated by tonsillar hypertrophy, obesity, or craniofacial dysmorphias and micrognathia limiting the oropharyngeal lumen. Patients with congenital myopathies and muscular dystrophies commonly have poor development of facial bones and the mandible.

Sedentariness in patients with altered muscular function promotes obesity, another factor that burdens ventilatory efficiency during sleep. Accumulation of fat in oropharyngeal soft tissues may contribute to restriction of the oropharyngeal lumen. Obese patients also suffer mechanical reduction of intercostal muscle function, and subjects with abdominal obesity exhibit marked diaphragmatic dysfunction that is particularly evident during REM sleep. In a study with nocturnal polysomnography of patients with abdominal obesity (8) (Fig. 1A), identifiable REM-sleep-related episodes of desaturation (>15% drop) were observed in patients with morbid obesity (>147 kg). Desaturations appeared in hypnograms (Fig. 1B) as abrupt nadirs or as unique profound drops in oxygen-saturation levels occurring only in REM sleep. Episodes of heart-rhythm instability and clusters of arousals were observed in conjunction with segments of profound desaturation. The study pointed out that computer-assisted hypnograms are useful to identify REM-sleep-related diaphragmatic insufficiency in obese patients with mechanical challenge of the diaphragm. Obese patients with a neuromuscular condition affecting the diaphragm are at even higher risk of developing REM-sleep-related disordered breathing.

Sleep-disordered breathing in patients with neuromuscular disease, many times coexisting with hypoventilation/hypoxemia and other factors as mentioned earlier, may cause nocturnal hypoxemia and episodes of desaturation associated with restlessness, partial arousals, and sleep fragmentation. Depending on the severity of the ventilatory deficit, patients may have continuous alveolar hypoventilation, even in the awake state that in the most advanced circumstances becomes complicated with CO₂ retention. Patients exhibit secondary daytime excessive somnolence, a development that should prompt a thorough investigation of sleep-related ventilatory function, including polysomnography. Excessive daytime somnolence in weak subjects could constitute a marker of preterminal muscular disease and herald pulmonary failure in the event of respiratory illness. Sitting positions in sleep, nocturnal cyanosis, morning drowsiness, headaches, and vomiting, and even cor pulmonale attributed to nocturnal hypoventilation have been reported in patients with advanced neuromuscular disease whose condition was reversed with appropriate ventilatory therapy (10).

Nocturnal hypoventilation with hypoxemia and hypercapnia, if not corrected, may lead to blunting of peripheral and central respiratory chemoreceptor responses that determine a state of chronic alveolar hypoventilation. However, in some forms of congenital myopathy, there is evidence of impairment of
56 year old male with obesity (BMI = 40.3) and globular abdomen.

FIGURE 1  (A) A 56-year-old patient with obesity (BMI = 40.3) and globular abdomen.  (B) Hypnogram of patient in Figure 1A shows clusters of respiratory disturbance (A + H), desaturation events (SaO2), heart instability (HR), and arousals (A/W) in REM sleep as a result of mechanical disadvantage of the diaphragm. Abbreviations: A+H index, apnea + hypopnea index; A/W, arousals and awakenings; HR, heart rate; POS, body position; SaO2, saturation of oxygen; Tx, unused channel for CPAP pressures; 1, 2, 3, etc., hours of nocturnal recording; BMI, body mass index.
respiratory chemosensitivity that may be familial in nature (11). The combination of ventilatory muscle effector dysfunction and reduced central ventilatory drive is a high-risk situation.

**PHRENIC NERVE AND DIAPHRAGMATIC PARALYSIS**

The phrenic nerve originates in the phrenic nucleus, which forms the ventral medial cell column of the cervical ventral gray horn, extending from the rostrocaudal extent of C3 to the caudal part of C5. Phrenic nerve damage resulting in diaphragmatic paralysis may be part of the spectrum of involvement in some diffuse neuropathies and in motor neuron disease. Unilateral paralysis, sometimes observed as an elevation of the diaphragm in chest films, may be asymptomatic, but bilateral paralysis is invariably symptomatic and may be life-threatening; paresis or weakness with partial diaphragmatic dysfunction may cause exertional dyspnea and other manifestations of ventilatory insufficiency that, despite their typical character, may remain undiagnosed. If the diagnosis is not made early, repeated nocturnal desaturation events may precipitate cardiopulmonary morbidity. Bilateral paralysis causes orthopnea with striking severe inspiratory impairment that is out of proportion to the cardiopulmonary status. In the erect posture, the gravitational force improves the mechanical advantage of the respiratory muscles. However, patients complain of profound difficulty in breathing when supine that reflects an increased inspiratory effort and is the result of a reduction in lung volume as the abdominal contents rise into the thorax. In severe or acute cases, patients present with nocturnal orthopnea, cyanosis, and fragmented sleep, followed by morning headaches, vomiting, and daytime lethargy. Polysomnography reveals hypoventilation that is particularly profound during REM sleep. As the desaturation event frequency increases in REM sleep, arousals and secondary daytime somnolence become increasingly prominent and the condition clinically resembles the sleep apnea syndrome. Undiagnosed bilateral diaphragmatic paralysis of any cause may lead to acute cardiopulmonary failure and death. Some reports describe unexplained failure to wean from a respirator as the presenting manifestation of diaphragmatic paralysis in patients with undiagnosed motor neuron disease (12) or myopathies.

Phrenic nerve paralysis has been reported in patients with Charcot-Marie-Tooth disease (hereditary motor and sensory neuropathy) complicated with diabetes mellitus (13). Other conditions in which diaphragmatic paralysis has been observed include spinal-cord injury, poliomyelitis, Guillain–Barré syndrome, diabetes, diphtheric neuropathy, beriberi, alcoholic neuropathy, brachial plexus neuropathy, lead neuropathy, trauma, amyotrophic lateral sclerosis (ALS), myotonic dystrophy, Duchenne muscular dystrophy, paraneoplastic syndrome, and idopathic conditions (12,13). In infantile muscular atrophy (Werdnig-Hoffmann disease) and adult motor neuron disease, the diaphragm is rarely involved early in the disorder. However, there are reports of chronic progressive motor neuron disease presenting in acute respiratory failure as a result of bilateral diaphragmatic paralysis secondary to phrenic nerve nucleus involvement (13).

The diagnosis of diaphragmatic paralysis is suspected when paradoxical respirations are observed in the supine posture and when major discrepancies in vital capacity are detected between the erect and supine postures. Phrenic nerve stimulation studies, nerve conduction measurements, and EMG of selected muscles may aid in the diagnosis, along with fluoroscopy and computerized
imaging studies of the chest. Nocturnal polysomnography is of critical importance to evaluate the presence and degree of sleep-disordered breathing in patients with suspected paralysis of the diaphragm. When the ventilatory muscle weakness is generalized, patients with the least diaphragmatic contribution to breathing are the most vulnerable to developing nocturnal oxygen desaturation (14). The severity of hypoventilation and the depth of oxygen desaturation in non-REM sleep are determined by the degree of involvement of chest-wall and accessory respiratory muscles.

