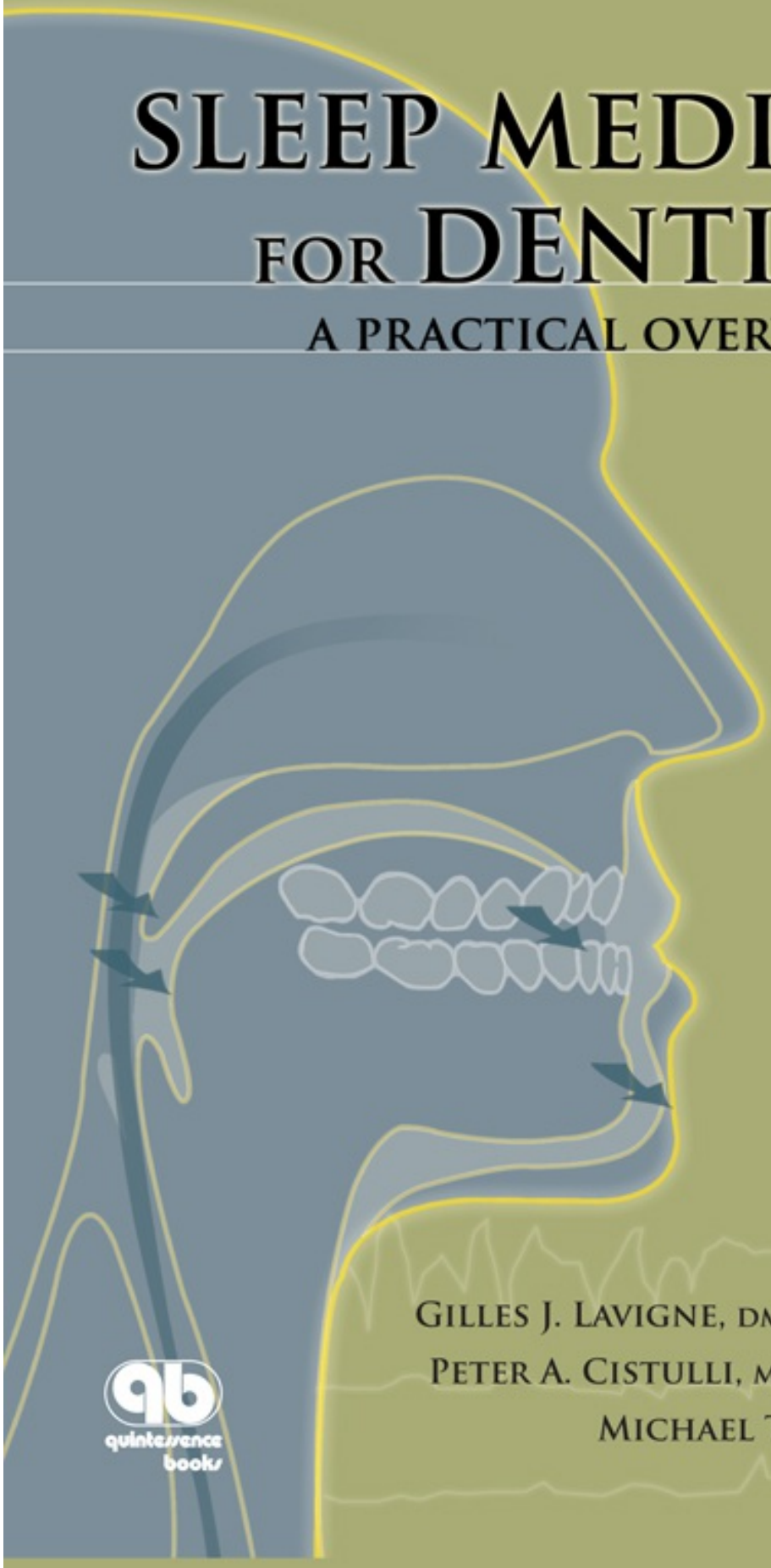
# SLEEP MEDICINE FOR DENTISTS

## A PRACTICAL OVERVIEW

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# A Practical Overview

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*Edited by*


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**To our students and research associates**
**who have contributed to the progress in dental sleep medicine**

# FOREWORD

Healthy sleep is vital for mental and physical well-being, and yet our understanding of the mechanisms that link sleep processes and brain and body function is relatively new. Until the discovery of rapid eye movement (REM) sleep in the 1950s, sleep was considered a passive state without particular import in the medical context. Today we understand that sleep is an active process that subserves many functions of the brain and body. In 1989, publication of the first book on sleep medicine (*The Principles and Practice of Sleep Medicine*, edited by Kryger et al) heralded sleep as a specialty in its own right. In a similar way, this new textbook heralds another phase in the development of clinical sleep practice for dental practitioners.

In his historical account of sleep medicine, Bill Dement points out that sleep apnea was overlooked by pulmonologists and otolaryngologists because they did not consider sleep. It was equally true that those doing research in human sleep (mostly neurologists and psychiatrists) also missed sleep apnea because they did not consider breathing. The great irony about the emergence of dental sleep medicine is that generations of dentists have looked in the mouths of countless individuals with sleep-disordered breathing without knowing of the disorder. Given that the dentist is often the first and only health care practitioner to look in the oral cavity, a good knowledge of sleep apnea should be part of the profession's knowledge base. From a broader perspective, these examples underscore the importance of a multidisciplinary approach; very few centers bring physician, surgeon, and dentist together to develop a management plan.

This book provides a compact introduction to sleep disorders. Appropriately, many chapters focus on sleep-disordered breathing because the dentist has a potentially major role in both its recognition and treatment. While continuous positive airway pressure (CPAP) remains the first-line therapy for sleep apnea, there is an important role for mandibular advancement appliances, which require adequate fitting by a well-informed dentist to be effective.

In addition, we should identify children who are at risk of developing sleep apnea. Approximately 10% of children who snore most nights are likely future apnea patients. Management plans designed to promote the growth of the upper airway and to prevent obesity provide a possibility for real prevention. This will happen only if the dental profession engages actively in the area.

The editors and contributors of this book are to be congratulated on putting together the first comprehensive text on dental sleep medicine.

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# FOREWORD

The science and clinical implications of sleep medicine should resonate strongly with the dental profession. Not only does the physiologic and behavioral state of our own and indeed our patients' sleep experiences involve a significant part of daily life, but dental sleep medicine is a rapidly evolving area of health care. A number of recognized sleep-related disorders have relevance to dental practice, and consequently, the availability of a book devoted to this subject has long been overdue. The book editors and authors collectively have impeccable academic credentials and clinical experience, and they have produced a lucid and apposite synthesis of the many topics that bear on sleep medicine and its particular applicability to dental practice.

The book is organized into four sections that deal first with general aspects of sleep and sleep disorders, then specifically sleep breathing disorders, sleep bruxism and other sleep-related movement disorders, and finally sleep–orofacial pain interactions. The inclusion of an exhaustive range of pertinent topics has ensured a perceptive and balanced approach to the subject. Unlike so many multi-authored texts on equally complex and fascinating health-related subjects, this one provides a mix of science, common sense, and pragmatism, particularly in the review of the management of sleep-related disorders.

We believe that this will prove to be a seminal text for the dental profession. It could very well turn out to be the catalyst required for the subject of dental sleep medicine to be included as an integral part of dental school curricula. The editors are to be commended for breaking new ground and ushering in an era of better understanding of a subject that has been relatively neglected in dental education and practice. Traditional and exclusive preoccupations with teeth, masticatory function, and related disorders—staples of dental education and texts—can now be broadened to include an awareness of our bodies' more extensive physiology and behavior.

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# PREFACE

The last 50 years have seen remarkable advances in the study of circadian biology and the neurophysiology of sleep. The genes that regulate these biologic rhythms have been isolated, and interactions between sleep and almost all other body systems (eg, respiratory, cardiovascular, endocrine, and neurologic) have become a focus for research. These scientific advances have emanated from diverse clinical disciplines, including internal medicine, pulmonology, neurology, otorhinolaryngology, pediatric medicine, psychiatry, psychology, and nursing. The range in specialties reflects the interdisciplinary nature of sleep and its disorders, and many critical contributions have also come from the field of dentistry. Currently, approximately 100 distinct clinical sleep disorders have been recognized. Certain disorders, including sleep apnea, sleep bruxism, and chronic pain, have a direct bearing on the practice of dentistry, which makes a working understanding of sleep biology (somnology) and sleep pathology (sleep medicine) a useful and necessary addition to the knowledge base of dental practitioners.

Sleep disorders decrease the quality of sleep by breaking its continuity, ie, they trigger a physiologic response that tends to push a sleeping person to a sublevel of wakefulness. Although the sleeping individual is unaware, his or her brain and autonomic nervous system are under a state of transient arousal. It is normal to observe brief arousals during sleep, but when these are too frequent or too long, they can cause mood alterations, memory problems, and performance deficits in healthy subjects after only a few days. Disordered breathing during sleep may cause serious alteration to patients' daytime vigilance, resulting in an increased risk of transport- or work-related accidents. In the long term, sleep apnea is known to be a serious and potentially modifiable factor for cardiovascular disease, including heart failure and stroke. The intrusion of snoring and tooth-grinding sounds are also a major cause of sleep disruption for the patient's bed partner and can be a source of marital conflict.

Orofacial pain may be associated with delayed sleep onset and disturbed sleep continuity; hence, it is a major cause of insomnia that may predispose patients to mood alteration and depression. Poor sleep is known to impair pain processing and can directly contribute to pain augmentation. Therefore, the prevention and management of sleep disorders should become a routine component of the treatment plan for chronic orofacial pain–related conditions.

Sleep medicine is often an overlooked part of public health. In many countries, access to sleep medicine constitutes a major public health challenge. In countries where therapy is available, treating sleep disturbances either as primary disorders or as comorbidities with other medical, psychiatric, or dental conditions is a significant opportunity to improve and prevent medical and psychiatric morbidity. It may also minimize the substantial financial burden related to the direct and indirect consequences of disturbed sleep. In Australia, for example, the overall cost of sleep disorders in 2004 was estimated to be US $7.5 billion with indirect costs of $808 million in related motor vehicle accidents.

The dentist plays an important role in sleep medicine by examining patients during their annual or biannual dental checkup for the risk of sleep-disordered breathing. Patients reporting snoring, sleepiness, and morning headaches in the presence of obesity, large tonsils, and/or dental malformation (eg, retrognathia, deep palate, large tongue) need to be guided by dentists to see their otorhinolaryngologist, respiratory-pulmonologist, or physician, as well as a sleep medicine expert. To manage the sound and tooth damage or pain generated by bruxism, oral appliances can be used, but the dentist needs to understand when such an appliance is indicated and the risks associated with its use. In cases where surgery is indicated, maxillofacial surgeons or otorhinolaryngologists collaborate closely with dentists to provide treatment.

When patients complain of morning headaches and temporomandibular disorders (TMDs), the exclusion of breathing disorders is a critical decision that is usually made in collaboration with the sleep medicine specialist, pulmonologist, neurologist, psychiatrist, and internal medicine physician. Dentists should refer patients who experience sleep bruxism in combination with a TMD for polysomnographic evaluation when they also complain of significant insomnia or poor sleep, even if they do not meet the traditional risk factors for sleep apnea. An increasing body of data suggests that both sleep bruxism and TMDs, which often occur in females of normal weight, are associated with increased risk for sleep disorder breathing.

Dentists caring for patients with chronic orofacial pain conditions (such as TMDs) also need to understand basic sleep hygiene principles and to know when to refer patients with chronic or intractable insomnia for behavioral sleep medicine evaluation. Behavioral treatments for chronic insomnia are considered first-line interventions over pharmacologic treatment options. A subset of chronic orofacial pain patients presents with a complex psychologic overlay that contributes to their ongoing pain and disability, a combination that can be managed by sleep

psychologists working in conjunction with the interdisciplinary team.

The key aim of *Sleep Medicine for Dentists* is to provide a rapid source of practical information to students, practicing dentists, and scientists. Section I introduces dental sleep medicine, while sections II to IV provide an overview of how to understand, recognize, and manage sleep disorders such as sleep apnea, sleep bruxism, and orofacial pain, which often interfere with or intrude into sleep and are critically important to the practice of dentistry.

Dental sleep medicine is a rapidly evolving field of preventive medicine. However, there remains a shortage of well-trained dental sleep medicine specialists. Those learning more about this field will discover an exciting interdisciplinary arena that is rife with opportunities to develop new dental interventions to treat complex clinical situations and improve the health and well-being of the estimated 20% of the population suffering from sleep disorders.

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# SECTION I

## INTRODUCTION TO DENTAL SLEEP MEDICINE

# CHAPTER 1

# THE NATURE OF SLEEP

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In the animal kingdom, sleep is a universal and imperative biologic process to maintain and restore health. *Sleep* is defined as a physiologic and behavioral state characterized by partial isolation from the environment. A baby's cry, the vibration of an earthquake, or a sudden pain intrusion will all interrupt sleep continuity; a sleeping brain maintains a sentinel function to awaken the organism for protection purposes.

The duration of sleep usually is 6 to 9 hours in adults. Although most adults sleep an average of 7.5 hours, some are short sleepers and some are long sleepers (ie, less than 5.5 hours and more than 9.0 hours, respectively). Good sleep quality is usually associated with a sense of having slept continuously through the night and feeling refreshed and alert on awakening in the morning. The perception of sleep quality is subjective, however, and varies widely among individuals. Some individuals perceive their sleep as satisfying most of the time, and some consistently report being poor sleepers (eg, having difficulties in initiating or maintaining sleep, feeling unrefreshed when they awaken, and having nightmares). However, sleep recording systems indicate that, in general, poor sleepers tend to underestimate the length of time they sleep (as do some good sleepers).

It is essential for dentists entering the field of dental sleep medicine to recognize sleep disorders, such as insomnia, respiratory or movement disorders (eg, snoring, obstructive sleep apnea, bruxism, gastroesophageal reflux), and pain interference. The direct and indirect costs of sleep disorders in Australia were estimated at US $7.5 billion for 2004.[1] The diagnosis, prevention, and management of sleep disorders are currently domains of high impact in public health (eg, prevention of

breathing disorders from childhood, management of daytime sleepiness to decrease the risk of transportation accidents, and the relationship of hypertension and sleep apnea). An understanding of the nature of sleep is essential to the dentist's role in management of such problems. The neurobiology of sleep is described in chapter 2, and a classification of the various sleep disorders relevant to dentistry is presented in chapter 3.

Like the management of pain, the diagnosis and management of sleep disorders are interdisciplinary. Dentists can achieve advances in sleep disorder management through collaboration with physicians (including pulmonologists, psychiatrists, neurologists, and surgeons), psychologists, respiratory therapists, and physical therapists.

## Sleep and Health

Sleep entails several functions, including physical recovery, biochemical refreshment (eg, synaptic function), memory consolidation, and emotional regulation[2–6] (Box 1-1). Lack of sleep is also known as *sleep deprivation*, that is, insufficient sleep resulting from short sleep duration or loss of a sleep segment because of environmental factors (eg, noise) or a contributing medical condition (eg, pain or diabetes). An experiment in young individuals comparing the consequences of sleep deprivation (4 hours of sleep over 3 to 4 days) to the effects of the subjects' usual 8 hours of sleep showed that sleep deprivation triggers mood alteration, sociability dysfunction, and complaints of bodily pain.[7] A persistent reduction in sleep duration can cause physical and mental health problems because of the cumulative effect of lack of sleep on several physiologic functions.

**Box 1-1 Functions of sleep**

**Fatigue reversal**

- Sleep allows the individual to recover and reenergize.

**Biochemical refreshment**

- Sleep promotes synaptic efficiency, protein synthesis, neurogenesis, metabolic (eg, glycogen) restoration, growth (secretion of growth hormone peaks during

sleep), etc.

**Immune function**

• Reset or protection.

**Memory**

• Daytime learning needs sleep for memory consolidation.

• Sleep seems to facilitate encoding of new information.

**Psychologic well-being**

• Dreams occur in all sleep stages. REM dreams are more vivid.

• Lack of sleep presents a risk of mood alteration to depression.

Moreover, both too-short and too-long sleep durations have been associated with higher risks of diseases and mortality. However, the complicated interactions among lifestyle, mortality risk, and sleep duration remain to be understood.[8] In fact, there is some evidence to support the relationship between sleep duration (too little or too much) and the risk of cardiovascular diseases (such as myocardial infarction and atherosclerosis), diabetes, obesity, depression, and even cancer.[7–10] Although these risk estimates are modest, they have been reproduced in too many studies to reject the putative effect of cumulative sleep debt on health maintenance. Higher risks of myocardial infarction have been found in women who are short sleepers as well as women who are long sleepers.[9] Elevated risks of cardiovascular problems and atherosclerosis also have been reported in people who sleep too much during the day.[10]

Because dentists are health professionals who, in some countries, see more than 50% of the population each year for annual dental checkups, they are in an excellent position to convey the message of the importance of good sleep habits for overall health.

## Sleep-Wake Cycle

An adult's 24-hour cycle is divided into 16 hours of wakefulness and 8 hours of sleep. Synchronization and equilibrium between the sleep-wake cycle and feeding behaviors are essential for survival. Mismatches in the synchronization of the

feeding cue and metabolic activity are associated with eating disorders.[11] Poor sleep can cause health problems, as already discussed, and can increase the risk of transportation- and work-related accidents and even death (see section II).[1]

## *Homeostatic process*

The propensity to sleep is directly dependent on the duration of the prior wakefulness episode. As the duration of wakefulness increases, sleep pressure accumulates and builds to a critical point, when sleep onset is reached. As this sleep pressure increases, an alerting circadian signal helps the person to remain awake throughout the day. The ongoing 24-hour circadian rhythm therefore runs parallel to the homeostasis process, also known as *process S* (Fig 1-1). The S process corresponds to the sleep pressure that individuals accumulate during the wakefulness period before being able to fall asleep. With increasing sleep pressure, sleep is proportionally longer and deeper in the following recovery period.