NEUROMUSCULAR CONDITIONS WITH SLEEP DISORDER

Amyotrophic Lateral Sclerosis

The pattern of neuromuscular involvement in ALS, as a result of progressive degeneration of corticobulbar, corticospinal, and anterior horn cells, highlights this disorder as a prime target for sleep-related ventilatory abnormalities. Sleep-related respiratory dysfunction has been investigated in patients with ALS with the intention of searching for ventilatory alterations that are commonly observed in conditions in which muscle weakness predominates. Evaluation of the quality of sleep in an early study (15) showed that only 4 of 12 patients described daily fatigue as an important symptom. In a prospective study of 21 patients with ALS to determine the relationship of pulmonary-function test abnormalities with quality of sleep and survival (16), the authors found that obstructive nocturnal events, although commonplace, were not accountable for nocturnal oxygen desaturation, while hypoventilation was found to be the primary explanation for the decline in oxygen saturation. Fasciculations were not reported to interfere with sleep, and affective depression was not evident. The group of patients had mild to moderate awake pulmonary-function deficits, and as a whole was not excessively somnolent as shown by the results of the multiple latency test, while the overall quality of sleep was surprisingly normal.

Patients with ALS may have dysfunction of the phrenic nerve, and, when paralysis of the diaphragm occurs, REM-sleep-related hypoventilation and oxygen desaturation are profound. This is exemplified in a case report (17) of a patient presenting with exertional dyspnea and hypersomnolence followed several months later by respiratory failure that necessitated intubation. Neurological examination, electromyographic testing, and histological examination of the central nervous system confirmed a diagnosis of ALS with specific involvement of anterior horn cells from C3 to C7, a segment that includes the phrenic nuclei, where recognizable nerve cells could not be found.

In a randomized trial of non-invasive ventilation (NIV), 41 patients with El Escorial criteria of ALS received NIV or standard care (18). Patients treated with NIV showed significantly prolonged survival, while quality of life was maintained. NIV improved mostly sleep-related symptoms. Patients with severe bulbar impairment were unlikely to derive survival benefit, although sleep-related symptoms were ameliorated. The subgroup of patients with good bulbar function experienced dramatic survival and quality of life benefits.

Noninvasive respiratory support with continuous positive airway pressure (CPAP) or bi-level apparatus is indicated in patients with motor neuron disease developing sleep-related respiratory disturbance, particularly when diaphragmatic paralysis or bulbar involvement occurs. Elimination of nocturnal respiratory
distress and restlessness, as well as alleviation of daytime somnolence and tiredness improves the quality of life without altering the scheme for dignified survival.

**Sleep and the Postpolio Syndrome**

Some survivors of an acute attack of poliomyelitis have developed 20 to 30 years later a condition characterized by progressive fatigue, joint pains, and weakness in previously unaffected muscles. In this condition—appropriately termed the postpolio syndrome—central respiratory control and peripheral respiratory function may be altered, and it has been hypothesized that some of the postpolio symptoms are due to breathing disorders during sleep (19). In patients with bulbar muscle weakness, sleep apnea is more frequent (20) and dysphagia, dysphonia, sleep disorders, and chronic respiratory failure may be associated (21). In one study, 31% of 183 patients surveyed complained of sleep disturbances, even those without prior bulbar involvement (22). In this study, early-morning headache was the most common sleep-related complaint.

Patients with kyphoscoliosis secondary to muscle atrophies often develop restrictive respiratory dysfunction, particularly if there is associated weakness of thoraco-abdominal and respiratory accessory muscles.

Sleep studies have shown central sleep apnea episodes in patients who had been weaned from respiratory support required by bulbar involvement (23). In the Steljes et al. (19) study with polysomnography of 13 postpolio patients with various degrees of involvement, most apneas observed were mixed or of the obstructive variety. The authors found that patients with obstructive and mixed apneas could often be treated with nasal CPAP, whereas those with hypoventilation and respiratory muscle weakness responded more favorably to the application of nasal-mask intermittent positive-pressure ventilation. They recommended that nocturnal polysomnography be performed in all postpolio patients complaining of sleep disturbance and respiratory manifestations, since some of the complaints typically attributed to the postpolio syndrome, such as increasing fatigue, may be the result of nocturnal respiratory dysfunction and thus potentially correctable.

In a study of 13 patients, half of the patients had bulbar involvement. Siegel et al. (24) found prolongation of latencies to the onsets of the first episode of muscle tone reduction, the first saw tooth wave, and the first REM period. The authors hypothesized that prolongation of these latencies may be due to prolonged recruitment time for neurons in the pontine tegmentum, following damage from polio. This may be a sensitive marker of a brainstem lesion, and may also represent a type of sleep pathology not previously explored.

Nearly two-thirds of polio survivors report abnormal movements in sleep and one-half report that their sleep is disturbed by these movements. In a small study of polio survivors (25), sleep studies demonstrated a variety of motor abnormalities. These included generalized random myoclonus, with brief contractions and even ballistic movements of the arms and legs, slow repeated grasping movements of the hands, slow flexion of the arms, and contraction of the shoulder and pectoral muscles. Two patients showed periodic limb movements in sleep with muscle contractions and ballistic movements of the legs, two had periodic limb movements in sleep plus restless legs syndrome, and one had sleep starts involving only contraction of the arm muscles. Abnormal movements occurred in stage 2 of sleep in all patients, in stage 1 in some patients, and could significantly disturb
sleep architecture. Management of abnormal movements in sleep using dopaminergic agents might be warranted.

Special precautions are warranted in patients with postpolio syndrome presenting for surgery because these patients may have respiratory impairment, sleep apnea, and swallowing difficulties (26).

**Myasthenia Gravis**

Excessive fatigability and weakness of skeletal muscles are the cardinal manifestations in patients with myasthenia gravis. The disorder is caused when autoantibodies against muscle acetylcholine receptor attack the receptor at the neuromuscular junction. Typically, cranial nerve muscles are involved early in the disease, causing diplopia, ptosis of eyelids, facial weakness, difficulty in chewing, and a speech impediment. In a large proportion of patients, the symptoms become generalized, affecting proximal limb muscles and involving the diaphragm and accessory respiratory muscles. Respiratory failure may occur in unmedicated, uncontrolled patients. Sleep-related complaints in some patients include waking up with a sensation of breathlessness, morning headaches, and daytime somnolence. Respiratory function may be altered during sleep, with respiratory failure and CO2 retention serious enough to require ventilatory assistance (27). Patients exhibit an increased sleep apnea index with predominantly mixed and obstructive sleep apnea episodes, along with oxygen desaturation of moderate severity. This is particularly evident during REM sleep when the diaphragm is the only muscle that remains active in the exchange of air. Respiratory muscles may be focally affected in patients with myasthenia gravis (28).