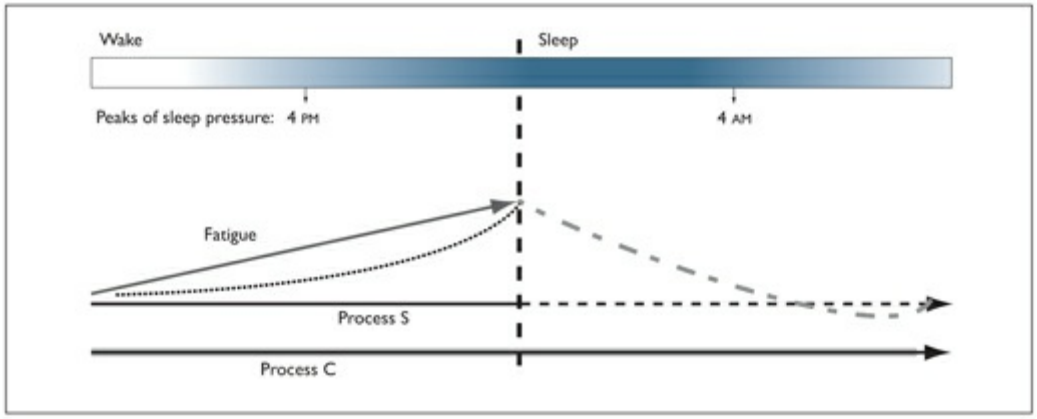


**Fig 1-1** Normal cycle for circadian rhythm (process C) *(black arrow)* and process S *(black line/dashed arrow)* over about 24 hours. During wakefulness periods, the increase in sleep pressure *(dotted line)*, parallels the increase in fatigue *(gray arrow)* and results in sleep *(dashed and dotted gray line)* at a given time over a 24-hour circadian cycle.

Changes in the frequency of slow-wave sleep waves can be estimated by a mathematic transformation of brain wave electrical signals or by quantitative spectral analysis of the electroencephalographic (EEG) activity. Rising or rebound of slow-wave EEG activity in the first hours of sleep is a marker of sleep debt.[12] In contrast, a reduction in slow-wave activity is observed in patients with chronic

pain.[13] However, the cause-and-effect association of these biologic signals with reports of fatigue and poor sleep is unknown. During the day, the effects of energy expenditure are accumulated, which may be connected to the feeling of tiredness.

Two times in the 24-hour cycle are characterized by a strong sleep pressure, 4 PM and 4 AM, +/-1 to 2 hours (see Fig 1-1). At a certain point, sleep pressure is so powerful that an individual will fall asleep regardless of the method or strategies used to remain awake.

## *Circadian rhythm*

Humans tend to alternate between a period of wakefulness lasting approximately 16 hours and a continuous block of 8 hours of sleep (see Fig 1-1). Most mammals sleep around a 24-hour cycle that is driven by clock genes that control the circadian rhythm (process C). Light helps humans synchronize their rhythm with the cycles of the sun and moon by sending a retinal signal (melanopsin) to the hypothalamic suprachiasmatic nucleus. The suprachiasmatic nucleus is a network of brain cells and genes that acts as a pacemaker to control the circadian timing function.[14]

The investigation of sleep-wake process C uses biologic markers to assess a given individual's rhythm. A slight drop (hundredths of a degree centigrade) in body temperature and a rise in salivary and blood melatonin and growth hormone release —peaking in the first hours of sleep, around midnight in the 24-hour cycle—are key indications of the acrophase (high peak) of the process C. Interestingly, corticotropins (adrenocorticotropic hormone and cortisol) reach a nadir (lowest level) during the first hour of sleep. They then reach an acrophase in the second half of the[11,15] The process C can also be studied using temperature recordings in relation to hormone release and polygraphy to measure brain, muscle, and heart activities.

## *Ultradian rhythm*

Under the 24-hour process C of sleep and wakefulness, sleep onset and maintenance are governed by an ultradian cycle of three to five periods in which the brain, muscles, and autonomic cardiac and respiratory activities fluctuate (Figs 1-2 and 1-3). These cycles consist of rapid eye movement (REM) sleep (active stage) and non-REM sleep (light and deep stages). The REM stage is known as *paradoxical sleep* in Europe.

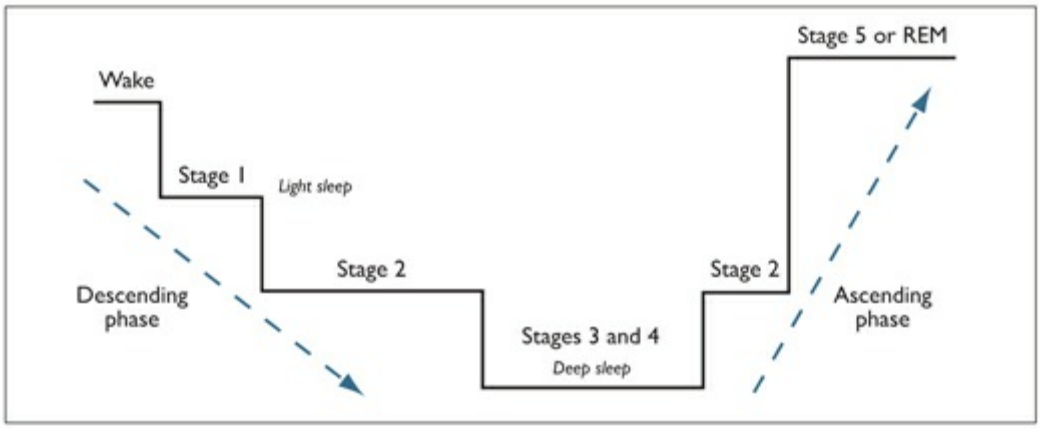


**Fig 1-2** One non-REM-to-REM cycle of consecutive sleep stages. This cycle is repeated every 70 to 110 minutes for a total of three to five non-REM-to-REM cycles per sleep period.

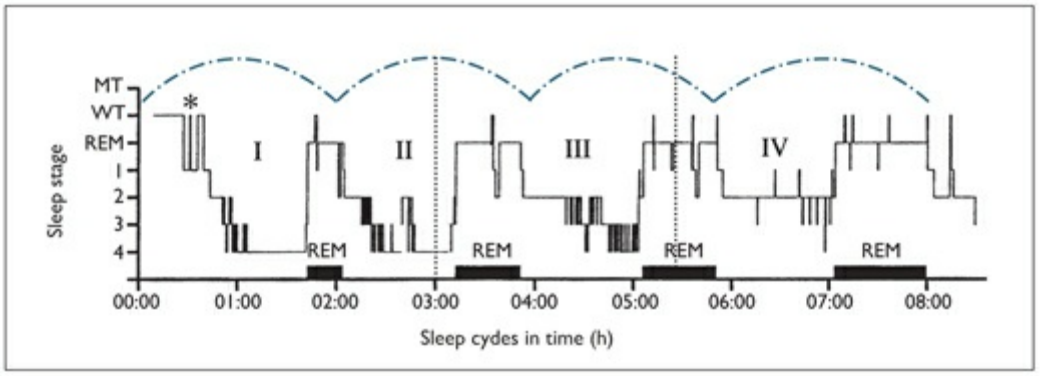


**Fig 1-3** Consecutive waves of non-REM-to-REM (solid horizontal boxes) sleep cycles (I to IV). During the first third of the night, slow-wave sleep (stages 3 and 4) is dominant. During the last third of the night, the REM stage is longer. (MT) movement time; (WT) wake time. (Adapted from Lavigne et al[16] with permission.)

In humans, a clear decline in electrical brain and muscle activities as well as heart rhythm is observed from wakefulness to sleep onset. This decline is associated with a synchronization of brain waves toward stage 1 sleep. Stage 1 is a transitional period between wakefulness and sleep. Stage 2 sleep then begins, accounting for about 50% to 60% of total sleep duration. Stage 2 sleep is characterized by two EEG signals, K-complexes (brief, high-amplitude brain waves) and spindles (rapid, springlike EEG waves), both of which are described as sleep-promoting and sleep-preserving factors. Sleep stages 1 and 2 are categorized as *light sleep*.

Next, sleep enters a quiet period known as *deep sleep*, or stages 3 and 4. These

stages are characterized by slow, high-amplitude brain wave activities. Stages 3 and 4 are usually scored together and are characterized by a dominance of slow-wave activity (delta sleep = 0.5 to 4.5 Hz). This sleep period is associated with a so-called sleep recovery process.

Finally, sleep enters an ascension period and rapidly turns into either light sleep or REM sleep. REM sleep is associated with a reduction in the tone of postural muscles (which is poorly described as "atonia" in literature but is in fact *hypotonia* because muscle tone is never zero) and a rise in heart rate and brain activity to levels that frequently surpass the rates observed during wakefulness. Humans can dream in all stages of sleep, but REM dreams may involve intensely vivid imagery with fantastic and creative content. During REM sleep, the body is typically in a paralyzed-like state (muscle hypotonia). Otherwise, dreams with intense emotional content and motor activity might cause body movements that could injure individuals and their sleep partners.

An understanding of the presence of ultradian sleep cycles is relevant because certain pathologic events occur during sleep, including the following sleep disorders:

- Most periodic body movements (leg or arm) and jaw movements, such as sleep bruxism, are observed in stage 2 sleep and with less frequency in REM sleep.
- Sleep-related breathing events, such as apnea and hypopnea (cessation or reduction of breathing), are observed in stage 2 and REM sleep.
- Acted dreams with risk of body injury, diagnosed as the sleep movement disorder REM behavior disorder, occur during REM sleep (see chapter 3).

## Sleep Recordings and Sleep Arousal

When a polygraphic sleep record of a sleeping patient (collected either at home with an ambulatory system or in a sleep laboratory) is assessed, the scoring of sleep fragmentation is a key element in assessing sleep quality. Poor sleep quality, as reported subjectively by the patient, is associated with frequent arousals, with or without body movements, frequent stage shifts (from a deeper to a lighter sleep stage), respiratory disturbances, and higher muscle tone. All these signs of sleep fragmentation interrupt the continuity of sleep and alter the sleep architecture.

Sleep efficiency is another important variable to evaluate through sleep

recordings. A standard index of sleep impairment, sleep efficiency is defined as the amount of time asleep divided by the amount of time spent in bed, expressed as a percentage. Sleep efficiency greater than 90% is an indicator of good sleep.

The ultradian cycle of sleep, described previously, includes another repetitive activity: sleep-related arousals. During non-REM sleep, arousals are recurrent (6 to 14 times per hour of sleep), involving brief (3 to 10 seconds) awakenings associated with increased brain, muscle, and heart activities (tachycardia, or rapid heart rate) in the absence of the return of consciousness.[17–19] In the presence of sleep movements, breathing disorders, or chronic pain, these arousals are more frequent. Sleep arousals can be viewed as the body's attempt to prepare the sleeping individual (who is in a low-vigilance state) to react to a potential risk, ie, a fight-or-flight state.

Sleep arousals are concomitant with or precede most periodic limb movements and sleep bruxism (described in section III). In contrast, sleep apnea and hypopnea (described in section II) are respiratory distress–like events that trigger sleep arousals. An index of motor events (leg or oromotor), respiratory disturbances, and frequency of shifts in sleep stage can be calculated to assess the presence of periodic limb movements, bruxism, snoring, and sleep-related apnea and hypopnea (see chapter 3 and sections II to IV for more information).

In addition to these methods to assess sleep fragmentation, the cyclic alternating pattern (CAP) can be used to evaluate the instability of sleep. CAP is an infraslow oscillation, with a periodicity of 20 to 40 seconds, between the sleep maintenance system and the arousal pressure involved in the dynamic organization of non-REM sleep and the activation of motor events. CAP is the estimate of the dominance of active phasic arousal periods, that is, the rise in heart rate, muscle tone, and EEG activities (phase A), over more stable and quiet sleep periods (phase B).[19–21] The active phase is subclassified as A1, a period that promotes sleep onset and maintenance; A2, a transition phase; and A3, the final phase, or the arousal window, involving a marked increase in muscle tone and cardiorespiratory rate. Most sleep bruxism events are scored in phase A3 (see chapter 15).

People appear to have individual levels of tolerance for sleep fragmentation. These levels may be genetically determined. Nevertheless, recurrent sleep deprivation or fragmentation produces a cumulative sleep debt, which in turn is likely to increase complaints of fatigue, memory and mood dysfunction, and bodily pain. The cause-and-effect relationship remains to be confirmed.

## Developmental Changes in Sleep-Wake Patterns

The human sleep-wake pattern changes with biologic maturation and aging. In the first 6 weeks of life, human infants mainly present a specific sleep stage, REM sleep, which occupies about 50% of their sleep time. Around age 6 to 9 months, their wakefulness and nighttime sleep pattern tends to become more synchronized with their parents' feeding and sleeping schedule.[22] Preschool children sleep about 14 hours per 24-hour cycle, and most stop napping somewhere between the ages of 3 and 5 years.

Pre-adolescents are sleep-wake phase advanced. They fall asleep earlier and awaken earlier than middle-aged adults. At the age of 16 years, teenagers tend to sleep about 9 hours per 24 hours (ranging from 6.5 to 9.5 hours). Teenagers tend to be phase delayed. They fall asleep and awaken later than their parents and younger siblings.

Most adults sleep about 6 to 7 hours on work days and more on the weekends. By about the age of 40 years, adults' sleep starts to become more fragile, and individuals are more aware of being awake for a few seconds to a few minutes a night. In the elderly, the sleep-wake pattern returns to a multiphase pattern typical of young children. Elderly people go to sleep earlier than middle-aged adults and awaken earlier in the morning, taking occasional naps (catnapping) during the day.

The human biologic clock can adapt to sleep deprivation and changes in the sleep-wake schedule within certain limits. For example, some people can adapt better than others to jet lag or sleep deprivation because of night work, but most individuals find such variations difficult.

The relevance of this information for dental clinicians is evident. Treating certain patients early in the morning (teenagers tend to sleep until 11 AM) is not always a rewarding experience. Similarly, treating patients at their usual nap time can be challenging because the patient may experience more discomfort and express more complaints. Moreover, pain sensitivity may increase toward the end of the afternoon and evening.[23,24] Therefore, it may be advisable to schedule an intervention at a time when the person is more alert, responsive, and cooperative and has a higher pain threshold.

## Conclusion

Good-quality sleep allows humans a means of physical recovery, biochemical refreshment, memory consolidation, and emotional regulation. The diagnosis, prevention, and management of disorders that interfere with the quality of sleep are currently domains of high impact in public health. Dentists should work with other health professionals to improve sleep disorder management for their patients. Strategies to improve the efficacy of the sleep-wake process, such as light exposure, exercise, general sleep hygiene, a relaxing situation, and use of medications, are described in the following chapters.

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# CHAPTER 2

# SLEEP NEUROBIOLOGY

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Sleep is the state during which the organism restores energy that has been exhausted during daily activity. This resting function, which was known since ancient times, has also been believed to extend to the brain, the structure that is the prime controlling organ of states of vigilance. However, numerous results of recent research have converged to emphasize that, in contrast to this long-held belief, the sleeping brain is the host of numerous and complex activities that are, at least partially, at odds with the cerebral activity during wakefulness.

Humans spend between 23% (older adults) and 67% (infants) of their time in sleep. This state encompasses two major and distinct states: the so-called slow-wave sleep, also known as *non–rapid eye movement (non-REM)* or *quiet sleep*, and paradoxical sleep, also known as *rapid eye movement (REM)* or *active sleep* (see chapter 1). Although most sleep states can produce dreams, REM dreams are associated with more active and fantastic content.

Sleep can be defined by means of behavioral criteria, such as reduced mobility and responsiveness to external stimuli, closed eyes, characteristic posture, and reversible unconsciousness, as well as electrophysiologic parameters. These parameters, including electrical activity of the brain, muscle activity, and ocular movements, are demonstrated on polygraphic recordings of electroencephalograms (EEGs), electromyograms (EMGs), and electrooculograms (EOGs), respectively.

Several basic questions concerning sleep have always been asked:

- Which key structures are responsible for the genesis of sleep and for the switching among various vigilance states?
- What cellular processes occur during sleep?

• Why is sleep necessary?

As will be shown in this chapter, some of these questions have been answered, some are still under debate, and others are unresolved.

## Structures Involved in the Genesis of Sleep

At the beginning of the 20th century, as a result of clinical reports and experimental investigations, it became clear that several structures lying deep in the brain are involved in modulating states of vigilance. Patients of von Economo (1916) with lesions in the brainstem showed either pathologic lethargic encephalitis or poor sleep quality. Several years later (1935), the Belgian neurophysiologist, Frédéric Bremer, demonstrated that the cerveau isolé preparation (collicular transection) is comatose, displaying an EEG pattern similar to that of sleep. By contrast, the midpontine pre-trigeminal preparation, realized by Moruzzi and his colleagues (1958) by means of a transection only a few millimeters behind the collicular cut, displayed persistent EEG and ocular signs of alertness. The unavoidable conclusion was that a small territory at the mesopontine junction, between the levels of collicular and midpontine transections, contains the structures involved in maintaining wakefulness.

Years later came the demonstration that this brainstem structure basically contains two nuclei (pedunculopontine tegmental and laterodorsal tegmental nuclei) with cholinergic neurons, whose projections extend toward the thalamus and are further relayed by wide-range projecting axons everywhere to the cortex.[1] Figure 2-1 depicts this area of the brain and the ascending brainstem-thalamocortical activating system during wakefulness. These neurons present high levels of activity during wakefulness and drastically diminish their activity in anticipation of sleep onset.

The cholinergic (ie, acetylcholine-related) activating system of the brainstem has two targets in the thalamus:

1. It stimulates the activity of the thalamocortical neurons, also called *relay neurons*, which generally relay sensory information of various modalities toward the cortex. They release glutamate.
2. It inhibits the reticular neurons of the thalamus, which receive glutamatergic projections from the cortex and project themselves onto the relay neurons of the

thalamus. By releasing γ-aminobutyric acid (GABA), they have an inhibitory action on thalamocortical cells.