In a study of 20 consecutive patients treated for myasthenia gravis, Quera-Salva et al. (27) evaluated body mass index, presence of upper-airway anatomical abnormalities, pulmonary function, presence of sleep-related complaints, and polygraphic measures during sleep. Results indicated that all patients had evidence of daytime diaphragmatic weakness, while older individuals with a higher body mass index and abnormal daytime blood–gas concentrations were primary candidates for the development of diaphragmatic sleep apneas and oxygen desaturation events during sleep, particularly during REM sleep.

In a study of randomly selected patients with myasthenia gravis, Nicolle et al. (29) investigated the prevalence of obstructive sleep apnea. The authors identified patients at risk of obstructive sleep apnea using the multivariable apnea prediction index. Apnea was diagnosed with polysomnography. The prevalence of obstructive sleep apnea was 36% compared to an expected prevalence of 15% to 20% in the general population. When including the presence of daytime sleepiness, the prevalence was 11% compared to 3% in the general population. The authors concluded that inquiring about apnea symptoms and calculating the body/mass index would identify patients most at risk of obstructive sleep apnea. They editorialized that without considering a role for obstructive sleep apnea, a history of increasing fatigue could lead to potentially harmful increases in steroid treatment.

Daytime somnolence in a patient with myasthenia gravis should suggest abnormal breathing during sleep, even in the absence of abnormal daytime respiratory activity. The dysfunction usually responds to the administration of slow-release pyridostigmine at night, although patients receiving appropriate treatment, with satisfactory daytime functional capacity may still have abnormal breathing during sleep.
Myotonic Dystrophy
Myotonic dystrophy is caused by a CTG triplet expansion in the 3' untranslated region of the DMPK gene on 19q13. Excessive daytime sleepiness and respiratory failure, both during wakefulness and in sleep, are commonly observed in patients with myotonic dystrophy, type 1. Hypersomnolence is characterized by prolonged morning sleep inertia (30) and sleepiness not relieved by naps, similar to the clinical picture observed in idiopathic hypersomnia (31). Occasionally, patients present features suggestive of narcolepsy, including sleep-onset REM periods (32). In eight patients with myotonic dystrophy, Broughton et al. (33) found disrupted sleep with nocturnal fragmentation, short REM-sleep latencies, reduced amounts of REM sleep and, in half the patients, sleep apnea and/or hypopnea mainly of central type. There was no statistically significant correlation between the degree of daytime cognitive deficit and the degree of sleep fragmentation or of respiratory problems at night. The authors concluded that the neuropsychological deficit in myotonic dystrophy cannot be attributed to a secondary effect of nocturnal sleep apnea or sleep disruption, but probably represents a direct effect of central nervous system lesions. Hypersomnolence may be aggravated by alveolar hypoventilation (34) and the sleep apnea syndrome, but it is not reversed entirely by CPAP applications (35), suggesting that hypersomnolence is an intrinsic disorder related to central nervous system disease not caused by sleep apnea (36).

Hypersomnolence, apathy, mental decline, and “slow alpha” rhythms in subjects with moderately advanced disease have been linked to histological changes and dysfunction of the dorsomedial nuclei of the thalamus (37). In myotonic dystrophy, 10% to 30% of nerve cells of the dorsomedial nuclei contain eosinophilic cytoplasmic inclusion bodies that manifest neuronal damage. Eosinophilic bodies (38) are round, oval, or elongated, with smooth, sharply defined contours and an occasional peripheral halo ranging from 4 to 8 μm in diameter. Staining histological methods indicate that the bodies are acidophilic and composed of protein but not of amyloid. Ultrastructural studies have shown a fibrillar material within ribosome-bearing membranes, suggestive of a proteic nature. Inclusion bodies probably develop as the contents of expanding cisternae coalesce and become enclosed by condensing membranes. Eosinophilic inclusion bodies may represent the morphological expression of a block in the excretion or transport of a protein formed by the thalamic nerve cells, as well as a sign of neuronal degeneration.

As the disease advances hypersomnolence, cognitive deficits, EEG alterations, and morphological brain changes worsen. Progressive enlargement of the third ventricle observed in some patients with myotonic dystrophy (39) may be the immediate consequence of progressive degeneration of the medial thalamus, which has been hypothesized to be the structural basis for central nervous system abnormalities in myotonic dystrophy (37). Mental decline, psychosocial deterioration, apathy, inattention, and memory defect support a medial thalamic syndrome, while EEG changes characterized by slow alpha rhythms also suggest a diencephalic disorder (40). Testing has shown that the neuropsychological deficit cannot be attributed to the effect of sleep apnea or sleep disruption (33).

The sleep-related breathing disorder in myotonic dystrophy may be yet another manifestation of central alteration. Nonobstructive sleep apneas and sleep-related alveolar hypoventilation are common (34) and likely contribute to increased somnolence. Sleep-related breathing abnormalities are probably the result of central neuronal lesions and declining muscular function. In one study (41), obesity was found to correlate with levels of sleep hypoxemia, and body-mass
index was significantly associated with the nadir of oxygen saturation, time spent at saturations below 85%, and the number of 4% drops in oxygen saturation. In a study comparing respiratory muscle weakness in patients with myotonic dystrophy and patients with nonmyotonic weakness (42), myotonic patients showed more frequent apnea and hypopnea events and more severe desaturation than the nonmyotonic group with muscle weakness. The study showed that abnormal breathing during sleep is common in myotonic dystrophy and suggested that sleep-related respiratory disturbance is not due solely to the direct effects of muscle weakness. Furthermore, somnolence was not clearly attributable to the sleep apnea/hypopnea syndrome or to the abnormal structure of nocturnal sleep.

Muscular weakness early in life in patients with myotonic dystrophy affects craniofacial and mandibular growth, contributing to the development of obstructive sleep apnea by increasing airway resistance in a stenotic oropharynx.

Muscular dystrophies and congenital and metabolic myopathies

Patients with Duchenne muscular dystrophy develop restrictive lung disease, as muscle weakness progresses and ribcage deformities appear. A polysomnographic...
study of six patients with advanced Duchenne muscular dystrophy revealed nocturnal hypoventilation in all sleep stages with profound desaturation during REM sleep, despite normal awake minute ventilation (14). Five of the six patients had oxygen desaturation events exceeding 5% during REM sleep while breathing room air. The authors concluded that patients with diaphragmatic weakness are especially vulnerable to desaturation during REM sleep. Redding et al. (49) conducted another polysomnographic study of five subjects with severe restrictive lung disease and respiratory muscle weakness due to Duchenne muscular dystrophy without respiratory failure or cor pulmonale. The authors found abundant fragmentation of nocturnal sleep, many sleep-stage changes, and reduced REM sleep, but no evidence of nocturnal hypoxia. The authors further hypothesized that, in the absence of nocturnal hypoventilation, sleep abnormalities in patients with Duchenne muscular dystrophy might be inherent to the central neurological dysfunction observed in these patients. In patients with Duchenne muscular dystrophy, a vital capacity of less than one liter and REM-sleep-related oxygen desaturation may be predictors of subsequent survival (50). Daytime predictors of sleep hypoventilation in Duchenne muscular dystrophy are a \( \text{PaCO}_2 \geq 45 \text{mmHg} \) and a forced expiratory velocity of less than 40% (51). In a retrospective review of 34 patients with Duchenne muscular dystrophy (52), the authors found a significant prevalence of sleep breathing disorder. They observed a bimodal presentation with obstructive sleep apnea found in the first decade and hypoventilation more commonly seen at the beginning of the second decade. They recommended polysomnography in children with symptoms of sleep apnea, or at the stage of becoming wheelchair-bound. In patients with the early stages of respiratory failure, assessment with polysomnography identified sleep hypoventilation and assisted in initiating NIV.