During wakefulness, by exciting thalamocortical elements and at the same time inhibiting reticular neurons, cholinergic projections from the brainstem ensure a safe and efficient transmission of sensory information from the periphery to the cortex. In contrast, the silenced activity of the brainstem's cholinergic nuclei during sleep diminishes the tonus of thalamocortical neurons and, at the same time, disinhibits thalamic reticular cells, resulting in further inhibition of the relaying function of thalamocortical elements. The final result is a functional blockage of sensory information (eg, sounds) through the thalamus and deafferentation (ie, isolation) of the cortex from the rest of the nervous system.

Interestingly, some thalamic nuclei (especially midline and intralaminar nuclei) also serve as activating structures to the cortex. This is possible because of the widespread excitatory glutamatergic projections of these nuclei toward the cortex.

Another activating system (see Fig 2-1) also originates in the brainstem but bypasses the thalamus. It is a less specific pathway originating in various monoaminergic nuclei, each of them releasing a particular neurotransmitter. For example, the locus coeruleus (noradrenergic), raphe (serotonergic), and tuberomamillary (histaminergic) nuclei all contribute to the maintenance of and increases in cortical activation during wakefulness and allow onset of sleep when inhibited. Additionally, neurons in the lateral hypothalamus, which release melatonin-concentrating hormone and orexin, and cholinergic neurons of the basal forebrain further increase vigilance and the cortical tonus during wakefulness.[2] Cholinergic neurons of the basal forebrain are the only source of acetylcholine in the cortex.

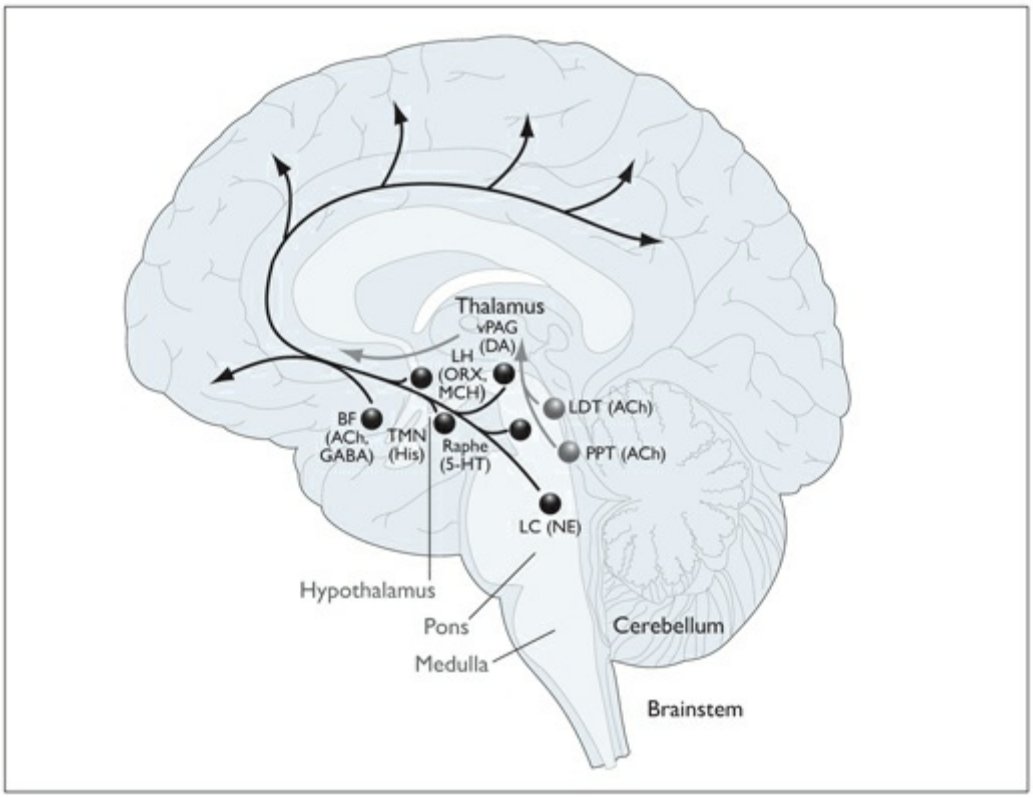


**Fig 2-1** Key components of the ascending arousal system. The cholinergic (ACh) activating system of the brainstem includes the pedunculopontine tegmental (PPT) and laterodorsal tegmental (LDT) nuclei. A second system activates the cerebral cortex directly and arises from neurons in the monoaminergic cell groups, such as the tuberomammillary nucleus (TMN), containing histamine (His); the A10 cell group, containing dopamine (DA); the dorsal and median raphe nuclei, containing serotonin (5-HT); and the locus coeruleus (LC), containing norepinephrine (NE). This pathway also receives contributions from peptidergic neurons in the lateral hypothalamus (LH), containing orexin (ORX) or melanin-concentrating hormone (MCH), and from basal forebrain (BF) neurons that contain GABA or ACh. During sleep, the activity of the two activating systems is reduced, allowing the progressive deafferentation (isolation) of the cortex from incoming sensory stimuli. In addition, the predominant oscillatory activity of the thalamocortical circuits adds to the gating of ascending information. (VPAG) ventrolateral periaqueductal gray matter. Adapted from Saper et al[2] with permission.

Slow-wave sleep (dominant in non-REM sleep and more specifically in deep sleep stages 3 and 4; see chapter 1) and REM sleep are associated with reduced presence of monoamines in the brain, while the release of acetylcholine is inhibited

only during slow-wave sleep, rising during REM sleep to levels comparable with those in wakefulness.

An important question emerges: What produces sleep? Awareness of the aforementioned structures may facilitate an understanding of the two major lines of thinking. The first thesis (also called *passive theory*) proposes that sleep results from a gradual deafferentation resulting from the voluntary withdrawal of sensory bombardment when the subject seeks a favorable environment for sleeping. The second concept (also called *active theory*) points to the ventrolateral preoptic nucleus (VLPO) as a common inhibitory input (it releases GABA) to all major nuclei in the hypothalamus and brainstem that participate in activating the brain.[3] Moreover, VLPO neurons are active during sleep, exerting a constant inhibitory pressure on the aforementioned structures.

During wakefulness the activity of the VLPO is kept at a low level by monoaminergic projections from the raphe and locus coeruleus nuclei and by GABAergic projections from the tuberomamillary nucleus. The transitions between sleep and wakefulness are therefore proposed to rely on a flip-flop switch model (Fig 2-2). During wakefulness, the monoaminergic nuclei inhibit the VLPO nucleus, thereby withdrawing the inhibition of monoaminergic, cholinergic, and orexin-containing neurons. In contrast, during sleep, the increased activity of VLPO cells inhibits the monoaminergic cell groups, thereby relieving their own inhibition and further inhibiting orexin neurons. The mutual inhibition between the VLPO and the monoaminergic cells would produce unstable transitions. The system is most likely stabilized by the orexin neurons during both sleep and wakefulness.[2]

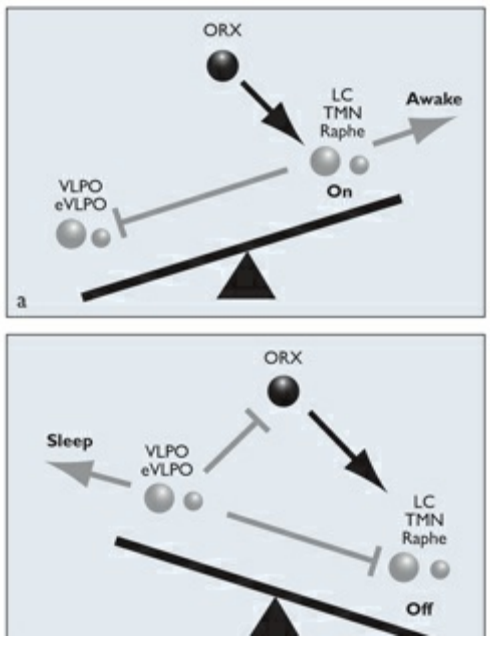


**Fig 2-2** Flip-flop switch model. *(a)* During wakefulness, the monoaminergic nuclei inhibit the VLPO, thereby relieving the inhibition of the monoaminergic cells and that of the orexin (ORX) neurons. Because the VLPO neurons do not have orexin receptors, the orexin neurons serve primarily to reinforce the monoaminergic tone, rather than directly inhibiting the VLPO on their own. *(b)* During sleep, the firing of the VLPO neurons inhibits the monoaminergic cell groups, thereby relieving their own inhibition. This also allows them to inhibit the orexin neurons, further preventing monoaminergic activation that might interrupt sleep. (eVLPO) extended ventrolateral preoptic nucleus; (LC) locus ceruleus; (TMN) tuberomammillary nucleus. (Adapted from Saper et al[2] with permission.)

## Sleep Homeostasis and Circadian Regulation

Like many other vital functions of the organism, sleep is highly regulated. At least two separate mechanisms have been suggested (see chapter 1): One depends on sleep pressure (process S) and the other on circadian rhythms (process C).[4] Sleep deprivation is followed by rebounding intensity in achieving sleep. This homeostatic mechanism suggests the existence of a physiologic indicator that would measure the need for sleep. Adenosine, as a metabolite but also as a neurotransmitter closely related to the levels of vigilance, has been proposed to fulfill this role. (The stimulating effect of caffeine is described to counteract the natural mechanism of adenosine.) Indeed, during wakefulness adenosine triphosphate is continuously degraded to adenosine diphosphate and further to adenosine, which accumulates in regions of the brain, such as the basal forebrain. Then, it has been shown, adenosine promotes sleep by a series of specific presynaptic and postsynaptic mechanisms.[5]

The circadian regulation of sleep critically depends on the oscillatory behavior of suprachiasmatic neurons (see chapter 1). This oscillation, which has a period of 24 hours, is reset by light cues arising from the retina during the day and by the levels of melatonin secreted by the pineal gland during the night. The activity of the suprachiasmatic nucleus is relayed by the dorsomedial nucleus of the hypothalamus to reach the VLPO nucleus and orexin neurons in the lateral hypothalamus. The VLPO projection is inhibitory, thus promoting wakefulness when activated, while the hypothalamus is excitatory (mainly glutamatergic), therefore enhancing wakefulness as well, by boosting orexin neurons.

# Electrophysiologic Correlates of Sleep

The modulatory activity of the brainstem, basal forebrain, and hypothalamic structures creates the environmental framework in which thalamocortical and limbic circuits alternate between conscious and unconscious states. These are accompanied by clear and distinct patterns of cellular activities that are ultimately translated into the global electrical activity of the brain.

Although the EEG patterns of activity during different vigilance states have been well identified for decades, their underlying cellular mechanisms have been disclosed only recently. However, these discoveries have been based, in most cases, on experimental procedures that employed anesthesia as a model of sleep. This has enabled important progress but also continues to be a limiting factor and a source of debate in the interpretation of the results.

## *Wakefulness*

Early EEG recordings immediately following the manufacture of the first EEG machine (1929) have described most of the waveforms and oscillations and their association with vigilance states. It was established that the main electrographic feature of wakefulness consists of irregular, fast (generally greater than 15 Hz, termed *beta* and *gamma*), and low-amplitude (less than 20 μV) waves (Fig 2-3). A continuous muscular tonus ensures rich EMG signals, occasionally superimposed with large deflections induced by active movements. Relaxed wakefulness with closed eyes is dominated in most subjects by the presence of continuous alpha oscillations (around 10 Hz) of increased amplitude (around 50 μV). This rhythm is abolished when the eyes are opened and is replaced with normal patterns of wakefulness.

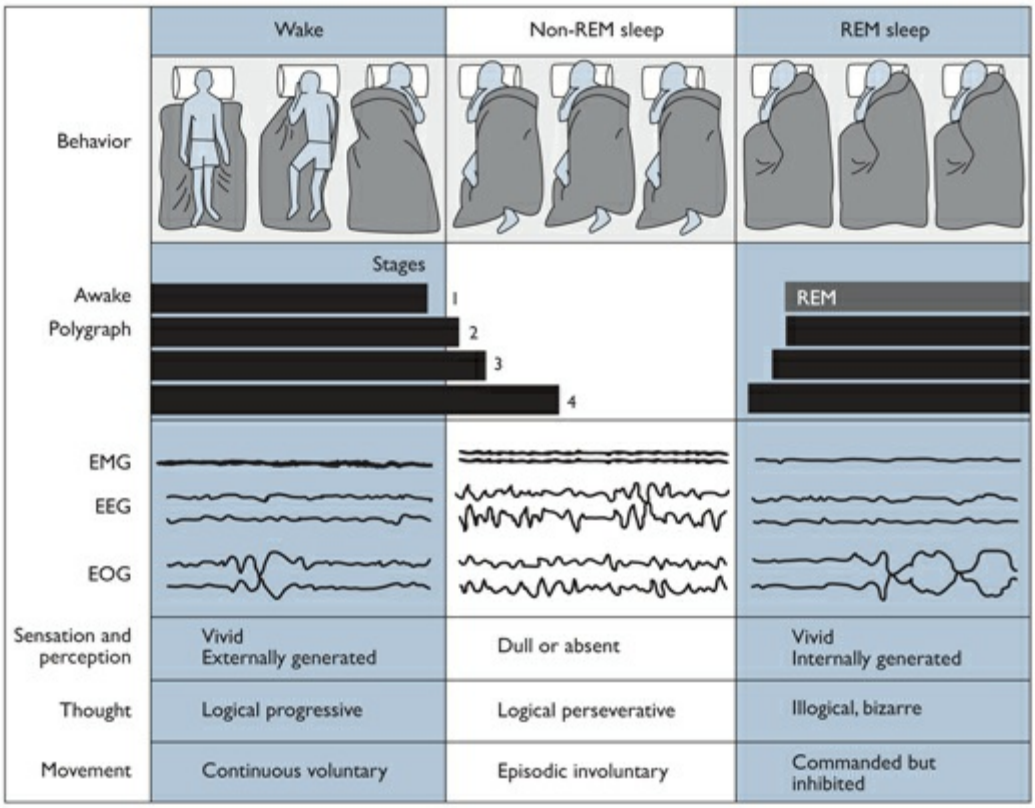


**Fig 2-3** States of waking, non-REM sleep, and REM sleep and their associated behavioral, polygraphic, and psychologic manifestations. In the row labeled *behavior*, changes in position can occur during waking and in concert with phase changes of the sleep cycle. Two different mechanisms account for sleep immobility: disfacilitation (during stages 1 through 4 of non-REM sleep) and inhibition (during REM sleep). During dreams, sleepers imagine that they move but do not. Sample tracings of three variables used to distinguish the state are shown: an electromyogram (EMG), an electroencephalogram (EEG), and an electrooculogram (EOG). The EMG tracings are highest during waking, intermediate during non-REM sleep, and lowest during REM sleep. The EEG and EOG are both activated during waking and inactivated during non-REM sleep. Each tracing sample shown is approximately 20 seconds long. The three bottom rows describe other subjective and objective state variables. (Adapted from Hobson[6] with permission.)

## *Sleep*

Rechtschaffen and Kales[7] introduced a standardization of human sleep that divides it into five distinct stages, the first four belonging to slow-wave (non-REM) sleep and

the last one being REM sleep. Quiet sleep is generally identified with slower EEG waves of larger amplitude.

The progression from stage 1 to REM sleep constitutes a sleep cycle. The duration of a sleep cycle is about 90 minutes, and the first cycles are shorter than the last ones. There are in general four to six sleep cycles during a night, depending on the total sleep time. The first two cycles are generally complete with successive attendance in all sleep stages. During the later cycles the contribution of stages 3 and 4 diminishes gradually, and sleep bounces between stage 2 and REM sleep. The REM episodes are generally short (5 minutes) in the early cycles but can attain 1 hour during the last cycle.

**Non-REM sleep**

Sleep begins with stage 1, which is a transitory epoch of about 1 to 10 minutes, characterized by a slight increase in the EEG amplitude and appearance of scattered triangular waveforms called *vertex waves* (they are most evident in the vertex leads).

Deepening of non-REM sleep toward stage 2 is announced by increased amplitude of the EEG. Vertex waves increase in amplitude and are termed *K-complexes*. They are quasi rhythmic and are often accompanied by sleep spindles (also termed *sigma waves*; generally 10 to 14 Hz).

Stage 3 is generally equivalent to the beginning of deep sleep. Between 20% and 30% of the EEG activity consists of high-amplitude (greater than 50 μV) slow waves (less than 4 Hz, termed *delta waves*). It has been proposed that vertex waves, K-complexes, and delta waves are part of a continuous evolution of slow oscillatory patterns in the sleeping brain (discussed in the next section).[8]

Sleep stage 4 is recognized when more than 50% of the EEG activity is spent in delta waves. The amplitude of the waves reaches the highest values (around 100 μV). During non-REM sleep the muscular tone, although somewhat diminished, remains present in the EMG. Ocular and axial muscular movements are virtually absent, with the exception of occasional postural adjustments. In clinical recordings, stages 3 and 4 are usually reported as one sleep state.

**Transition to REM sleep**

Stage 4 is ended by a return to lighter sleep (stages 3 and 2) and subsequent entrance into REM sleep. REM sleep and wakefulness are difficult to tell apart based only on

EEG criteria (see Fig 2-3). However, two major features are specific for REM sleep: *(1)* axial muscular hypotonia, reflected by very low EMG activity,[9] and *(2)* rapid eye saccades that trigger large deflections in the EOG. It is generally accepted that these REMs betray the tracking of imaginary targets during active and more fantastic dreaming.[8] It is also known that awakening of a subject during or immediately after REM sleep may yield recollection of a dream, while this is not the case if awakening is imposed during non-REM sleep. There are, however, reports of dreaming with a more stoic—life-related, less creative—content during slow-wave sleep.[10]

## Cellular Activities During Sleep

All the previously described patterns of EEG activity are generated within cerebral circuits of neurons and glial cells. Recent studies have emphasized that, contrary to previous beliefs, glial cells (especially astrocytes and oligodendrocytes) assume an active role in the dialogue with neurons during the genesis of oscillatory patterns.[11] Moreover, although sleep activity results from complex interactions among various cerebral structures, cortical as well as subcortical, it is generally accepted that the EEG mainly reflects electrical potentials that are expressed by cortical neurons. Subcortical potentials thus make negligible contributions to the EEG.

In some particular situations that go beyond the scope of the present chapter, the blood-brain barrier may also play a role in generating EEG potentials. These need special techniques of recording, however, which are not yet implemented in the clinical routine.

The main cellular correlate of sleep is the functional deafferentation of the thalamocortical circuit as a result of the reduced activity of activating systems, described earlier. The removal of these tonic inputs to the thalamic and cortical neurons creates a favorable condition for the development of stereotyped and synchronized oscillations.[10]

Cortical neurons and glial cells generate a slow oscillatory activity with a frequency of around 1 Hz, within the frequency range of delta activity. It has to be emphasized that the oscillatory frequency of this phenomenon is not a magical figure with a precise value but instead a dynamic phenomenon under the modulation of intrinsic and network properties. During the initial phases of sleep, the slow oscillation is less organized and synchronous, resulting in EEG waves of lower

amplitude and irregular patterns. As sleep deepens (stages 3 and 4), the high synchronicity of this oscillation ensures its presence in virtually all cortical areas and, at the same time, its strong commanding input to other subcortical structures, including the thalamus. Moreover, changes in neurotransmitter release modify the membrane properties of neurons with the direct consequence of changing the shape of the associated EEG waveforms and thus increasing the contribution to delta activities.

In addition, by playing the role of a master oscillator, the slow oscillation periodically triggers other sleep oscillations, such as spindles. Spindle activity is generated in the reticular nucleus of the thalamus once its neurons are relieved from the inhibitory cholinergic drive of brainstem neurons. The periodic excitatory corticothalamic projections sporadically trigger thalamic spindles, which will borrow the returning thalamocortical pathway to regain the cortex. This is a typical example of coalescing sleep rhythms that generate complex EEG patterns.

Interestingly, the slow cortical oscillation also constitutes one of the triggering factors of epileptic seizures of the spike-wave type during sleep. Both slow sleep oscillations and paroxysmal discharges share common networks (the cortex) and mechanisms of synchronization. A slight impairment of the inhibitory control may transform the already synchronous sleep oscillation into hypersynchronous epileptic seizures.[12]

## Functional Role of Sleep

Despite improved understanding of the mechanisms of sleep, the question of why humans sleep remains unanswered (see chapter 1). Life without sleep is impossible, as demonstrated by the outcome of fatal familial insomnia, which is a familial prion disease that starts with impairment of attention and vigilance and results in memory deficits, impairment of temporal ordering of events, a confusional state, and ultimately death.[13]

Sleep is a state during which cerebral networks maintain sustained activity. It may be argued that the orderly pattern of oscillations (and thus decreased entropy) reduces metabolic demands. This is partially confirmed by a relatively low (15%) decrease in the energetic consumption during sleep. Blood flow is reduced in non-REM sleep and rises again during REM sleep.[14,15] Furthermore, sleep might be useful in slowing the production of free radicals, thus reducing oxidative stress. A

recent theory endows sleep with the property of enhancing synaptic plasticity for the sake of memory and learning processes. A recent alternative view proposes that sleep is meant to save energy and regulate the synaptic overload undergone during the previous waking period.[16]

The fact that neonates sleep significantly longer than adults might suggest that sleep is important in growth and development. This idea has received support from experiments in which adult neurogenesis was dramatically reduced after sleep deprivation and may explain why human cognitive performance is impaired by lack of sleep. Increased levels of bacteria in blood after sleep deprivation further suggests diminished immune function, emphasizing the role of sleep in helping to fight or prevent illness.[17,18]

## Conclusion

Although the biologic purpose of sleep is still not fully known, research has shown that the sleeping brain is the host of numerous and complex activities. Sleep can be defined by electrophysiologic parameters such as electrical activity of the brain, muscle activity, and ocular movements. Polygraphic and intracellular recordings of these activities have helped to determine some of the structures responsible for the genesis of sleep and the fluctuation among various vigilance states.

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CHAPTER 3

# CLASSIFICATION OF SLEEP DISORDERS

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This chapter aims to help dentists faced with the difficult process of using the current classifications of sleep medicine to recognize a sleep disorder. A better understanding of the differential diagnosis of sleep disorders is essential for dentists involved in the management of snoring, sleep apnea, sleep bruxism, and orofacial pain conditions that intrude on sleep periods.

## Differential Diagnosis of Sleep Disorders

Many health care professionals are involved in the diagnosis and treatment of sleep disorders. Physicians bear the responsibility of diagnosing sleep-disordered breathing, insomnia, and sleep movement disorders. Dentists collaborate with physicians in recognizing various sleep disorders and in managing snoring and sleep-disordered breathing with oral appliances. Psychologists and other health care professionals also make valuable contributions to the management of insomnia, sleep rhythm–related problems, and other sleep disorders. These problems are frequently concomitant in patients with chronic pain and sleep-disordered breathing. Respiratory therapists and sleep technicians assist the patient in the selection of the best positive airway pressure device and the most appropriate mask interface (nasal or oronasal) for treatment of sleep apnea-hypopnea syndrome.

The areas of expertise of dentists in sleep medicine include clinical assessments (Box 3-1), differential diagnosis, and referral of patients to the appropriate specialists and sleep medicine laboratories for final diagnosis. After a diagnosis has been made, dentists offer sleep hygiene advice; provide oral appliances (eg, occlusal splints or mandibular advancement appliances); perform or refer patients for orthodontic treatment or maxillofacial surgery; manage comorbid orofacial problems (eg, bruxism, orofacial pain, sleep-related xerostomia); and refer patients for sleep laboratory follow-up to monitor the safety and efficacy of oral appliances.

**Box 3-1 Elements of the medical and social history and clinical examination to include in the patient's medical record**

**History**

- Symptoms related to insomnia:
  - Sleep duration (when the patient goes to sleep and when the patient awakens)
  - Number of awakenings
  - Trouble falling or staying asleep (number of nights per week)
  - Number of times the patient gets up in the night to go to the bathroom
  - Use of medication or alcohol to fall asleep
  - Use of pain or anxiety-related medication
- Symptoms related to sleep-disordered breathing:
  - Snoring
  - Cessation of breathing
  - Choking
  - Awakening gasping for breath
  - Tendency to fall asleep during the daytime (Epworth sleepiness scale [see figure 7-1])
  - History of hypertension and other cardiovascular disorders (eg, ischemic heart disease, stroke, night sweating, loss of memory, morning headache, difficulty concentrating)
  - Nocturia/enuresis
- Symptoms related to movement disorders:

- Tooth grinding sounds during sleep (sleep bruxism)
- Tooth tapping (faciomandibular myoclonus or sleep-related epilepsy)
- Leg or arm movement during sleep, with or without injuries (periodic limb movement, REM behavior disorder)
- Body rocking or head banging

• Other symptoms:
- Eating during the sleep period (may exacerbate insomnia or sleep-disordered breathing)

**Clinical examination**

• Weight, height, and body mass index
• Neck circumference (at risk if greater than 41cm [women] or 43 cm [men])
• Retrognathia (Class II)
• Deep palate
• Narrow dental arches
• Tongue size (macroglossia)
• Tongue indentation (tongue thrusting habit or tic)
• Adenoids and tonsil size
• Oropharyngeal size, viewed through the mouth (Mallampati classification)
• Nose shape (narrowing) and obstruction
• Usual body position (supine is a risk factor for respiratory disorders and bruxism)
• Tooth wear or damage or use of oral splint (bruxism or orofacial pain)
• Absence of tooth or protrusive mandibular movement (precludes use of oral appliance to treat sleep-disordered breathing)

Many sleep disorders can be concomitant. At least one-third of patients with bruxism in the general population may also have sleep-disordered breathing conditions such as sleep apnea, periodic limb movements during sleep, and headache.[1,2] Emerging data also suggest that rates of obstructive sleep apnea may be elevated (approximately 30%) in patients with temporomandibular disorders (TMDs) (unpublished data, 2008) and other related idiopathic pain disorders such as fibromyalgia (chronic widespread pain).[3] These data are particularly remarkable

because the traditional demographic and risk factors associated with sleep apnea, including male sex, older age, and high body mass index, are not commonly associated with TMDs, and therefore many practitioners may not refer patients with TMDs for polysomnographic evaluations. In the presence of comorbidities, dentists are advised to request a consultation with sleep medicine experts most likely in a department of respiratory medicine, neurology, psychiatry, or a comprehensive interdisciplinary center. These referrals are even more important if patients report daytime sleepiness or violent motor activity during sleep.

Recently, under the auspices of the American Academy of Sleep Medicine, a task force of experts was brought together to review the literature on sleep disorders available up to 2004. The results were published in 2005, in a revised editon of the *International Classification of Sleep Disorders* (*ICSD-2*).[4] This classification comprises eight sections (Box 3-2). The recognition and scoring criteria of sleep disorders are reviewed later (see section II). A later article by Walters et al[5] summarizes the process and decisions made by the American Academy of Sleep Medicine during development of the classification. The classification and scoring criteria must be considered works in progress because they are mainly drawn from evidence-based literature, and in the absence of strong evidence, the task force members reached a consensus by vote.

**Box 3-2 Sections of the *ICSD-2*[4]**

I. **Insomnia:** Delayed sleep onset or difficulty in sleep maintenance, often precipitated by an acute stressor, medical or psychiatric disorders, or pain (see section IV of this volume); may become chronic because of behavioral factors

II. **Sleep-related breathing disorders:** Sleep apnea-hypopnea; central, obstructive, or both (see text and section II of this volume)

III. **Hypersomnia:** Intense or excessive sleep (eg, narcolepsy or sudden sleep during the wake period, known as *cataplexia*); drug or substance abuse causing prolonged sleep duration

IV. **Circadian rhythm sleep disorders:**Disorders that disrupt the patient's biologic rhythm over the 24 hours of light and dark (eg, delayed or advanced sleep phase: an inability to fall asleep at same time every evening; irregular sleep-wake periods with a sleep duration that is too long

or too short, or several waking periods during the night; jet lag in jetsetters, night workers, and the parents of young children)

V. **Parasomnias:** Disorders that intrude on the sleep period (eg, sleepwalking, somnambulism, sleep terrors, REM behavior disorder, enuresis, groaning [see text for definition])

VI. **Sleep-related movement disorders:** Periodic limb movement (leg kicks or arm movements); sleep bruxism (see text and Box 3-3 and section III of this volume)

VII. **Isolated symptoms:** Snoring; sleep talking; myoclonus (sudden and brief [less than 0.25-second] muscle jerks that can be observed in limbs or in face and jaw muscles with tooth tapping)

VIII. **Other sleep disorders and disorders associated with other conditions (miscellaneous):** Fibromyalgia; headaches; sleep-related epilepsy; gastroesophageal reflux, which may be dominant in the presence of a peptic ulcer, angina, or respiratory effort or link to respiratory disorder; abnormal swallowing and pooling of saliva in the mouth (patient responds by choking and awaking, possibly wetting the pillow); mood and anxiety disorders that prevent sleep onset or continuity; disorders first diagnosed in infancy, childhood, or adolescence such as attention-deficit/hyperactivity disorders; personality disorders (see section IV of this volume)

For the purposes of this chapter, the most relevant sleep disorders found in the *ICSD-2*[4] will be subdivided into the following categories based on the patient's complaint or report:

- Sound-related complaints (eg, snoring, bruxing, or choking; see sections II and III)
- Movement-related conditions (eg, jaw movement with sleep bruxism or tic or limb and body movements; see section III)
- Pain-related conditions (eg, morning jaw pain or headache, neck pain, or fibromyalgia; see section IV)

## Sound-Related Complaints

## *Snoring*

This commonly occurring loud sound is reported by the patient's sleep partner or family. Snoring is generated at the level of the upper airway. It is associated with the vibration of the soft palate and the restriction of air passage with noisy air turbulence. About 40% of men and 24% of women are aware of snoring sounds as reported by a sleep partner. In children, the incidence, based on parents' reports, is about 10%. The prevalence of snoring tends to increase threefold during pregnancy. Patients who snore are reported to be at greater risk of cardiovascular diseases (eg, hypertension), especially if snoring is associated with obstructive sleep apnea (see chapter 6).

These findings lend support to the recommendation that dental patients should attend a medical consultation before receiving an oral appliance for sleep-disordered breathing. Moreover, it has been suggested that about 20% of patients who snore may also suffer from obstructive sleep apnea. A sleep medicine consultation is mandatory for patients who report snoring in conjunction with daytime sleepiness, sleep disruption, or insomnia (see Box 3-2 for definition), hypertension or other cardiovascular conditions, unrefreshing sleep, or consistently impaired concentration. The differential diagnosis of snoring includes obstructive sleep apnea-hypopnea, upper airway resistance, laryn-gospasm, sleep talking, and other oral sounds.

## *Sleep apnea-hypopnea*

An *apnea* is defined as a cessation of breathing for 10 seconds or more. There are two types of apnea: *(1)* obstructive sleep apnea (most common), resulting from the presence of an obstruction in the upper airway; and *(2)* central sleep apnea, demonstrated by the absence of respiratory effort (no chest movements) resulting from reduced signals from the brain to drive inspiration and expiration. Both kinds of apnea can be present simultaneously.

*Hypopnea* is most commonly defined as a decrease in airflow of more than 50% or a decrease in airflow of more than 30% that is associated with oxyhemoglobin desaturation (of greater than 3% or 4%) or an electroencephalographic arousal (sometimes referred to as a *respiratory event–related arousal*). Hypopnea is observed in both light sleep (stage 2) and rapid eye movement (REM) sleep, also called *stage 5 sleep*, *paradoxical sleep*, or *active sleep*.

The severity of sleep apnea is commonly defined as the number of apneas or hypopneas per hour of sleep, graded with the apnea-hypopnea index (AHI): 5 to 15 is considered *mild*; 15 to 30 is considered *moderate*; and more than 30 is considered *severe*. Sleep apnea-hypopnea syndrome is defined as an AHI of 5 or more per hour of sleep and either excessive daytime sleepiness (as rated by questionnaires such as the Epworth sleepiness scale) or at least two of the following symptoms: choking, re-current awakenings from sleep, unrefreshing sleep, daytime fatigue, or impaired concentration.

According to a large cohort study (the Wisconsin Sleep Cohort study), the prevalence of an AHI greater than 5 per hour among people aged 30 to 60 years old is 24% for men and 9% for women. Within this population, sleep apnea syndrome is found in 4% of middle-aged men and 2% of middle-aged women.[6] When the rising prevalence of obesity is considered, updated estimates suggest that 17% of adults have at least mild obstructive sleep apnea (AHI of 5 or more per hour) and 5.7% have at least moderate obstructive sleep apnea (AHI of 15 or more per hour).[7]

Patients with untreated sleep apnea may have a sevenfold greater risk of car accidents than do matched controls.[8] Repeated oxyhemoglobin de-saturation (up to 100 drops per hour of sleep) and sudden transient awakenings caused by sleep apnea also induce a significant level of physiologic stress in the patient, which is thought to be responsible for an increased risk of cardiovascular diseases such as stroke, hypertension, or myocardial infarction.

The clinical examination should include notation of the main risk factors for obstructive sleep apnea: obesity, male sex, menopause, nasal obstruction, large tonsils, large tongue base, and narrow upper airway caused by abnormal bone structure such as retrognathia, micrognathia, or high-arched palate (see Box 3-1 and section II of this book). As indicated earlier, however, patients with TMDs, who are predominantly women during child-bearing years, may also be at increased risk for obstructive sleep apnea (unpublished data, 2008). Alcohol consumption and sedatives such as benzodiazepines also contribute to upper airway obstruction by relaxing upper airway dilator muscles. Concomitant medical conditions include acromegaly, hypothyroidism, Down syndrome, rhinitis, nasal congestion, and smoking.

In children, obstructive sleep apnea is usually related to enlarged tonsils and/or adenoids. Moreover, in children, sleep apnea may be associated with an inward movement of the rib cage (paradoxical breathing), enuresis, morning headache, slow growth rate, excessive daytime sleepiness, poor school performance, hyperactivity, or aggressive behavior. In the presence of the above findings, the threshold for

diagnosing sleep apnea in children is low: An AHI of 1 event or more per hour of sleep is considered abnormal.

Considering the life-threatening consequences of sleep apnea, dentists should refer patients suspected of having the syndrome to a sleep laboratory for recordings. Initially, sleep recording (ambulatory or in a sleep laboratory) and differential diagnosis must be performed to rate the severity of the sleep apnea-hypopnea and to exclude hypoventilation syndromes, fatigue, and headache (also found with upper airway resistance) in otherwise healthy people or the Cheyne-Stokes breathing pattern (characterized by a periodic crescendo-decrescendo pattern of respiration, usually occurring in patients with congestive heart failure).

Sleepiness is a key element to investigate in the differential diagnosis. Sleepiness may be secondary to insomnia (see Box 3-1), narcolepsy, or periodic limb movement disorder (eg, leg kicks that may occur more than 10 times per hour of sleep). In rare cases, confusional arousal can be observed with apnea-hypopnea events and may be associated with events mimicking the non-REM (stages 3 and 4 of sleep) parasomnias, such as sleepwalking or sleep terrors, or REM behavior disorder (RBD). RBD is a neurologic disorder characterized by the absence of muscle paralysis during REM sleep and violent movement that can lead to bodily injury; it is described in more detail later in this chapter.

In some patients, gastroesophageal reflux disease (GERD) is concomitant with sleep apnea-hypopnea; it is therefore important to exclude respiratory disorders in those patients who consult their dentist primarily about the problem of tooth damage caused by GERD.

## *Sleep bruxism*

Sleep bruxism (tooth grinding) is a repetitive activity (repeated at least 3 times per episode) in the jaw muscles (rhythm at 1 Hz, of bursts lasting more than 0.5 and up to 2.0 seconds) that generates tooth grinding sounds and occasional jaw clenching (a sustained muscle contraction of more than 2.0 seconds). As is the case with snoring, generally sleep partners are the ones who complain of tooth grinding sounds.