Severe nocturnal respiratory failure has been described in two siblings with nemaline myopathy (53). This is a congenital myopathy with a relatively benign prognosis that affects all skeletal muscles, including the diaphragm. Both patients developed marked sleep inertia in the morning with headaches, vomiting, and daytime lethargy. Subsequent medical evaluation disclosed marked hypoxia, hypercapnia, and cor pulmonale. Breathing at night was very irregular, with progressive hypercapnia as soon as they fell asleep. Nocturnal respiratory failure was attributed to a disturbance of central respiratory control with poor sensitivity to CO\(_2\) inhalation, also detected in relatives. Nocturnal mechanical ventilation reversed respiratory failure in both siblings and permitted a return to daytime activities, including school attendance.

Various combinations of nocturnal respiratory dysfunction have been described in patients with congenital fiber-type disproportion syndrome (13) and acid maltase deficiency (1). In a study of 27 patients with juvenile and adult acid maltase deficiency (54), the authors found that vital capacity correlates with respiratory muscle function. Diaphragm weakness is the major cause of sleep apnea and respiratory failure. Sleep apnea and nocturnal hypoventilation are predictable from daytime function tests. The same group of authors reported later on successful treatment of the condition with noninvasive ventilation (55).

Hypersomnia was reported in a patient with bithalamic lesions and Kearns-Sayre syndrome (56). The nocturnal polysomnogram showed total absence of sleep spindles, and the authors hypothesized a thalamic dysfunction as a result of spongy degeneration, a commonly observed brain lesion in the Kearns-Sayre syndrome.
GENERAL APPROACH AND MANAGEMENT

Diaphragmatic weakness and failure are the most important determinants of sleep-related respiratory insufficiency in patients with a neuromuscular disorder. Hypoventilation becomes particularly severe in REM sleep when diaphragmatic function fails. Chest-wall weakness, along with restrictive lung disease, contributes to hypoventilation in all stages of sleep. Weakness of the pharyngeal wall compounded by obesity of sedentary origin and craniofacial maldevelopment facilitate the development of obstructive sleep apneas. Some patients with neuromuscular disorder exhibit nocturnal hypoventilation in the absence of airway obstruction or of major muscular weakness, suggesting an alteration of central respiratory drive. In many patients all these pathogenetic mechanisms coexist with variable intensity, although in terminal stages sleep-related hypoventilation/hypoxemia predominate.

Symptoms and signs that should alert the clinician to the presence of sleep-related ventilatory difficulty include nocturnal restlessness, frequent unexplained awakenings, snoring loudly on occasions, and nocturnal awakenings gasping for breath. Difficulty in awakening in the morning and prolonged sleep inertia may interfere with morning activities. Daytime somnolence, fatigue, and inappropriate napping underlie failure to thrive in the very young and contribute to declining school grades or poor work performance at a later age. In advanced cases, patients develop nocturnal cyanosis, severe insomnia, morning lethargy, headaches, vomiting, and leg edema suggestive of acute respiratory failure and cor pulmonale.

Polysomnographic evaluation is necessary to distinguish among the different causes of sleep disturbance and to assess the severity of the respiratory disorder (57). Sometimes nocturnal disruption indicates nocturnal postural discomfort in a weak, incapacitated, or deformed patient. The daytime test may show excessive somnolence proportionate to the nocturnal alteration or, as in the case of myotonic dystrophy, may reveal excessive daytime somnolence that is not explained by the nocturnal findings. This suggests an intrinsic form of hypersomnolence that in some cases has been associated with REM-sleep abnormalities.

Therapeutic goals are directed at elimination of excessive daytime somnolence, improvement of nocturnal desaturation, restoration of sleep architecture, and correction of respiratory and heart failure. Nocturnal application of CPAP and bi-level ventilation can correct most nocturnal ventilatory abnormalities found in patients with neuromuscular disorder and should be considered whenever a sleep-related ventilatory deficit exists. Positive-pressure breathing eliminates obstructive sleep apnea, improves hypoventilation, assists diaphragmatic failure, and reduces arousals. Supplemental oxygen bled into the mask is recommended when positive air-pressure therapy is insufficient to overcome mean levels of hypoventilation of 85% or less. Bi-level ventilation is better tolerated by patients with weak chest-walls and poor diaphragmatic function who cannot overcome expiratory forces. Supplemental oxygen via a nasal cannula may be sufficient in some cases to correct REM-sleep-related desaturations. Long-term noninvasive ventilation reduces morbidity and mortality in patients with neuromuscular and chest-wall disease with hypercapnic ventilatory failure (58). Patients with neuromuscular disease with nocturnal hypoventilation are likely to deteriorate with the development of daytime hypercapnia and/or progressive symptoms within two years and may benefit from the introduction of nocturnal noninvasive ventilation before daytime hypercapnia ensues.
Patients with advanced restrictive lung disease, severe chest-wall muscle weakness, loss of sleep-related respiratory drive, and diaphragmatic paralysis pose special problems. Tracheotomy may be indicated in a few cases, but dependence, social disruption, and medical complications have to be weighed against the benefits obtained. Because children under the age of six years tolerate poorly nasal ventilation (59), other therapeutic measures may have to be considered, including temporal use of tracheotomy.

Protriptyline at bedtime slightly increases muscle tone in sleep and is of some value in patients with modest obstructive sleep apnea in whom a weak pharyngeal wall is a component. It may also be useful to reduce REM sleep in patients with REM-sleep-related hypoventilation. Methylphenidate and modafinil are of some value in patients with myotonic dystrophy and hypersomnolence who do not respond fully to the application of noninvasive ventilation.

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Stimulant-Dependent and Hypnotic-Dependent Sleep Disorders

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INTRODUCTION

The use of stimulant and hypnotic medications in Neurology, Sleep Medicine, and general Medicine and Surgery settings has become ubiquitous. Published data (Table 1) for pharmacological treatment of insomnia in 2002, based on estimates of 3400 physicians representing 29 medical specialties across the U.S.A., reporting data for all patient visits in a 24-hour period once per month, projected estimates of more than 11,000,000 “drug occurrences” for “hypnotic/sedative/promote sleep” actions (1). If taking into account the additional non-prescribed use of stimulants and/or hypnotics by the general population, the magnitude of stimulant and hypnotic use is potentially staggering. The impact of the use or misuse of stimulants or hypnotics results in a myriad of medical symptoms and disorders. The constellation of these problems when “things go wrong” with stimulants or hypnotics is encompassed in stimulant-dependent sleep disorder and hypnotic-dependent sleep disorder.

STIMULANT-DEPENDENT SLEEP DISORDER

Definition and Background

Stimulant-dependent sleep disorder involves disruption of sleep or insomnia as a consequence of using central nervous stimulants and excessive somnolence or disrupted wakefulness following withdrawal of stimulants. The second edition of the International Classification of Sleep Disorders classifies stimulant-dependent sleep disorder under two categories: Insomnia due to drugs or substances and Hypersomnolence due to drugs or substances (2). Stimulant-dependent sleep disorder has been codified as a “reduction of sleepiness or suppression of sleep by central stimulants, and resultant alterations in wakefulness following drug abstinence” (3). Both medicinally prescribed stimulants and nonprescribed stimulant abuse may result in the features of stimulant-dependent sleep disorder.

The earliest medical reports of sleep disruptions due to stimulants were published in the 1930s, even though medicinal stimulant use has been present for centuries (4,5). More detailed reports of the negative impacts of stimulants were elucidated in what was labeled “Amphetamine Psychosis” in the 1950s and 1960s. These reviews touched upon the impacts of stimulants on sleep and wakefulness, and emphasized the overall clinical and psychiatric sequelae (6,7).

Amphetamine stimulants result in increased wakefulness and also reduce total sleep time as well as reduce the time spent in rapid eye movement (REM) sleep (Table 2). In addition, amphetamines were found electrophysiologically to increase the time to the first REM period while asleep, that is, increased REM...
latency. Stimulant withdrawal results in notable increase in total sleep times—in some individuals, up to 18 to 48 hours of continuous sleeping. During the withdrawal period, REM sleep often increases substantially (“REM sleep rebound”) and the latency to REM sleep is often much shorter—the opposite of the effects seen during stimulant use (8,9). The uncharacteristically high percentage of REM sleep relative to total sleep time and the very short latency to REM sleep in the stimulant withdrawal state have been described as not occurring until one or two nights after the last dose of stimulant (10).

More sophisticated electrophysiological studies of sleep revealed that different categories of stimulants resulted in dissimilar impacts on wakefulness and sleep. Derivatives of amphetamines used for weight loss, such as the anorexiants fenfluramine and mazindol, do not result in any substantial sleep–wake or REM

<table>
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<th>Amphetamine withdrawal</th>
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<tr>
<td>Increased wakefulness</td>
<td>Reduced wakefulness</td>
</tr>
<tr>
<td>Reduced total sleep time</td>
<td>Increased total sleep times (up to 48 hrs)</td>
</tr>
<tr>
<td>Reduced time in REM sleep</td>
<td>Increased time in REM sleep</td>
</tr>
<tr>
<td>Increased time to first REM sleep period</td>
<td>Reduced time to first REM sleep period</td>
</tr>
</tbody>
</table>

*Abbreviation:* REM, rapid eye movement.
sleep disruptions (11,12). Caffeine, a xanthine, does not affect sleep, wakefulness, or REM sleep when compared with the amphetamines, until doses of 300 mg of caffeine are reached. When caffeine intake is at or above 300 mg, total sleep time is reduced and REM periods later in the night are delayed (13,14).

Methylphenidate, a heterocyclic derivative of amphetamine, results in very similar sleep, wake, and REM sleep effects as the parent compound. Cocaine use reduces REM sleep and increases latency to REM sleep; conversely, cocaine withdrawal results in REM sleep rebound and shortens latency to REM sleep (15,16).

Modafinil withdrawal has not resulted in excessive somnolence in animal studies (17,18). The unique mechanisms of action of modafinil appear to minimize the adverse effects on sleep, rebound wakefulness, and REM sleep seen with amphetamines.

Identifying and Pharmacological Features

Though the precise etiology of stimulant-dependent sleep disorder is not yet clearly defined, stimulant use may result in euphoria or self-perception of improved performance and aptitude, which prompts continued use or abuse of the stimulant (19). Amphetamine-like stimulants’ release of norepinephrine results in the subjective “high,” and mesolimbic dopamine pathways mediate repetitive stimulant use behavior (20). During the period of stimulant abuse, repetitive behaviors such as sorting, cleaning, assembling, and disassembling may occur, which has been described as “punding” (21). Molecular mechanisms of sensitization via dopaminergic pathways result in stimulant-induced changes and relapses in the stimulant use or abuse (22,23).

Pre-existent psychiatric illness may predispose individuals to stimulant-dependent sleep disorder (3). In addition, those who abuse stimulants may develop periods of complete sleep deprivation followed by hypersomnia and the withdrawal phase. This may result in psychiatric symptomatology, particularly in chronic abusers. The clinical features may be subtle, such as restlessness, akathisia, or nervousness. More obvious manifestations could include hypomania or euphoria, and, on occasion, a toxic psychosis similar to paranoid schizophrenia.

When stimulant abuse is interrupted by abstention or withdrawal, hypersomnia occurs. Uninterrupted sleep lasting up to several days may result, and depression may be seen in the abstinent period. Stimulant-dependent sleep disorder withdrawal effects may persist for several months (11). Polysomnographic studies for sustained periods during stimulant withdrawal reveal a pattern of acute hypersomnia and REM sleep rebound for the first seven to ten days. This pattern then reverses with reduced REM sleep and disrupted nocturnal sleep and reduced total sleep time for two to three weeks following stimulant abstinence (24,25).

The indirect sympathomimetic type of stimulants are those most likely to cause stimulant-dependent sleep disorder. Amphetamines, cocaine, and methylphenidate block the reuptake and enhance the release of central nervous system norepinephrine, dopamine, and serotonin. The dopaminergic system effects are those with the most prominent neuropharmacological activity for indirect sympathomimetics (20,26). Tolerance to this category of stimulants and rebound hypersomnia seen with these agents are the most pronounced of all stimulants and are major contributing factors to stimulant-dependent sleep disorder.
Tolerance and rebound are less intense with pemoline, which also has a catecholamine uptake inhibition mechanism of action. Pemoline, in doses up to 90 mg, does not result in the same adverse sleep-related effects as the indirect sympathomimetics, perhaps, in that it does not seem to involve dopaminergic systems as prominently (27).

Modafinil appears to have mechanisms of action that are unique, but as of yet not entirely defined. Both alpha1-noradrenergic agonist and beta-receptor activity have been proposed for modafinil activity (28). Activation of hypocretin-containing cells in the lateral hypothalamus may also be involved (29). Similar to some amphetamine-like stimulants, modafinil may also involve dopamine transporter systems (30). Re-uptake of norepinephrine in ventrolateral preoptic nuclei has been demonstrated for modafinil in an animal model (31). Though clinical experience with modafinil is relatively limited temporally compared with amphetamine stimulants, there appears to be no significant rebound hypersomnolence and no significant abuse potential, though tolerance aspects are not yet entirely known (32–34).