The causes of sleep bruxism are unknown. Anxiety and life stress have both been suggested to be risk factors, but more studies are needed in a general population to confirm this association. Most sleep bruxism events tend to occur in clusters in relation to recurrent arousals (7 to 14 times per hour of sleep) with transient (3.0- to 10.0-second) reactivation of muscle tone, brain, and heart activities during sleep

(see chapter 15). According to the reports of children's parents, awareness of tooth grinding sounds in infants stands at 14% to 18%. Findings based on the reports of sleep partners show that 8% of adults make tooth grinding sounds, a level that drops to 3% in older individuals, although this estimate is less precise because of the presence of dentures and habits of sleeping alone.[9]

The consequences of sleep bruxism may include tooth destruction (tooth wear or restoration destruction), morning headache, jaw pain, and a limited ability to open the mouth due to muscle tension or meniscus displacement.

A dentist's decision to request a sleep laboratory examination may be based on frequent tooth grinding as reported by parents or sleep partners, tooth damage, and orofacial pain or headache in relation to sleep. The diagnosis is confirmed by polygraphic recordings of masseter muscle activity and audio-video recordings. Patients with mild sleep bruxism will exhibit more than two jaw muscle contractions per hour of sleep, and patients with moderate-to-severe sleep bruxism will exhibit more than four such events per hour of sleep.

The differential diagnosis of sleep bruxism must exclude the tooth tapping activity and sounds associated with faciomandibular myoclonus. This disorder causes rapid jaw muscle contractions (of less than 0.25 seconds' duration) and is found in 10% of tooth grinding events. Faciomandibular myoclonus is dominant in REM sleep and, because it may be associated with sleep-related epilepsy or RBD, a full electroencephalographic examination is recommended.[10,11]

Sleep-disordered breathing such as sleep apnea in children or in older individuals also must be verified in the sleep laboratory. Children may exhibit various tics during sleep, including throat grunting, enuresis, and sleep talking, and these also have to be excluded in the diagnostic process. The persistence of wakeful dyskinetic movement (dystonia, tremor, chorea, and dyskinesia) is also possible, but it is rarely concomitant with sleep bruxism.[12]

## *Other conditions*

Some rare but nonetheless important conditions for dentists to recognize are the following:

### Groaning

Also called *catathrenia*, groaning is a rare condition (presented by 0.5% of patients

in a sleep clinic) characterized by oral sounds that are dominant during REM sleep. Most frequently reported in young male subjects, catathrenia is associated with inarticulate phonation during a deep expiration. It may resemble sleep apnea. Again, the patient reports the activity based on the remarks of his or her sleep partner. The patient's medical and psychologic histories are normal.

The cause and pathology of this condition are unknown. The differential diagnosis is first made by an otorhinolaryngologist to exclude airway or glottic dysfunction or obstruction. Sleep apnea-hypopnea syndrome and snoring also must be excluded using the usual diagnostic tools (see chapters 7 and 14).

**Stridor**

*Stridor* is a high-pitched sound that occurs in clusters and has both an inspiratory phase and a long *Stridor* expiratory phase. This condition generally signifies some form of laryngeal obstruction and can be intermittent (eg, laryngospasm), sleep-related, or continuous (eg, partial or complete vocal cord paralysis). Stridor may also be confused with groaning because both conditions occur during REM sleep. Audio-video sleep respiratory recordings are helpful aids for diagnosing this condition.

**Sleep-related laryngospasm**

*Sleep-related laryngospasm* is characterized by abnormal laryngeal muscle activity. Patients report a sense of suffocation and anxiety, resulting in awakenings in response to the interruption of airflow (5 to 45 seconds). The presence of a long-lasting stridor sound makes differential diagnosis difficult because it may be confused with snoring and groaning.

**Hypersalivation and abnormal swallowing and gurgling sounds**

Clinicians will recognize these problems when patients complain of pillow wetting and their sleep partners report related sounds. These conditions may occur in patients with obstructive sleep apnea.

**Sleep talking**

Also called *somniloquy*, such sounds are usually associated with articulate speech with the production of words. Sleep talking should be included in the differential diagnosis of groaning. Sleep talking occurs in 50% of children and only 5% of

adults; it can be observed in all sleep stages. Again, the patient's sleep partner is the key person when it comes to reporting this activity; as is the case for the other oropharyngeal sounds, the patient is usually unaware of making sounds.

When sleep talking is the dominant activity, the patient should be investigated for the presence of groaning sounds, RBD, nocturnal seizures, sleep terrors, and posttraumatic stress disorder. Dentists must be aware that sleep talking, enuresis, and tooth grinding are reported to occur together in children.

**Grunting**

The throat clearing sound is a daytime tic that may persist during sleep.[13] Grunting is easily differentiated from bruxism and other oral sounds through the use of electromyography of jaw and airway muscles with audio-video recordings.

**Sleep suckling and smacking sounds**

The cause of this rare condition is not known. Concomitant sleep bruxism and excessive oropharyngeal dryness (eg, mouth breathing) may occur with this condition.

**Sleep terrors**

Sleep terrors are observed during non-REM deep sleep (stages 3 and 4). Sleep terrors are mainly observed in young patients but are also reported in 3% to 4% of adult patients. This condition is characterized by a sudden awakening accompanied by a piercing scream or cry and incoherent vocalizations. Most patients are confused and rarely report dream content associated with the event. Body injuries can be reported as a result of the motor activity generated in the process. Sleep-disordered breathing, sleep-related epilepsy, and cardiac ischemia must be excluded during the differential diagnosis.

**Nightmares**

Nightmares are much more frequent than sleep terrors and occur in REM sleep. They may be present if posttraumatic stress is part of the patient's history. Because REM sleep is prolonged in the last third of the night and deep sleep is more prominent in the first third of the night, a careful history may assist in establishment of a preliminary differential diagnosis between night terrors or nightmares. Polysomnographic evaluation is necessary to confirm diagnosis.

## Movement-Related Disorders

Movement disorders during sleep can be simple or complex (Box 3-3). The consequences of movement disorders can be minor or they can be associated with neurologic disorders that require a medical evaluation.

**Box 3-3 Types of movement disorders that occur during sleep***

**Simple sleep-related movement disorders**

- Jaw and face: Bruxism, faciomandibular myoclonus (see text)
- Legs: Restless legs syndrome/periodic limb movements in sleep (rare with sleep bruxism, occurring in less than 10% of cases, but may be concomitant with chronic pain); leg cramps (induce pain; increase with age; present in pregnant women); hypnagogic foot tremor/alternating leg muscle activation (can be triggered by antidepressant medications)
- Childhood: Benign sleep myoclonus of infancy (neonatal occurrence; myoclonic jerks of the whole body; full electroencephalographic examination must be used to exclude epilepsy); rhythmic movement disorders (head banging/body rocking; from infancy to childhood; beginning before naps or sleep; child must be protected from bodily injuries)
- Miscellaneous: Excessive fragmentary myoclonus (small movements of fingers, toes, corners of mouths; more frequent in older men); sleep starts (normal for patients to experience a whole-body jerk at sleep onset [prevalence: 70% of population])

**Complex sleep-related movement disorders**

- RBD (parasomnia; see text)
- Disorders of partial arousal (parasomnia; sleepwalking, sleep terrors, confusional arousal)
- Epilepsy during sleep (neurologic condition; must be excluded if the patient reports tooth tapping)

**Movement disorders primarily observed during wakefulness and reduced during sleep**

- Parkinson disease

- Huntington disease
- Myoclonus
- Ataxia
- Dystonia
- Essential tremor
- Tourette syndrome
- Hemiballismus

*Most patients are unaware of their presence before they are told by parents or a sleep partner. (Data taken from Walters.[14])

## *Sleep bruxism*

This condition has been discussed earlier in the chapter.

## *Faciomandibular myoclonus and/or tooth tapping*

This condition has been discussed earlier in the chapter.

## *REM behavior disorder*

This sleep-related movement disorder occurs in the REM sleep period, during which very little movement is usually noted. The patient makes powerful body movements that mimic motor behavior and may be associated with potential bodily injury. The patient's vocalization may be loud with an emotional or profane content in relation to mental activity while dreaming.

Patients suspected of having this condition must be investigated by a neurologist because RBD is associated with an important risk of neurodegenerative disorder (eg, dementia and Parkinson disease).[15] One study has reported that patients with RBD may also present with tooth grinding,[16] and a laboratory sleep investigation of 13 RBD patients supported such an observation.[17]

## *Abnormal swallowing and choking*

It is normal to swallow saliva during sleep but at a lower frequency in comparison to the wakeful state. However, in some patients, an excessive accumulation of saliva can occur, predisposing a patient to choking.[18] The condition may cause patients to become very anxious because of the sensation of suffocation, inability to breathe, and awakening in response to the high heart rate that may result from the condition. In extreme cases, abnormal swallowing may cause death.

Abnormal swallowing during sleep must be differentiated from the transient hypersalivation caused by the recent use of an oral appliance (eg, a mandibular advancement appliance). A neurologic evaluation will exclude motor neuron disease as well as multiple system atrophy that may also modify the function of laryngeal and pharyngeal muscles.

# Pain-Related Conditions

## *Gastroesophageal reflux disease*

Also known as *heartburn*, GERD is characterized by the regurgitation of stomach contents into the esophagus and mouth. These events are common during sleep because the supine position facilitates regurgitation. The patientmay also produce wheezing-gasping sounds in addition to coughing and choking. During sleep, GERD can trigger painful sensations and awakening. GERD may mimic chest pain. It is reported that 7% to 10% of the population may suffer from GERD during waking hours, but the sleep-related prevalence is unknown.

A medical investigation of patients reporting this complaint is recommended. The differential diagnosis includes a peptic ulcer, angina, or respiratory effort linked to respiratory disorder as well as the condition known as *Barrett esophagus* (a possible precursor of adenocarcinoma). Investigators may find pH monitoring with a nasoesophageal probe a useful tool to confirm the diagnosis during sleep.

## *Fibromyalgia*

Fibromyalgia (also called *widespread pain*) is a clinical constellation of chronic symptoms that includes pain, poor sleep, headache, anxiety, and mood alteration. It is reported that more than 80% of patients with fibromyalgia may also suffer from

poor sleep quality (also reported as a sensation of unrefreshing sleep) and TMDs or pain.[19,20]

The sleep-related brain activity termed *alpha-delta sleep* is no longer considered a pathognomonic finding in these patients.[21,22] Clinicians making a differential diagnosis in these patients must exclude periodic limb movement during sleep and sleep-disordered breathing.[22,23]

## *Headaches*

When a patient reports temporal or tension-type headaches on awakening, the dentist must assess for sleep-disordered breathing or sleep bruxism because these are frequently related complaints. Dentists should gather the patient's and the sleep partner's reports of snoring, cessation of breathing, and sleepiness by using the Epworth sleepiness scale questionnaire.

Migraine attacks can also be reported during the sleep period because about half of such attacks are reported to occur between 4 and 9 AM. Migraine attacks mainly occur in relation to REM sleep, although they sometimes occur during deep sleep (stages 3 and 4). Patients may also report the occurrence of cluster headaches during REM sleep; such headaches are unilateral periocular or temporal in nature and accompanied by autonomic reaction. A rare form of sleep-related headache is the hypnic headache, which occurs at sleep onset. The hypnic headache is mainly found in older patients and tends to be bilateral.[24]

## *Tooth tapping and sensory complaints*

Tooth tapping, when present in conjunction with head (faciomandibular) jerks, may be associated with sleep-related epilepsy. The patient's sensory complaints will include tooth sensitivity to hot or cold, cervical pain, and orofacial pain. Sleep recordings with audio and video are required to exclude the diagnosis of sleep-related epilepsy.

# Conclusion

Dentists, in collaboration with physicians, can apply their expertise to recognize

various sleep disorders and to manage snoring, sleep-disordered breathing, sleep bruxism, and sleep-related orofacial pain. Current classifications of sleep disorders provide a better understanding of the differential diagnosis of sleep disorders and serve as guidelines for clinical practice.

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# SECTION II

## SLEEP BREATHING DISORDERS

CHAPTER 4

# SLEEP-RELATED BREATHING DISORDERS

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Sleep-related breathing disorders are a group of disorders characterized by abnormalities of respiration during sleep. The second edition of the *International Classification of Sleep Disorders, (ICSD-2)*[1] classifies sleep-related breathing disorders into five major categories (Box 4-1):

1. Obstructive sleep apnea (OSA) syndromes
2. Central sleep apnea (CSA) syndromes
3. Sleep-related hypoventilation syndromes
4. Sleep-related hypoventilation resulting from a medical condition
5. Other sleep-related breathing disorders

**Box 4-1 Classification of sleep-related breathing disorders**

**Obstructive sleep apnea syndromes**
- Adult obstructive sleep apnea (OSA)
- Upper airway resistance syndrome (UARS)*

- Pediatric OSA

**Central sleep apnea syndromes**

- Primary central sleep apnea (CSA)
- CSA resulting from Cheyne-Stokes breathing pattern (eg, in cardiac failure or stroke)
- CSA resulting from high-altitude periodic breathing
- CSA resulting from a medical condition
- CSA resulting from a drug or substance
- Primary CSA of infancy

**Sleep-related hypoventilation syndromes**

- Idiopathic sleep-related nonobstructive alveolar hypoventilation
- Congenital central alveolar hypoventilation syndrome

**Sleep-related hypoventilation resulting from a medical condition**

- Obesity hypoventilation syndrome*
- Sleep-related hypoventilation resulting from pulmonary parenchymal or vascular pathology
- Sleep-related hypoventilation resulting from lower airway obstruction
- Sleep-related hypoventilation resulting from neuromuscular or chest wall disorders

**Other sleep-related breathing disorders**

*In the *ICSD-2* classification, UARS and obesity hypoventilation syndrome are not classified as separate entities from OSA.[1]

*OSA* is characterized by the repetitive complete or partial collapse of the upper airway during sleep, causing a cessation (obstructive apnea) or a significant reduction (obstructive hypopnea) of airflow. In contrast, *CSA* is characterized by repeated episodes of absent or diminished respiratory effort, causing cessation (central apnea) or a significant reduction (central hypopnea) of airflow (Fig 4-1). Hypoventilation is defined by *hypercapnia*, an elevation of the arterial carbon dioxide ($PaCO_2$), in excess of the rise in $PaCO_2$ that occurs during sleep in normal subjects.[1]

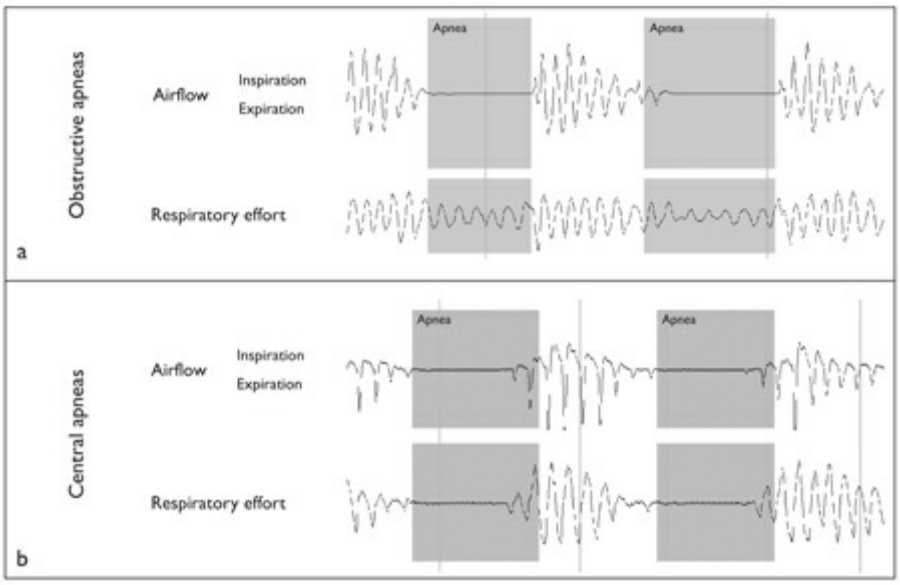


**Fig 4-1** Comparison of obstructive apneas and central apneas. *(a)* In obstructive apneas, there is evidence of continuing respiratory effort as cessation of airflow occurs as a result of collapse of the upper airway during sleep. *(b)* In central apneas, cessation of airflow occurs as a result of diminished respiratory effort.

This chapter gives an overview of OSA syndromes; however, there will be a more detailed discussion in subsequent chapters with a focus on adult OSA. This chapter also provides an overview of CSA syndromes and sleep-related hypoventilation syndromes.

## Obstructive Sleep Apnea

OSA represents a spectrum of abnormality, ranging from upper airway resistance syndrome (UARS) to OSA syndrome. Characterized by the repetitive complete or partial collapse of the upper airway during sleep, causing apneas or hypopneas,[1] OSA syndrome affects 2% to 4% of middle-aged adults.[2]

UARS is characterized by partial collapse of the upper airway, without the occurrence of obstructive apneas and hypopneas.[3] It is thought to be an intermediate form of sleep-related breathing disorder, between snoring and frank OSA. There is an increase in respiratory effort in an attempt to compensate for the reduction in airflow, which may lead to brief awakenings from sleep (cortical arousals) and

other physiologic and clinical consequences similar to those seen in frank OSA. In the *ICSD-2* classification, UARS is considered part of the spectrum of OSA and not a separate entity.[1]

## *Risk factors and consequences*

Obesity is a major risk factor; however, OSA also occurs in nonobese individuals. Other important predisposing factors are male gender, aging, craniofacial abnormalities (see chapter 11), family history of OSA, ethnicity, nasal obstruction, alcohol consumption, and cigarette smoking.[2] Obstructive apneas and hypopneas result in intermittent arterial blood gas abnormalities (hypoxemia and hypercapnia), brief awakenings from sleep (cortical arousals), and surges of sympathetic activity. These respiratory events can occur in any stage of sleep but are usually longer and associated with more severe oxygen desaturation when they occur in rapid eye movement (REM) sleep.[1] The pathophysiology of OSA is described in chapter 5.