Sodium oxybate has both wakefulness promoting and sedating properties. Though not considered a stimulant per se, its use in combination with, or as a replacement for, stimulant medication prompts mention for stimulant-dependent sleep disorder. The mechanism of action of sodium oxybate, which is the sodium salt of gamma-hydroxybutyrate, at least in part may involve modulation of noradrenergic, dopaminergic, and serotonergic neurons in the central nervous system (35–37). There are numerous reports of gamma-hydroxybutyrate abuse, addiction, and withdrawal in the setting of “club drug” or polypharmacy abuse, but when used therapeutically, issues of tolerance, abuse, and rebound to date appear to be insignificant (38,39).

Stimulant-dependent sleep disorder is most often seen with misuse or intentional abuse of stimulants. However, stimulant-dependent sleep disorder may also be seen as an unintentional sequelae of those who are using stimulants medicinally. Individuals who are prescribed stimulants at dosages exceeding published guidelines were found to have significantly higher occurrences of psychiatric admissions and psychosis compared to those prescribed recommended doses (40). Practice parameters are regularly published for stimulant prescription for sleep disorders (41). In addition, in those who are prescribed stimulants medicinally, insomnia may occur at the initiation of treatment or if the medication dose or schedule are changed. Withdrawal symptoms of hypersomnolence may occur if the dosage is abruptly reduced or if the medication is withdrawn. Even in proper dosages, stimulants used clinically may result in side effects such as headache, mydriasis, tremor, irritability, nervousness, anorexia, and palpitations (42).

There is an important distinction about stimulant-dependent sleep disorder in those who abuse stimulants and in those who are using stimulants in recommended compliant schedules and dosages. The same degree of sleep-related abnormalities are rarely seen in those individuals using proper medicinal regimens compared with those who misuse stimulants. However, many physicians often remain hesitant to prescribe stimulants for documented medical disorders (43,44). The prevalence of stimulant-dependent sleep disorder is not known.

A variation on stimulant-dependent sleep disorder has become the focus of much discussion. This controversy about stimulants and sleep disorders could be described as “stimulant-obscured sleep disorders” (19). The increasingly wide use of stimulants as strictly symptomatic management of fatigue or sleepiness
may be preventing specific diagnosis and proper management of underlying sleep disorders in pediatric and adult age groups (45–50). As such, whether stimulant use is inadvertent/symptomatic, or self-obtained by the individual non-medicinally, it must be considered that an underlying sleep disorder may have prompted the use of the stimulant. Narcolepsy, sleep apnea, insufficient sleep, or other disorders of excessive somnolence need to be acknowledged as potential underlying factors for stimulant use.

The diagnostic approach to stimulant-dependent sleep disorder is initiated with thorough histories of sleep, medical, and psychiatric aspects. Attention must be given to any history suggestive of substance abuse, and emphasis also is focused on any symptoms of sleep–wake disorders. Consideration may be given to blood and urine screening for drugs of abuse including metabolites of stimulants, sedative-hypnotics, alcohol, anxiolytics, and other abused substances. If there is any suspicion of underlying sleep disorders, polysomnographic evaluation possibly followed by multiple sleep latency test or maintenance of wakefulness test should be considered, with the testing completed after at least two weeks of documented stimulant abstinence.

Stimulant-dependent sleep disorder must be differentiated from substance abuse disorders. Occasionally, stimulant abusers may attempt to obtain stimulants from physicians by offering a history of a disorder of excessive somnolence. Oftentimes, the history may be “too perfect” or sound as if memorized from a textbook or the Internet. The diagnostic approaches above will often differentiate the drug-seeking individual from those with true sleep-and-medical disorders. Insomnia that is sometimes present with stimulant use needs to be differentiated from anxiety-related insomnia, psychophysiological insomnia, or other disorders of initiation or maintenance of sleep. The hypersomnolence seen after stimulant withdrawal needs to be distinguished from sleep apnea, narcolepsy, or other disorders of excessive somnolence. The psychiatric symptoms that are occasionally present in those using stimulants must be differentiated from pre-existent or concurrent psychiatric disorders (3).

**Treatment**

The cornerstone of treatment of stimulant-dependent sleep disorder is to implement preventative clinical strategies with initiation of stimulant use. If realistic goals are discussed at the onset of treatment, reasonable expectations may prevent stimulant-dependent sleep disorder. For example, emphasizing that perfect control is not expected, but rather educating that alertness being present when alertness is most needed, may prevent the individual titrating the medication dose and schedule on their own which would then start the spiral to stimulant-dependent sleep disorder. Education of the individual and enrolling family members’ participation, at the outset, in emphasizing these realistic goals, and in addition the benefits, risks, side effects, and dangers of the possibility of stimulant-dependent sleep disorder with stimulant medication is an essential preventative treatment strategy. Teaching or providing the individual aspects of good sleep hygiene is of value, as is encouragement to become involved early with counseling and participation with local or national support groups. Consideration should be given to starting with the lowest effective stimulant dose and titrating to clinical response. Multiple sleep latency testing or maintenance of wakefulness testing may be useful laboratory-based monitors for medication titration. A pediatric
study demonstrated that interspersed weekend medication holidays reduced sleep-related side effects without interfering with the stimulant benefits (51). A separate pediatric open label study suggests that melatonin may help with the insomnia associated with stimulant use (52).

Acute intoxication with stimulants usually require hospitalization to carefully manage psychiatric and medical complications. Psychotic and violent manifestations have been treated with haloperidol and diazepam. Risperdone has been reported to reduce discriminative-stimulus effects of amphetamine (53). Ammonium chloride could be considered, if necessary, in promoting renal excretion of amphetamine.

For stimulant withdrawal, the depression that is sometimes seen may proceed to suicidal ideation. Antidepressant medication would be of value and may also be useful in preventing relapse. In addition, stimulant-dependent sleep disorder in the stimulant abstinence setting has been successfully treated with psychological and psychosocial therapies. Chemical dependency treatments, both inpatient and outpatient, have a significant role in the management of stimulant abuse and stimulant-dependent sleep disorder. Most individuals with stimulant-dependent sleep disorder return to normal sleep–wake patterns with proper treatment.

**HYPNOTIC-DEPENDENT SLEEP DISORDER**

**Definition and Background**

Hypnotic-dependent sleep disorder is defined as insomnia or daytime somnolence in association with hypnotic use. Similar to stimulant-dependent sleep disorder, hypnotic-dependent sleep disorder is classified with Insomnia due to drugs or substances and Hypersomnia due to drugs or substances in the International Classification of Sleep Disorders, second edition (2). Insomnia, defined as difficulty initiating and/or maintaining sleep and non-restorative sleep with associated waking mood or function disturbances, is the more common symptom of hypnotic-dependent sleep disorder but daytime somnolence may also occur. Hypnotic-dependent sleep disorder may be seen in the setting of medicinally prescribed hypnotics and in the setting of non-prescribed hypnotic abuse.

In the 1960s, initial reports of medication tolerance, rebound insomnia on discontinuation of treatment, and abnormal sleep physiology were described in reference to barbiturates used as hypnotics (54). Individuals were reported to manifest significantly disrupted sleep physiology with barbiturates and similar compounds even when continued on high doses of these medicines, with tolerance to the medications appearing to be the central factor (55). The disrupted sleep–wake patterns worsened when the hypnotic was discontinued, which promoted long-term use of hypnotics in some individuals despite the drug's ineffectiveness. Drug-dependence developed as a result of withdrawal effects on sleep that transiently improved with restart of hypnotics. The spectrum of what we now know as hypnotic-dependent sleep disorder was referred to as “drug-withdrawal insomnia,” “sleeping pill-withdrawal insomnia,” or “hypnotic drug-dependence” (56).

**Identifying and Pharmacological Features**

Hypnotic-dependent sleep disorder includes symptoms of insomnia and daytime sleepiness. Insomnia is a symptom, not a diagnosis or disorder per se, and the insomnia symptom encompasses numerous physiological and psychosocial etiologies with a large number of precipitating and perpetuating factors (57). In
any given year, 30% to 35% of the adult population report insomnia, and one-half of these individuals feel that their insomnia problem is serious (58). Ten percent of the latter use hypnotics regularly and 4% of these individuals use hypnotics more than three nights per week for more than six months.

Hypnotic-dependent sleep disorder may occur in persons with acute or chronic sleep problems. In the acute setting, an individual may develop a transitory (days to weeks) disruption in their normal sleep. They use a hypnotic and their sleep improves. When the hypnotic is stopped, disrupted sleep and waking symptoms return. If the hypnotic is restarted, their symptoms decrease and the cycle of hypnotic-dependent sleep disorder escalates. Hypnotic-dependent sleep disorder pre-supposes that there is no pre-existent substance abuse disorder, and that the sleep complaint was present before use of hypnotics, and that the hypnotic resulted in improvement of the symptoms. When the hypnotic is stopped, the sleep complaint returns leading to continued hypnotic use.

In those with chronic sleep problems, the sleep complaint may be related to chronic medical or psychiatric disorders, or may be intrinsic. Hypnotic-dependent sleep disorder in persons with chronic sleep complaints often is manifested as cycles of good sleep or poor sleep depending on their use of hypnotics. The longer hypnotics are used, the use becomes more regular and habitual (59).

Sleep physiology, when studied polysomnographically in hypnotic-dependent sleep disorder, reveals that those who are in the phase of not using hypnotics for at least one week will have reduced sleep efficiency and increased number of arousals and awakenings. When studied on the usual hypnotic dose, there are reduced arousals and improved sleep efficiency comparatively, but increased alpha intrusions, increased beta activity and sleep spindles on EEG, reduced delta sleep, decreased amplitude of delta waves, and occasionally reduced REM sleep (56).

The etiology of hypnotic-dependent sleep disorder is not precisely known. Though use of hypnotics is central to the disorder, hypnotic use alone is not sufficient. Disturbed sleep complaints must precede use of the hypnotic, and insomnia and daytime sleepiness become persistent after the use and/or discontinuation of the hypnotic. A possible explanation for hypnotic-dependent sleep disorder is on a behavioral basis. The individual equates that hypnotic pill use equals good sleep and no pill equals bad sleep. Thus, hypnotic taking behavior is reinforced, and further promoted when anxiety of not taking the pill results in reduced ability to sleep well. In addition, tolerance to the medication reduces its efficacy in sleep, leading to a spiral of increasing doses, reduced efficacy, and severe rebound insomnia and daytime symptoms with any attempt to discontinue the medication (60). Rebound insomnia may be related to receptor tolerance, but this issue is still not entirely settled (61–63).

A different behavioral explanation for hypnotic-dependent sleep disorder is described as “insomnia relief-seeking behavior.” Those individuals with objective insomnia are more likely to self-administer hypnotic medication than those with sleep-state misperception or subjective insomnia. The objective insomnia individual’s hypnotic use is tied to physiological sleep disturbance, and the dose is increased when efficacy reduces (64). Objective insomnia individuals will also be far more prone to self-administer the hypnotic before sleep, whether the formulation is placebo or active drug (65).

Rebound insomnia usually occurs one to three nights after hypnotic medication discontinuation and is more likely to occur with abrupt abstinence, with
short half-life medication (especially benzodiazepines), and if the hypnotic being used is at a high dose (66,67).

Rebound insomnia does not seem to be a core issue for H1 anti-histamine medication in hypnotic-dependent sleep disorder (perhaps because of long half-life), but rapid tolerance to these medications’ sedating effects is potentially contributory to hypnotic-dependent sleep disorder developing.

Rebound insomnia has rarely been reported with the imidazopyridine zolpidem or with the pyrazolopyrimidine zaleplon (68,69). There are isolated case reports of tolerance and withdrawal seizures with zolpidem, but the cases always involved massively supratherapeutic use of the medicine (e.g., 40 times the recommended dose in one case) (70–72). Tolerance has not yet been reported with zaleplon or with the cyclopyrrolone eszopiclone (73,74). The role that these medicines may play in hypnotic-dependent sleep disorder remains uncertain (75,76).

The daytime somnolence effects in hypnotic-dependent sleep disorder may be in part related to “hangover” aspects. “Hangover” effects increase with increasing half-life of hypnotics, but even shorter half-life preparations may result in cognitive impairment and reduced psychomotor performance the day following bedtime use of the medication. These residual effects may result in vehicle driving risks (77,78). Zolpidem and zaleplon did not impair morning vehicle driving performance when these medications were used at bedtime. However, benzodiazepine hypnotics and zopiclone significantly impaired morning driving abilities following bedtime administration of these hypnotics, and occasionally, the impairments persisted into afternoon hours as well (79).

The prevalence of hypnotic-dependent sleep disorder is not known, but has been estimated from case series to be 3% to 17% of patients with insomnia that have a primary or secondary diagnosis related to substance use (80–82). One epidemiological study indicated that 5% of the insomnia population used medication for hypnotic purposes, at least in part, and though the medications were usually used chronically, there was minimal subjective sleep improvement (83). A survey of hypnotic use with sample totals of more than 57,000 individuals reported that 4% to 9% used sleeping pills chronically, across all age ranges. Females were more likely than males to use sleeping pills with a ratio of 3:2. In those older than age 65, rates of chronic hypnotic use were 25% to 35% (84). In a survey of pediatricians, 75% had recommended non-prescription medication for sleep and more than 50% had prescribed hypnotics for children (85). The prevalence of hypnotic-dependent sleep disorder in children remains unknown.