The symptoms of OSA include snoring, witnessed apneas, choking, nocturnal awakenings, and excessive daytime sleepiness. The occurrence of OSA has also been linked to serious long-term adverse health consequences such as hypertension, metabolic dysfunction, cardiovascular disease, neurocognitive deficits, and motor vehicle accidents.[4] These aspects are discussed more fully in chapter 6.

Upper airway obstruction tends to evolve gradually over time as a result of factors such as obesity (Fig 4-2). As the severity of upper airway obstruction increases, so do the clinical consequences.[2]

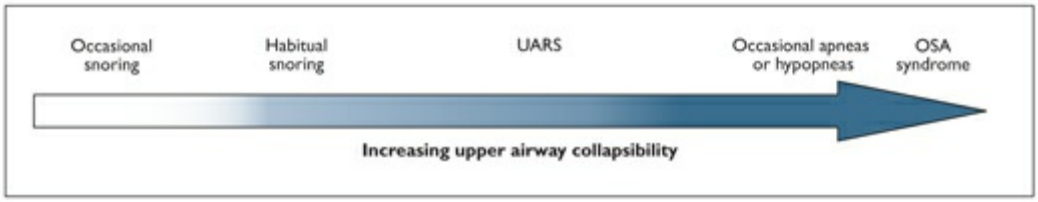


**Fig 4-2** Evolution of upper airway obstruction from snoring to OSA syndrome.

## *Diagnosis and management*

The apnea-hypopnea index (AHI) refers to the total number of apnea and hypopnea episodes per hour of sleep. The AHI is derived from overnight polysomnography

and is the key measurement used to describe the presence and severity of OSA. The presence of OSA syndrome is defined by an AHI of more than 5 events per hour in association with symptoms (such as excessive daytime sleepiness). The severity of OSA is judged by a composite of the severity of symptoms (for example, excessive daytime sleepiness) and the polysomnographic findings (including AHI and oxygen desaturation). The American Academy of Sleep Medicine recommends the following criteria for grading the severity of OSA based on AHI: *mild* is 5 to 15 events per hour, *moderate* is 15 to 30 events per hour, and *severe* is more than 30 events per hour.[5]

Another index reported in the literature is the respiratory disturbance index (RDI); however, the definition of this term is variable. Sometimes it is used interchangeably with the AHI, but it may be used to include respiratory events that do not meet the criteria for an apnea or hypopnea.

Treatment of OSA aims to reverse the pathophysiology and clinical consequences. The management options include weight loss, positional therapy, oral appliances, continuous positive airway pressure (CPAP), and surgery (see chapter 9).[6]

## Central Sleep Apnea

CSA is characterized by repeated episodes of absent or diminished respiratory effort, causing central apneas or central hypopneas. CSA can be idiopathic (that is, primary CSA) or secondary to another medical condition.[1]

### *Risk factors and consequences*

CSA is much less common in the general population than OSA; however, it is more prevalent in the elderly, in males, and in those with certain comorbidities (such as heart failure or stroke). Primary CSA can lead to sleep fragmentation and insomnia. Other symptoms include witnessed apneas, nocturnal awakenings, and excessive daytime sleepiness. However, a substantial proportion of patients do not complain of these symptoms. Secondary CSA may have a clinical presentation similar to that of primary CSA, in combination with symptoms of the underlying disease process. The occurrence of Cheyne-Stokes respiration, a cyclic pattern of breathing characterized by central apneas or hypopneas, with waxing and waning of the tidal

volume in a crescendo-decrescendo fashion,[1] is a sign of poor prognosis in patients with cardiac failure and is associated with an increased risk of premature death.

Secondary causes of CSA include Cheyne-Stokes respiration (usually resulting from cardiac failure or stroke), high-altitude periodic breathing, other medical conditions (for example, acromegaly, hypothyroidism, and renal failure), and drugs or substances (eg, long-acting opioids). Unstable ventilatory control seems to be the underlying pathophysiologic mechanism.[1]

### *Diagnosis and management*

The diagnosis of CSA generally requires overnight polysomnography. Cheyne-Stokes respiration is commonly observed in patients with cardiac failure or stroke.

The management of CSA should be supervised by a pulmonologist or sleep physician. The initial treatment of CSA should be directed at any causal or exacerbating factors. Other treatment options include positive airway pressure modalities (for example, CPAP or adaptive servoventilation), supplemental oxygen, and pharmacologic therapy.[7]

## Sleep-Related Hypoventilation

Sleep-related hypoventilation is characterized by decreased alveolar ventilation, resulting in sleep-related oxygen desaturation and hypercapnia.[1]

### *Risk factors and consequences*

Sleep-related hypoventilation can be idiopathic or secondary to a medical condition (such as pulmonary parenchymal or vascular pathology, lower airway obstruction, obesity, or neuromuscular or chest wall disorders). The secondary forms are much more common than the idiopathic forms.

Although symptoms are not required to make the diagnosis, patients may report excessive daytime sleepiness, nocturnal awakenings, or insomnia. Other potential consequences of nocturnal hypoxemia include pulmonary hypertension and neurocognitive dysfunction. OSA may coexist with sleep-related hypoventilation.[1] In

particular, obesity hypoventilation syndrome, characterized by obesity and an elevated awake $PaCO_2$ in the absence of other known causes of hypoventilation, may have a similar clinical presentation to that of OSA without hypoventilation. However, it is important to differentiate obesity hypoventilation syndrome from OSA without hypoventilation because this will have implications for treatment.[8]

The pathophysiologic mechanisms are varied and include impaired control of ventilation (such as in idiopathic sleep-related nonobstructive alveolar hypoventilation or congenital central alveolar hypoventilation syndrome), impaired pulmonary mechanics (such as in sleep-related hypoventilation resulting from neuromuscular or chest wall disorders), or a combination of these factors.[1]

## *Diagnosis and management*

During overnight polysomnography, sleep-related hypoventilation is recognized by sleep-related oxygen desaturation (Fig 4-3) and hypercapnia in excess of the rise in $PaCO_2$ that occurs during sleep in normal subjects. It is more marked during REM sleep because of loss of muscle tone and impaired arousal mechanisms.[1]

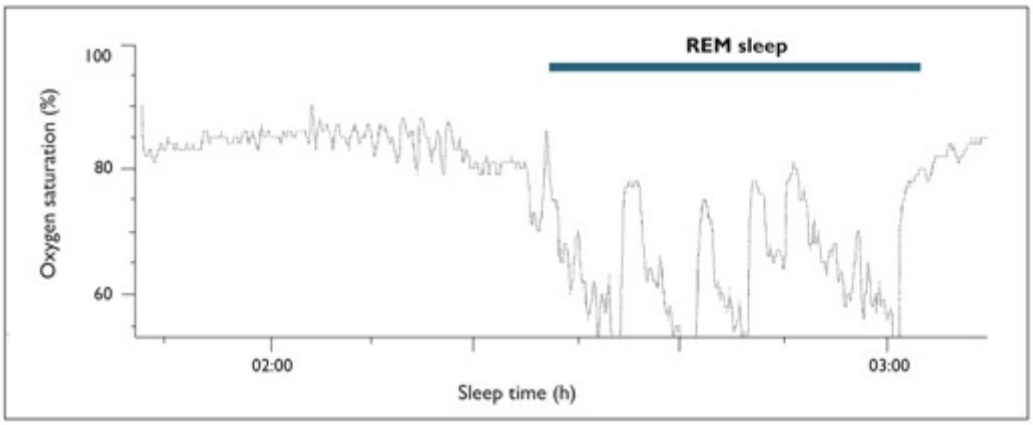


**Fig 4-3** Pattern of oxygen desaturation in sleep-related hypoventilation. The baseline oxygen saturation is low (less than 85%) and falls further (less than 60%) during REM sleep.

The management of sleep-related hypoventilation should be supervised by a pulmonologist or sleep physician. The initial treatment should be directed at any causal or exacerbating factors. Other treatment options include positive airway pressure modalities (for example, bilevel positive airway pressure).

## Conclusion

Sleep-related breathing disorders are a group of disorders characterized by abnormalities of respiration during sleep. The broad categories of sleep-related breathing disorders are OSA syndromes, CSA syndromes, sleep-related hypoventilation syndromes, sleep-related hypoventilation resulting from a medical condition, and other sleep-related breathing disorders. In addition to causing symptoms, these disorders may have long-term adverse health consequences.

Correct diagnosis of the different types of sleep-related breathing disorders is important in determining the approach to management. Polysomnography is generally required to differentiate these conditions. The limitations of ambulatory studies must be emphasized (particularly for UARS, CSA syndromes, and sleep-related hypoventilation syndromes) because of the risk of misdiagnosis and suboptimal treatment. Certain comorbid medical conditions may raise the suspicion of specific sleep-related breathing disorders (such as CSA in cardiac failure, or sleep-related hypoventilation in pulmonary disease or morbid obesity).

The dentist should diagnose and manage these conditions in conjunction with a pulmonologist or sleep physician.

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CHAPTER 5

# PATHOPHYSIOLOGY OF OBSTRUCTIVE SLEEP APNEA

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Obstructive sleep apnea (OSA) is the most common sleep-related breathing disorder. The critical abnormality in OSA is the repetitive complete or partial collapse of the upper airway during sleep.[1] This chapter will describe the relevant physiologic characteristics and pathophysiologic mechanisms that contribute to OSA.

## Upper Airway Structure and Function

The upper airway is composed of bony structures (mandible, maxilla, and hyoid bone) and soft tissues (tongue, soft palate, parapharyngeal fat pads, pharyngeal muscles, and lateral pharyngeal walls). The upper airway can be divided into four sections (Fig 5-1): the nasopharynx (from the nasal turbinates to the hard palate), the velopharynx (from the hard palate to the tip of the uvula), the oropharynx (from the tip of the uvula to the tip of the epiglottis), and the hypopharynx (from the tip of the epiglottis to the level of the vocal cords).

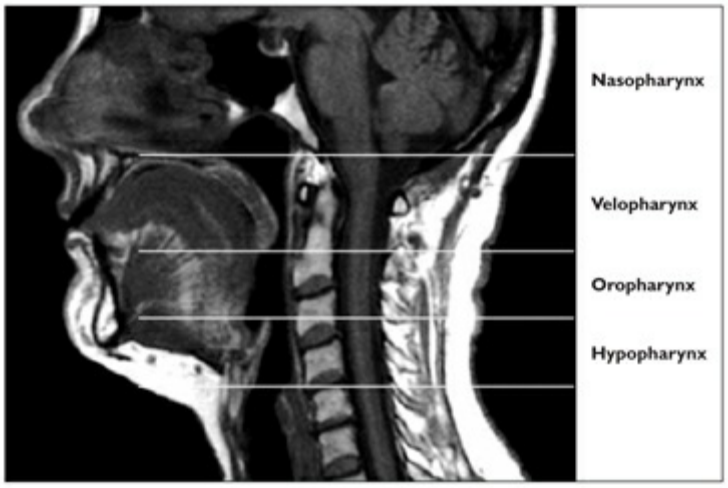


**Fig 5-1** Segments of the upper airway as seen on midsagittal magnetic resonance imaging: nasopharynx, velopharynx, oropharynx, and hypopharynx.

The normal functions of the upper airway (such as breathing, swallowing, and speech) require the capacity for both patency and closure. The upper airway has a collapsible segment, extending from the hard palate to the vocal cords, that accommodates these functions but also allows the occurrence of OSA in susceptible individuals.[2] The most common site of upper airway collapse in OSA is the velopharynx. The collapse usually extends to other sites; however, it can also begin at other locations within the upper airway.[3]

## Anatomic Factors in OSA

Given the relationship between structure and function, upper airway anatomy is an important consideration in the pathophysiology of OSA. Physical principles suggest that a smaller upper airway is more vulnerable to collapse. Thus, the size and probably the shape of the upper airway influence the likelihood of upper airway collapse. Imaging studies have shown that the volume of the upper airway is smaller in OSA patients than in control subjects (see chapter 8). This has been demonstrated using a number of imaging modalities, including computed tomography, acoustic reflection, and magnetic resonance imaging (MRI). In addition to size, there may also be differences in airway configuration, with some studies suggesting that the long axis of the upper airway tends to be oriented in an anteroposterior direction in

OSA patients, rather than laterally. However, most of these studies were performed during wakefulness, when pharyngeal dilator muscle activity contributes to the maintenance of upper airway patency.[3]

The degree of patency of the upper airway can be regarded as a function of factors that collapse the airway and those that promote airway patency. This is the *balance of pressures* concept. Factors that collapse the airway include the negative intraluminal pressure generated by the diaphragm during inspiration and the pressure of the surrounding extraluminal tissues. Factors that promote airway patency include the elastic properties of the pharyngeal wall and the contraction of pharyngeal dilator muscles. The specific pathophysiologic mechanisms causing OSA are likely to vary among individuals.

The airway pressure required to collapse the upper airway is known as the *critical closing pressure*. The upper airway generally remains patent in normal individuals, even in the absence of pharyngeal dilator muscle activity, with a critical closing pressure in the order of –5 cm $H_2O$. Thus, in normal individuals, the *extraluminal tissue pressure,* a force that will tend to collapse the airway, is lower than the elastic properties of the pharyngeal wall. The extraluminal tissue pressure is the result of the pressure from surrounding soft tissue and bony structures. The magnitude of the extraluminal tissue pressure is determined by the interaction of the volume of soft tissue within the upper airway and the size of the bony compartment (Fig 5-2). In OSA patients, an excess of soft tissue (such as in obesity), restriction in the size of the bony compartment (such as that caused by retrognathia), or a combination of these factors can cause an increase in extraluminal tissue pressure, thereby reducing the caliber of the upper airway.[4,5]

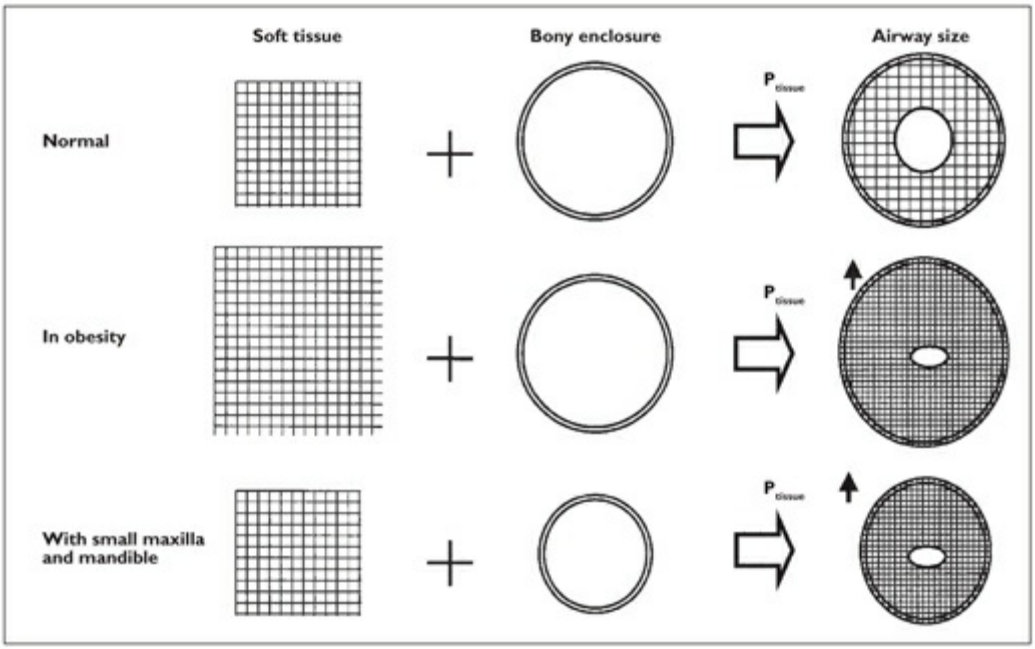


**Fig 5-2** Anatomic factors in the pathophysiology of OSA. The magnitude of the extraluminal tissue pressure ($P_{tissue}$) is determined by the interaction of the volume of soft tissue within the upper airway and the size of the bony compartment. (Reprinted from Watanabe et al[4] with permission.)

In support of this anatomic model of OSA, research studies have found differences in the bony and soft tissue structures in patients with OSA. There is a high prevalence of OSA in patients with congenital craniofacial syndromes (such as retrognathia and mandibular hypoplasia in patients with Treacher Collins syndrome). However, cephalometric studies have identified more subtle skeletal abnormalities in OSA patients, including a reduction in the length of the mandible, retropositioning of the maxilla, and an inferiorly positioned hyoid bone. It has been hypothesized that some of these skeletal abnormalities, such as the development of dental malocclusion, could be related to childhood respiratory problems (see chapter 11). Imaging studies of the upper airway using MRI have shown that the volume of soft tissue structures (such as the tongue, soft palate, and lateral pharyngeal walls) is larger in patients with OSA (see chapter 8). Thus, it appears that patients with OSA tend to have an anatomically compromised upper airway resulting from skeletal abnormalities, soft tissue abnormalities, or a combination of these factors.[3]

## Nonanatomic Factors in OSA

In addition to anatomic factors, the activity of the pharyngeal dilator muscles and the central control of ventilation are important in the pathophysiology of OSA. The pharyngeal dilator muscles can be divided into the following groups: muscles influencing hyoid bone position (such as the geniohyoid and sternohyoid), muscles of the tongue (such as the genioglossus), muscles of the palate (such as the tensor palatini and levator palatini), and muscles that protrude the mandible (such as the pterygoid muscles). The genioglossus muscle is the largest of these muscles.

Negative intraluminal pressure is the major stimulus of an upper airway reflex that activates pharyngeal dilator muscles during wakefulness. During wakefulness, the activity of pharyngeal dilator muscles compensates for the anatomic deficiency in the upper airway, evidenced by the greater activity of the genioglossus muscle in patients with OSA compared to that in control subjects. However, this compensatory effect is substantially diminished when the action of upper airway reflexes and pharyngeal dilator muscles decreases during sleep, and, in particular, during rapid eye movement sleep.