The initial approach to diagnosis of hypnotic-dependent sleep disorder is very similar to that with stimulant-dependent sleep disorder: detailed histories of sleep, medical, and psychiatric aspects. Clarification of the presence of a sleep complaint before use of hypnotics, and the subsequent complications that ensue when hypnotics are used are critical to diagnosing hypnotic-dependent sleep disorder, and separating from substance abuse disorders. Use of a sleep diary by the individual with and without medication may validate the diagnosis, and be of considerable utility to the person in understanding their sleep disorder. If the history data seems unreliable, urine and blood drug screening may be of value. If there is a suggestion that a sleep disorder such as sleep apnea or periodic limb movements, or a medical disorder such as nocturnal epilepsy is present, polysomnography should be performed (86,87). To differentiate pathological daytime somnolence from mood disturbances or hypnotic side effects, multiple sleep latency testing or maintenance of wakefulness testing would be valuable.
In individuals with primary substance abuse, the history of substance abuse predating the sleep complaints may aid in differentiating from hypnotic-dependent sleep disorder. Most persons with hypnotic-dependent sleep disorder take hypnotics only at bedtime and do not misuse other substances such as alcohol, analgesics, stimulants, or anxiolytics. Differentiating hypnotic-dependent sleep disorder from other causes of insomnia such as psychophysiological insomnia, restless legs syndrome, and circadian rhythm disorders is often achieved by a thorough sleep history. Primary psychiatric disorders, often affective or personality disorders, may be comorbid congeners in those with hypnotic-dependent sleep disorders. To determine a psychiatric diagnosis in addition to the hypnotic-dependent sleep disorder often requires several visits to be clearly differentiated.

**Treatment**

Insomnia is a symptom of heterogeneous origin and not a disorder per se. Accepting this premise, prescribing hypnotics is symptomatic therapy. Five strategies should be applied in hypnotic therapy: (i) use the lowest effective dose; (ii) consider intermittent hypnotic use, for example, for every two good nights’ sleep on hypnotics, use no hypnotics on the third night; (iii) limit use of hypnotics to not more than three to four weeks at a time; (iv) taper and discontinue the hypnotic gradually; and (v) alert and educate individuals that transient rebound insomnia may occur, and that this is not a reason to restart the hypnotic. If these principles are inculcated at the beginning of the treatment, hypnotic-dependent sleep disorder may be avoided.

Use of nightly hypnotic medication as an initial treatment for chronic insomnia continues to be controversial. Non-nightly use of hypnotics may result in effective treatment outcomes while avoiding hypnotic-dependent sleep disorder. Combining behavioral and hypnotic therapies at the outset resulted in better treatment responses and may also minimize the possibility of hypnotic-dependent sleep disorder. An example of this approach was reported with use of zolpidem “as needed” to a maximum of five tablets per week, with behavioral therapies available on drug-free nights. Insomnia was effectively managed and use of hypnotic medication reduced significantly within three weeks.

Behavioral treatment with cognitive-behavioral therapy was preferred by 37 of 43 persons when offered as an alternative to pharmacological treatment in one study. Cognitive-behavioral therapy has been reported to be an effective stand-alone therapy for chronic insomnia. Behavioral therapy resulted in improvements of sleep latency and similar short-term treatment outcomes when compared with hypnotic medication therapy.

Education about sleep hygiene is an important first step in the management of hypnotic-dependent sleep disorder. Use of regular daytime exercise,

<table>
<thead>
<tr>
<th><strong>Prevention of Hypnotic-Dependent Sleep Disorder</strong></th>
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<tbody>
<tr>
<td>Use the lowest effective hypnotic dose</td>
</tr>
<tr>
<td>Consider intermittent use of hypnotics interspersed with hypnotic-free nights</td>
</tr>
<tr>
<td>Limit use of hypnotics to 3–4 wks at a time</td>
</tr>
<tr>
<td>Taper and discontinue hypnotics slowly</td>
</tr>
<tr>
<td>Alert the individual that transient rebound insomnia may occur and that this rebound should not prompt restarting the hypnotic</td>
</tr>
<tr>
<td>Consider combining behavioral and hypnotic treatments at the outset</td>
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evening relaxation, elimination of alcohol, caffeine, and nicotine near bedtime, and judicious use of short naps may all be useful. The bedroom should be reserved for sleep, and waking activities except for sexual activity should be excluded from the bedroom (56).

If hypnotics are to be eliminated, the motivation of the individual must be assessed. Those with high levels of anxiety and pessimism about symptom control often have poorer treatment outcomes (99). A sleep diary is initiated, and verbal and written treatment plans are agreed upon. Very gradual hypnotic reduction is implemented. Four to twelve weeks may be required to taper and discontinue the hypnotic. Occasionally, if significant sleep disruption or anxiety occurs, temporary (several nights to a week) slight increases in the hypnotic may be necessary before resuming the tapering. Positive reinforcement and continuous education and encouragement are provided to the individual (100). Many individuals expect a “quick fix”; reassurance is given that slow and steady progress is to be expected. Many insomnia patients demonstrate hyperarousal and treatment issues may need to be modified for this as well (101). Stress management and cognitive-behavioral therapies may be considered. Relaxation technique treatments have been reported to be beneficial (102).

If insomnia reoccurs, cognitive-behavioral therapy should be instituted. If absolutely necessary, low doses of hypnotics may be re-started for a brief period of time. Once the hypnotic-dependent sleep disorder is again under control, reduction of the hypnotic is reimplemented as outlined earlier.

Most individuals with hypnotic-dependent sleep disorder will successfully respond to the treatment interventions elucidated earlier. However, some will continue to use hypnotics chronically, occasionally to the point of substance abuse. Chronic use of high doses of hypnotics, sometimes in combination with alcohol, may lead to liver dysfunction. Cognitive and memory dysfunction may occur with hypnotic use (103). A review of more than 10,000 women over age 70 on hypnotics revealed increased incidence of falls and accidents (104). Hypnotics with or without concurrent therapy with tranquilizers in cancer patients resulted in poorer quality of life (105). Higher mortality is seen with chronic use of hypnotics independent of the presence or absence of insomnia (106,107).

REFERENCES


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<table>
<thead>
<tr>
<th>Suggestion</th>
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<tbody>
<tr>
<td>Regular daytime exercise at least 3 hrs before bedtime</td>
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<tr>
<td>Evening relaxation before retiring to bed</td>
</tr>
<tr>
<td>Avoid caffeine, alcohol, and nicotine before bed</td>
</tr>
<tr>
<td>Sleep as much as you need to feel refreshed, and not attempt to achieve a set amount of sleep time</td>
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<tr>
<td>Try to arise at the same time every morning</td>
</tr>
<tr>
<td>Avoid going to bed hungry, but do not eat large quantities of food immediately before retiring</td>
</tr>
<tr>
<td>Room temperature and darkness should be comfortable for you</td>
</tr>
<tr>
<td>If unable to sleep for more than 20–30 min while in bed, get up and do something else until sleepy</td>
</tr>
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