The respiratory control pattern generator, located in the brainstem, is responsible for the automatic control of ventilation. Rhythmic respiration is initiated by pacemaker cells that appear to be located entirely in the pre-Bötzinger complex and is modulated by other nuclei located in the brainstem.[6,7] Respiratory rhythm is regulated by chemoreceptors and by neural input from the upper airway and lungs to the brainstem neuronal network. The peripheral and central sensory systems are sensitive to levels of carbon dioxide ($PaCO_2$) and oxygen ($PaO_2$). Several neurotransmitters, including acetylcholine, norepinephrine, histamine, serotonin, dopamine, and others, have important functions in the control and maintenance of respiration and ventilation.[6,7] Instability of ventilatory control may be a contributing factor in the pathophysiology of OSA.[8]

Other factors that may contribute to the pathophysiology of OSA include surface tension and the effect of caudal traction exerted by lung volume on upper airway structures.[3] It has also been suggested that inflammation of and trauma to the upper airway, caused by snoring, may lead to injury of sensory pathways and impair the activation of upper airway neuromuscular reflexes.[9]

## Pathophysiologic mechanisms and Epidemiologic Risk Factors for OSA

The pathophysiologic mechanisms of OSA underpin the major risk factors for OSA that have been identified in clinical studies. Box 5-1 summarizes the anatomic and nonanatomic factors that predispose individuals to collapse of the upper airway and clinical risk factors for OSA. That obesity is a major risk factor for OSA may reflect the increased collapsibility of the upper airway, resulting from deposition of fat around the upper airway and a reduction in lung volume. The importance of craniofacial abnormalities and the mechanism by which they contribute to upper airway dysfunction has already been described. The male predisposition to OSA appears to be related to a greater deposition of fat around the upper airway. The length of the upper airway tends to be greater in males, a factor that may affect upper airway collapsibility. Differences in ventilatory control stability, mediated through hormonal differences between males and females, may also be important. With aging, there appears to be greater deposition of fat around the upper airway and a deterioration of upper airway neuromuscular reflexes.[2,3,5,8,10]

**Box 5-1 Factors predisposing to collapse of the upper airway and the development of OSA**

- Restriction in size of bony compartment
  - Mandibular hypoplasia or retrodisplacement
  - Maxillary hypoplasia or retrodisplacement
- Increase in soft tissue volume
  - Deposition of fat around upper airway (eg, in obesity)
  - Enlargement of tongue (macroglossia)
  - Enlargement of soft palate
  - Thickening of lateral pharyngeal walls
  - Adenotonsillar enlargement
  - Pharyngeal inflammation and edema
- Increase in pharyngeal compliance
- Decrease in pharyngeal dilator muscle activity

- Impairment of mechanoreceptor sensitivity
  - Impairment of upper airway neuromuscular reflexes
  - Impairment of strength and endurance of pharyngeal dilator muscles
- Decrease in lung volume
- Instability of ventilatory control
- Increase in surface tension
- Hormonal factors
  - Presence of testosterone (eg, male gender or testosterone replacement)
  - Absence of progesterone (eg, menopause)
  - Endocrine disorders (eg, hypothyroidism or acromegaly)

Genetic influences are likely to determine upper airway anatomy, neuromuscular activity, and ventilatory control stability, leading to clustering of OSA in families. Genetics may also explain the occurrence of OSA in particular ethnic groups. For example, craniofacial abnormalities are common in Asians with OSA, whereas enlargement of the soft tissue structures of the upper airway appears to be important for African Americans with OSA.[3,10] Genomic approaches have the potential for investigating the causes of OSA and studying its clinical expression. They may also have a role as a screening tool for OSA.[11]

## Conclusion

The critical abnormality in OSA is the repetitive complete or partial collapse of the upper airway during sleep. This tends to occur in the context of an anatomically compromised upper airway, resulting from skeletal abnormalities, soft tissue abnormalities, or a combination of these factors. However, other factors such as upper airway neuromuscular reflexes, lung volume, ventilatory control stability, and surface tension may also play a role.

Because OSA has been associated with serious long-term adverse health consequences (including hypertension, metabolic dysfunction, cardiovascular disease, neurocognitive deficits, and motor vehicle accidents),[12] it is a major public health problem. Treatment of OSA should target the specific pathophysiologic

processes that contribute to the collapse of the upper airway, in an attempt to alleviate symptoms and modify the long-term health consequences.

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CHAPTER 6

# LONG-TERM CONSEQUENCES OF OBSTRUCTIVE SLEEP APNEA

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Keith Wong, MBBS, PhD

In the clinical setting, patients with obstructive sleep apnea (OSA) often present as centrally obese individuals with accompanying sleepiness. Closer investigation often reveals an array of abnormalities that indicate compromised cardiometabolic and neurobehavioral function. Cardiometabolic derangements include hypertension, hyperglycemia, and hyperlipidemia, while neurobehavioral deficits include excessive daytime sleepiness, altered mood states, and problems with memory consolidation.

Substantial evidence from cross-sectional and longitudinal studies (both clinic and community based) suggests that OSA plays a causative role in worsening cardiometabolic and neurobehavioral function. There is also growing evidence that treatment of OSA improves both, further implicating it as a causative factor. Observational (population) studies also indicate that treatment of OSA is associated with reductions in morbidity and mortality. This chapter summarizes the epidemiologic and some mechanistic evidence of the role of OSA in deteriorating cardiometabolic and neurobehavioral health.

## Long-term Cardiovascular Consequences

### *Epidemiologic evidence*

A number of cross-sectional and longitudinal studies have shown a strong association between OSA and the development of coronary artery disease (CAD) and stroke.

In a series of studies,[1] Swedish investigators found an increased incidence of OSA in patients with established CAD, independent of known confounders. If OSA was left untreated, patients had a greater risk of cardiovascular mortality than did CAD patients without OSA. Also, subjects with OSA who were free of known CAD had an increased risk for developing new CAD over a 7-year follow-up period if they were not effectively treated with continuous positive airway pressure (CPAP).

A 10-year Spanish cohort study found a moderately greater risk of fatal and nonfatal cardiovascular events in patients with untreated severe OSA (mean apnea-hypopnea index [AHI] of 43 events per hour) than in a healthy population without OSA.[2] In contrast, patients with severe OSA who accepted CPAP treatment had significantly reduced numbers of such events, comparable to the numbers experienced by healthy subjects. This was the first large cohort study to report that OSA increases cardiovascular risk for morbidity and mortality. However, although this study was prospective in design, there was potential for referral bias because the study only included patients from a sleep clinic population, and it is possible that their risk may not reflect that of the population at large. Also, patients entering the trial were not randomized to treatment, raising the possibility that subjects who agreed to have treatment may also have been more likely to pursue healthy lifestyle habits, such as a healthy diet, regular exercise, and not smoking.

A cohort study from the United States examined the association between OSA at baseline and strokes and deaths after a mean of 3.4 years.[3] Although this study did not involve any intervention for OSA, the results suggested that OSA was associated with the risk of stroke or death from any cause, independent of other risk factors, including hypertension. However, participants were again from a clinic population, which raises the possibility of selection bias. On the other hand, inclusion and exclusion criteria in clinic population studies can often restrict the extrapolation of results to the population level.

Apart from the aforementioned clinic-based studies, there have also been two recently reported community-based cohort studies from Australia and the United States that further support a causative role for OSA in morbidity and mortality. The Australian Busselton cohort study demonstrated a moderately increased risk of all-cause mortality after 14 years in subjects identified to have moderate-to-severe OSA by a portable sleep apnea monitor worn at home (adjusted hazard ratio 6.24). This equated to a 33% mortality rate associated with moderate-to-severe OSA compared

to 7.7% and 6.5% mortality rates for mild or no OSA, respectively.[4]

In agreement with the Australian findings, a Wisconsin study revealed that, over a mean follow-up of 13.8 years, subjects with severe OSA (AHI greater than 30) at baseline had a greater risk of all-cause and cardiovascular mortality (adjusted hazard ratios of 3.8 and 5.2, respectively) than did subjects without OSA (AHI less than 5).[5] These findings represent the first community-based evidence that OSA is a predisposing risk factor for all-cause and cardiovascular mortality, independent of traditional cardiovascular risk factors. However, it is still unclear if mild OSA conveys a significant cardiovascular risk.

## *Mechanisms of disease*

The increased morbidity and mortality in patients with OSA is likely to involve several intermediate pathways, including hypertension, glucose intolerance, and dyslipidemia—features that, when clustered with central obesity, define the metabolic syndrome (Fig 6-1). Indeed, some data suggest an independent association between OSA and features of metabolic syndrome and its overall prevalence.[6] It follows that OSA may also ultimately contribute to the development of type 2 diabetes.

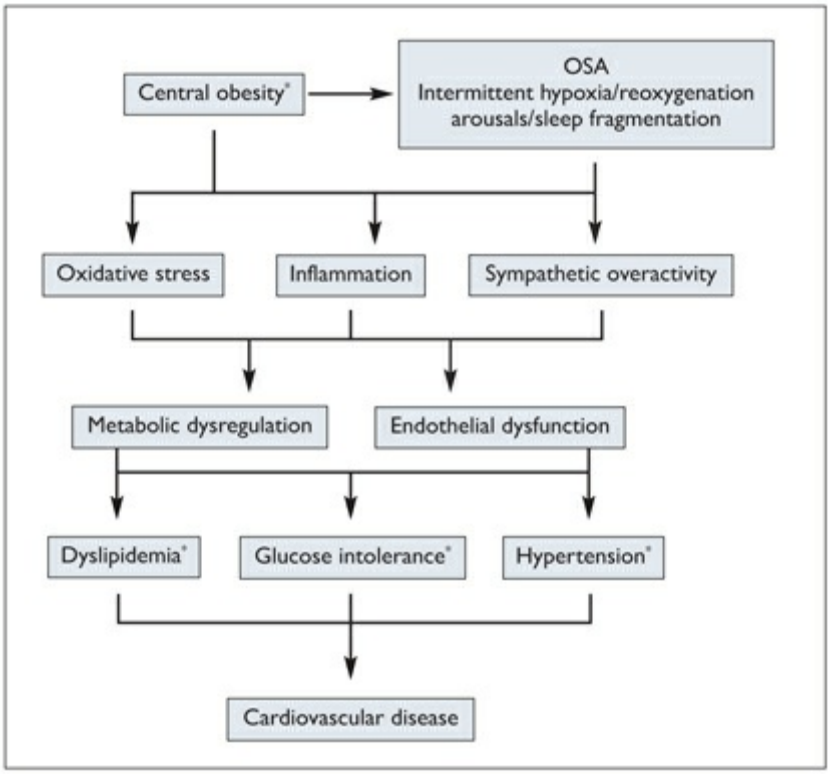

**Fig 6-1** Potential mechanisms linking obesity and OSA with cardiovascular disease. *Components of metabolic syndrome.

Of all the metabolic syndrome components, OSA has been most strongly linked with hypertension. Epidemiologic evidence suggests that the association is dose dependent.[7] Furthermore, several randomized controlled trials have shown that treatment of OSA with either CPAP (see chapter 9) or mandibular repositioning appliances (see chapter 10) causes blood pressure to fall. However, the effects are generally only modest (approximately 2 to 3 mm Hg)[8] and appear to be modulated by multiple factors, including OSA severity (AHI), symptoms (sleepiness), and compliance with treatment.[9]

In contrast to hypertension, however, the few relatively well designed short-term studies investigating the effects of OSA treatment on other components of metabolic syndrome have to date failed to show any effect. These include two randomized trials examining the effect of OSA treatment on insulin resistance (in subjects with and without type 2 diabetes) and one study examining all components together.[10] The negative findings from these interventional studies are also supported by the 4-year epidemiology data from the population-based Wisconsin Sleep Cohort study, which revealed no causal role for OSA in promoting type 2 diabetes.[11] However, it has been suggested that improvements in glucose and lipid metabolism may still occur if OSA treatment periods are longer and treatment compliance (nightly use) is improved[10]; further studies are required to clarify this point.

Regardless of mechanisms, it is still unclear which components of OSA (hypoxia and/or sleep fragmentation) have the greatest impact on development of cardiometabolic disease. The Cleveland Family Study found a stronger association between sleep arousals and incident hypertension, while impaired glucose tolerance was more closely associated with hypoxemia.[12] In contrast, the Sleep Heart Health Study found that hypoxia may ultimately be the most important component mediating cardiovascular disease (CVD) itself.[13] Further studies are required to carefully dissect the relative roles of hypoxemia, arousals, and other aspects of sleep disturbance in mediating the development of CVD in patients with OSA.

## Long-term Neurocognitive Consequences

The impact of OSA on the brain is thought to be due to a combination of sleep fragmentation and intermittent hypoxia from the repetitive respiratory events in sleep. Studies examining the pattern of cognitive dysfunction show variable results, in part because of small sample sizes and differences in tests used to assess cognitive function.[14]

The most consistent pattern of cognitive deficits identified relate to vigilance, memory, and executive function.[15] The first two are related to the common symptom of sleepiness, and the last refers to qualities such as mental flexibility, planning, and problem solving. This pattern of deficit is thought to arise from the sensitivity of the prefrontal cortex to the effects of sleep loss.[16] It should be noted that neurocognitive testing is not in routine use in the clinical assessment of patients with OSA: No tests have been shown to be reliable predictors of important outcomes such as motor vehicle accidents, despite studies reporting a 2- to 10-times increased risk of these events among patients with untreated OSA.[17]

Larger randomized trials currently in progress employ a more comprehensive and standardized battery of tests that may provide further insights into the nature of these cognitive impairments, the best method of assessment, and the extent to which treatment of OSA reverses the observed cognitive deficits.[18,19] The literature to date has shown that treatment of OSA reduces sleepiness[20]; however, some studies suggest that recovery of cognitive impairment is incomplete after CPAP treatment for OSA.[21] This may relate to irreversible long-term effects of untreated OSA or to other comorbidities.

This phenomenon of incomplete recovery may be due to suboptimal treatment of OSA, but it is also possible that it may arise from permanent injury to the brain secondary to the chronic intermittent hypoxia.[21] Apart from prospective epidemiologic studies showing increased risk of strokes in patients with OSA,[2] small neuroimaging studies have shown loss of gray-matter volume in patients with OSA compared with non-OSA controls.[22] In addition, abnormal utilization of glucose was revealed by positron-emission tomographic scanning in the frontal lobe of patients with persistent sleepiness even after the use of CPAP.[23]

The neurocognitive effects of OSA may also have potential long-term consequences in children. Up to 5% of school-aged children meet polysomnographic criteria for OSA, and the condition has been associated with increased behavioral problems and impaired academic performance.[24]

# Conclusion

There is a growing body of evidence to suggest that OSA, particularly if severe, worsens cardiometabolic and neurobehavioral outcomes (Table 6-1). However, it is important to highlight that the strongest evidence to date comes from observational cohort studies, which suffer from all the usual pitfalls, including selection bias and lack of control for known confounders, or from small, short-term, randomized trials. These shortcomings can only be adequately addressed by longitudinal and randomized controlled trials that incorporate appreciable numbers of subjects and are controlled for the influence of known risk factors. At present, ongoing trials have been undertaken to clarify the long-term consequences for OSA both from the cardiometabolic and neurocognitive perspectives.

**Table 6-1** **Cardiovascular, metabolic, and neurocognitive consequences of OSA**

| Effect | Magnitude odds ratio (95% CI) | Study |
|---|---|---|
| *Cardiovascular* | | |
| Incident hypertension | 2.89 (1.46–5.64) | Peppard et al[7] |
| Prevalent coronary artery disease | 1.27 (0.99–1.62) | Shahar et al[25] |
| Incident stroke | 3.08 (0.74–12.81) | Arzt et al[26] |
| Prevalent congestive heart failure | 2.38 (1.22–4.62) | Shahar et al[25] |
| *Metabolic* | | |
| Prevalent impaired fasting glucose | 1.35 (1.04–1.76) | Stamatakis et al[27] |
| Prevalent diabetes | 2.3 (1.28–4.11) | Reichmuth et al[11] |
| *Neurocognitive* | | |
| Motor vehicle accidents | 7.2 (2.4–21.8) | Teran-Santos et al[28] |
| Occupational accidents | 2.2 (1.3–3.8) | Lindberg et al[29] |
| Incident depression | 2.6 (1.7–3.9) | Peppard et al[30] |

| | | |
|---|---|---|
| *Mortality* | | |
| All causes* | 3.0 to 4.4 | Marshall et al,[4] Young et al[5] |
| Cardiovascular | 2.87 (1.17–7.51) | Marin et al[2] |

*Hazard ratio (instead of odds ratio).

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CHAPTER 7

# CLINICAL APPROACH TO DIAGNOSIS OF OBSTRUCTIVE SLEEP APNEA

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Obstructive sleep apnea (OSA) syndrome is a highly prevalent condition characterized by repetitive complete or partial airway obstruction, oxygen desaturation, and sleep fragmentation, together with a constellation of symptoms such as snoring, witnessed apneas, and excessive daytime sleepiness. Despite its prevalence, recognition of the condition remains low in the community, and the majority of sufferers of OSA are as yet undiagnosed.[1] Clinicians should have a high index of suspicion for OSA, especially among those patients at increased risk of the condition, as described in chapters 4 and 5 (Box 7-1). Diagnosis should be based on history and physical examination findings in conjunction with appropriate objective testing that demonstrates the presence of sleep-disordered breathing.[2,3]

**Box 7-1 Risk factors for OSA**

**Unmodifiable**

- Increasing age
- Male gender
- Menopause
- Ethnicity
- Genetics

**Potentially modifiable**

- Obesity
- Neck or visceral fat distribution
- Craniofacial abnormalities
- Upper airway soft tissue abnormalities
- Alcohol consumption

**Associated conditions (examples)**

- Hypothyroidism
- Acromegaly
- Down syndrome
- Marfan syndrome

# Clinical Assessment

## *Snoring*

Snoring is the hallmark presenting symptom, occurring in up to 95% of patients with OSA. Patients are often unaware of their snoring sounds unless they have been told by their sleep partner or family members. When snoring becomes loud and disruptive, it can result in significant social and relationship disharmony. In the general population, snoring has a prevalence of up to 60% and 50% in middle-aged men and women, respectively; this is significantly higher than the population prevalence of OSA syndrome.[4] The absence of snoring makes OSA unlikely but does not exclude it. The presence of snoring alone is a poor predictor of OSA because of its high prevalence in the community; therefore, other supporting clinical features should be sought.

## *Witnessed apneas*

The presence of witnessed apneas is the most specific symptom of OSA. Observation of breathing pauses is often a concerning symptom for the sleep partner,

although obtaining a reliable account of this symptom during sleep can be difficult. Patients are often unaware of this symptom, but sometimes they may report awakening during episodes of nocturnal choking. Witnessed apneas tend to be less commonly reported among females and can also be reported among subjects without OSA.

## *Excessive daytime sleepiness*

Daytime sleepiness in patients with OSA is related to sleep fragmentation caused by microarousals. Excessive daytime sleepiness is a highly subjective symptom and is often underreported by patients. Because of the high frequency of sleepiness reported in the general population (20% to 30%), this symptom is also a poor predictor for OSA. Furthermore, a correlation between daytime sleepiness and OSA severity is often not demonstrated. It is important to differentiate between sleepiness and symptoms such as lethargy or tiredness, because these may indicate alternative diagnoses.

Daytime sleepiness is most commonly assessed by the Epworth sleepiness scale, which is a questionnaire that provides a measure of sleep propensity (Fig 7-1).[5] A score greater than 10 (of a maximum of 24) is consistent with excessive daytime sleepiness and a score greater than 16 is indicative of a high level of daytime sleepiness. However, even subjects without OSA can have a wide range of scores, from 2 to 10.[5] Objective sleep laboratory tests for daytime sleepiness include the Multiple Sleep Latency Test (MSLT) and Maintenance of Wakefulness Test (MWT), but they are time consuming and expensive.

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

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

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

**Fig 7-1** Epworth sleepiness scale. A score of greater than 10 is consistent with excessive daytime sleepiness and a score of greater than 16 is indicative of a high level of daytime sleepiness. (Reprinted from John[5] with permission.)

## *Other nocturnal and daytime symptoms*

OSA is also associated with a range of nocturnal and daytime symptoms (Box 7-2). These symptoms are generally nonspecific for OSA but can give an indication of the impact this condition has on the patient.

**Box 7-2 Symptoms and signs of OSA**

**Symptoms**

- Snoring
- Witnessed apneas
- Excessive daytime sleepiness
- Nocturnal choking
- Unrefreshed sleep

- Poor sleep quality
- Insomnia
- Morning headaches
- Impaired concentration
- Impaired memory
- Nocturia
- Impotence
- Anxiety and depression
- Esophageal reflux

**Signs**

- Obesity
- Increased neck circumference
- Increased waist circumference
- Retrognathia
- Maxillary constriction
- Overjet
- Overbite
- Tonsillar hypertrophy
- Macroglossia
- Oropharyngeal narrowing (Mallampati class)
- Soft palate erythema and edema
- Nasal obstruction
- Hypertension

## *Obesity*

The association between obesity or increased body mass index (BMI) and OSA is well established. BMI is calculated by weight divided by height squared. In a sleep clinic population, 28% of patients had a BMI greater than 30 kg/m$^2$, and 47% had a BMI between 26 and 30 kg/m$^2$.[6] Specifically, distribution of fat around the neck and waist, known as *central obesity*, is particularly important. Both neck and abdominal

circumference are strong predictors for OSA.[6,7] The metrics of obesity generally have a linear association with the likelihood and severity of OSA, and there is no single threshold value of neck or abdominal circumference above which OSA occurs.

## *Craniofacial and oropharyngeal anatomy*

Craniofacial factors can predispose individuals to compromised airway space and the development of OSA. Mandibular retrusion, maxillary deficiency, inferior displacement of the hyoid bone, and cranial base abnormalities are among the most commonly reported findings on cephalometry of patients with OSA (see chapter 8).[8–10] Clinical examination should include an assessment for these craniofacial factors (see Box 7-2).

Tonsillar hypertrophy, macroglossia, oropharyngeal narrowing, edema, and erythema of the soft palate are soft tissues abnormalities that can relate to OSA and snoring. The level of obstruction of the oropharynx can also be assessed with the modified Mallampati classification[11] (Fig 7-2). Nasal obstruction should be assessed because it is often an exacerbating factor.

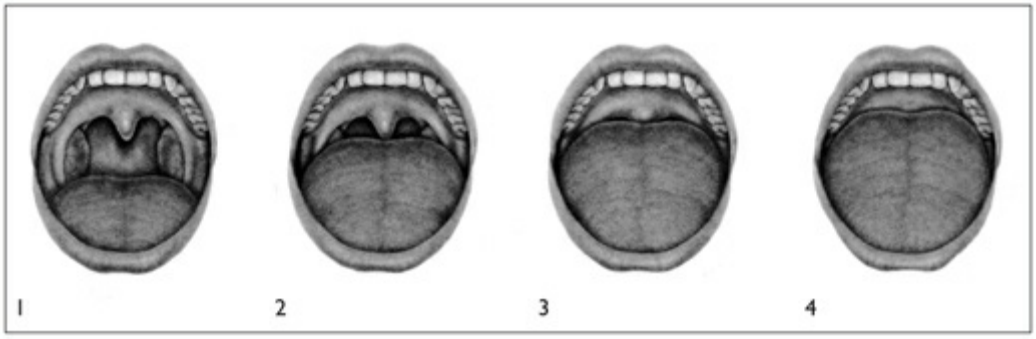


**Fig 7-2** Modified Mallampati classification. Oropharyngeal crowding is assessed with the patient's mouth wide open and the tongue resting inside the oral cavity. (class 1) Tonsils, pillars, and soft palate are clearly visible. (class 2) Uvula, pillars, and upper pole are visible. (class 3) Only part of the soft palate is visible; the tonsils, pillars, and base of the uvula cannot be seen. (class 4) Only the hard palate is visible. (Reprinted from Friedman et al[11] with permission.)

### *Associated comorbidities*

History of hypertension, cardiovascular diseases, strokes, diabetes, and thyroid disease should be elicited during the clinical history, and these conditions should be looked for during the physical examination because some of them could be important aggravating factors for or consequences of OSA.

# Diagnostic Testing

## *Questionnaires and clinical prediction models*

Although clinical assessment alone is generally not adequate for the diagnosis of OSA, a combination of OSA symptoms and risk factors in a prediction algorithm may improve the diagnostic certainty. These questionnaires and models are usually developed with a large sample of subjects who have undergone formal diagnostic testing. Many such tools are available, but the most commonly used ones are the Berlin questionnaire and the multivariable apnea prediction index (MAPI)[12,13] (Table 7-1). Such questionnaires incorporate clinical information such as gender, age, snoring, BMI, the occurrence of choking episodes, and the presence of hypertension.

**Table 7-1** **Questionnaires and clinical prediction models for OSA**

| Study | Clinical predictors | Model characteristics* |
|---|---|---|
| Friedman et al[11] | BMI, tonsil size, and modified Mallampati class | PPV: 90%<br>NPV: 67% |
| Maislin et al (MAPI)[12] | Apnea index, age, sex, and BMI | Area under the ROC curve: 0.7 |
| Netzer et al (Berlin questionnaire)[13] | Snoring,witnessed apneas, daytime sleepiness, hypertension, and obesity | Sensitivity: 86%<br>Specificity: 77% |
| Kushida et al[15] | BMI, neck circumference, palatal height,maxillary and mandibular intermolar distances, and overjet | Sensitivity: 97.6%<br>Specificity: 100% |
| Tsai et al[17] | Cricomental space, pharyngeal grade, and overbite | Sensitivity: 40%<br>Specificity: 96% |

*The types of model characteristics reported varied among the studies. (BMI) body mass index; (ROC) receiver operating characteristic; PPV) positive predictive value; (NPV) negative predictive value.

Overall, prediction models tend to have high sensitivities (76% to 96%) but much lower speci-ficities (13% to 54%).[14] That is, patients with OSA will usually be identified correctly, but a significant proportion of subjects without OSA may be identified incorrectly as having OSA. Therefore, these prediction models might have a role in disease exclusion, but their routine use in clinical practice remains limited. Incorporation of oral cavity measurements (palate height, overjet, and intermolar distances) in a prediction model may be a clinically useful screening tool for OSA.[15] Nevertheless, the accuracy of these questionnaires and models may vary significantly depending on the context (eg, community, primary care, or sleep clinics) in which they are used.

## *Polysomnography*

Polysomnography performed in a sleep laboratory is the gold standard for the diagnosis of OSA. It involves continuous overnight recording of a minimum of 12 channels of sleep- and breathing-related measurements, such as electroencephalogram, electrooculogram, electromyogram, nasal airflow (preferably measured by nasal pressure cannula), oral airflow (thermistor), respiratory effort, oxygen saturation, body position, and electrocardiogram.[16] Recordings require manual scoring of the events by trained sleep technologists and interpretation of the results by sleep medicine physicians, taking into account the clinical context. The examinations monitor the occurrence of apneas (complete cessation of airflow for 10 seconds or more) and hypopneas (reduction in amplitude of airflow or tho-racoabdominal wall movement for 10 seconds or more with an accompanying oxygen desaturation of at least 3% and/or associated arousals). OSA is defined as a total of more than 5 events per hour of sleep. Notably, variations exist in scoring definitions, especially for hypopneas.

The severity of sleep apnea is assessed with the apnea-hypopnea index, although other factors such as the degree of oxygen desaturation and the extent of sleep fragmentation are important for the clinical interpretation of OSA severity. Some laboratories report a respiratory disturbance index (RDI), which often incorporates all respiratory events (beyond apneas and hypopneas), although the definition for this score may vary.

Generally, diagnosis of OSA can be based on a single night of testing, although night-to-night variability in results should be considered, especially if test results are negative for a patient with high clinical risk of OSA. Apparent variability in the severity of OSA may result from a number of factors, including differences in sleeping position, alcohol use, prior sleep debt, sleep efficiency, and sleep stage distribution. Furthermore, variation in the definitions and scoring of the respiratory events can also significantly alter the apnea-hypopnea index. The major limitations of polysomnography are that it is expensive and labor intensive and thus waiting lists for the procedure tend to be very long.

## *Portable sleep studies*

Compared to laboratory polysomnography, portable sleep monitoring performed in the home setting is more readily available and generally offers greater convenience for patients. These monitors are usually simpler and measure only one or two physiologic parameters (eg, snoring, oxygen saturation, nasal airflow, or heart rate) during sleep, although some monitors can measure multiple parameters, up to the full range of channels, similar to a laboratory study.[16] Oximetry remains the most commonly available portable monitor, and it can be useful for identifying severe OSA, although milder cases are often not excluded by a negative test result.

Overall, the accuracy and reliability of portable sleep monitors vary significantly depending on the types of parameter monitored, analytic techniques, and definitions of events. The lack of supervision during the study to ensure against dislodgment of leads increases the likelihood of technically unsatisfactory studies (up to 25%). Information about sleep duration and staging is often not available for the correct estimation of events frequency. Furthermore, other sleep disorders may not be detected by portable sleep studies, eg, central sleep apnea, periodic limb movements during sleep, or nocturnal epilepsy. Therefore, portable sleep studies would not be appropriate for patients who are suspected to have these disorders. There might be a role for portable sleep monitors in the reevaluation of patients following treatment interventions.

## *Imaging*

A number of imaging modalities are available for the evaluation of the upper airway and craniofacial structures (see chapter 8), but their role in the diagnosis of

OSA is limited. Although the assessment of airway caliber and its change with dynamic maneuvers may predict the risk of airway collapse during sleep, further evaluation with objective sleep testing remains necessary. Cephalometry and nasopharyngoscopy may have utility in the assessment of adenotonsillar hypertrophy and planning of treatment. The utility of pharyngometry in airway evaluation for diagnosis of OSA remains to be scientifically evaluated.

## Conclusion

Assessment of subjects for possible OSA requires a thorough clinical evaluation to determine the likelihood of the condition as well as objective testing to demonstrate the presence of sleep-disordered breathing, before treatment is initiated. Recognition of the symptoms and signs of OSA (eg, snoring, witnessed apneas, excessive daytime sleepiness, and obesity), appropriate investigations, and when needed, referral are key steps toward the diagnosis of this disorder and differentiation from nonapneic snorers.

The choice between polysomnography and a home sleep study for diagnosis should take into account the pretest clinical probability of OSA and any limitations of resources. Portable sleep studies could be useful for confirming disease in patients with high index of suspicion for OSA, but the limitations of unattended studies should be recognized. For patients with intermediate or low clinical risk of OSA, polysomnography remains the gold standard for definitive diagnosis. The value of portable monitoring in the follow-up of treatment response deserves further evaluation.

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CHAPTER 8

# UPPER AIRWAY IMAGING IN OBSTRUCTIVE SLEEP APNEA

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Richard J. Schwab, MD

Despite the high prevalence and major public health ramifications of obstructive sleep apnea (OSA), more information is needed about its pathogenesis and the anatomic risk factors for this condition (see chapters 5 and 11). Upper airway imaging techniques such as cephalometry, acoustic reflection, fluoroscopy, optical coherence tomography, nasopharyngoscopy, magnetic resonance imaging (MRI), and computed tomography (CT) have provided insight into the biomechanical basis of OSA. These diagnostic images also have helped to elucidate the mechanisms by which therapeutic interventions (continuous positive airway pressure, weight loss, oral appliances, and surgery) increase the caliber of the upper airway.

In the following sections, the advantages and disadvantages of various imaging modalities and their ability to help in the diagnosis and guide the treatment of sleep-disordered breathing are reviewed (Table 8-1). At this time, the predictive value of airway imaging techniques in determining diagnostic or treatment success in patients with OSA is not fully proven. Clinicians must be cautious in interpreting findings collected with these imaging tools; rigorous studies of their clinical validity are still required.

**Table 8-1** Advantages and disadvantages of different upper airway imaging modalities

| Imaging modality | Advantages | Disadvantages |
|---|---|---|
| | | • Lacks standardization in radiographic |

| | | |
|---|---|---|
| Cephalometry (lateral cephalometric radiography) | • Widely available<br>• Easily performed<br>• Inexpensive<br>• Useful in diagnosis of skeletal types<br>• Useful in evaluation of oral appliances and orthognathic surgery<br>• No weight limitation | equipment, technique, and interpretative skills<br>• Performed with patient in standing position<br>• Provides two-dimensional representation of three-dimensional object (magni-fication, distortion, and volumetric analysis difficult)<br>• Provides limited information about soft tissues<br>• Not dynamic imaging modality |
| Acoustic reflection | • Noninvasive<br>• Free of radiation<br>• Reproducible<br>• Dynamic imaging modality<br>• No weight limitation | • Performed with patient in sitting position<br>• Performed through patient's mouth (modification of the upper airway anatomy)<br>• Does not provide direct information on airway structure or geometry |
| Fluoroscopy | • Dynamic imaging modality<br>• Allows state-dependent imaging | • Requires high radiation exposure<br>• Superimposes upper airway soft tissue structures<br>• Impractical for routine use |
| Optical coherence tomography | • Free of radiation<br>• Generates quantitative, real-time images of upper airway<br>• Capacity to continuously measure changes in the airway dimensions when patient is asleep or awake<br>• Minimally invasive | • Does not allow examination of soft tissue or craniofacial structures<br>• Does not allow tracking of changes in airway caliber when patient's breathing is rapid |
| Nasopharyngoscopy | • Accessible imaging modality<br>• Free of radiation<br>• No weight limitation<br>• Can be performed in supine or sitting position<br>• May be useful to determine obstruction sites, for guiding surgical procedures, and for guiding oral appliance treatment<br>• May add important information on possible site of obstruction when used in combination with Müller maneuver | • Invasive<br>• Requires nasal anesthesia<br>• Examines only the lumen of upper airway (no measurements of surrounding soft tissue structures) |

**Table 8-1** ***(continued)*** **Advantages and disadvantages of different upper airway imaging modalities**

| Imaging modality | Advantages | Disadvantages |
|---|---|---|
| CT | • Widely available<br>• Performed with patient in supine position<br>• Ideal for airway and bony structures<br>• Allows direct three-dimensional reconstructions (helical CT)<br>• Provides excellent temporal and spatial resolution (ultrafast or dynamic CT)<br>• Possible state-dependent imaging | • Expensive<br>• Requires radiation exposure<br>• Limited soft tissue contrast resolution<br>• Weight limitation |
| MRI | • Free of radiation<br>• Performed with patient in supine position<br>• Possible state-dependent imaging<br>• Provides excellent resolution of upper airway structures (including adipose tissue)<br>• Allows accurate measurement of cross-sectional airway area and volume<br>• Allows multiplanar imaging (axial, sagittal, and coronal) for three-dimensional re-constructions of upper airway soft tissue and craniofacial structures<br>• Dynamic imaging modality (ultrafast MRI) | • Expensive<br>• Not always available<br>• Weight limitation<br>• Can cause claustrophobia<br>• Excluded by presence of ferromagnetic prostheses, including pacemakers |

# Cephalometry

Cephalometry involves the use of a standardized lateral radiograph of the head and neck to assess craniofacial and soft tissue structures of the upper airway (Fig 8-1). This technique must be performed in a standardized fashion as the patient's head is stabilized by a cephalostat (in natural head position or with Frankfort horizontal plane parallel to the floor) and at the end of expiration.[1] This method is widely available, easily performed, inexpensive, and can be useful in the evaluation of oral appliances or orthognathic surgery. However, cephalometrics has several disadvantages: problems are associated with standardization of the radiographic equipment, technique, and interpretation; the procedure is not performed while the

patient is in the supine position; the image is a two-dimensional representation of a three-dimensional object (magnification, distortion, and volumetric analysis is difficult); the image provides limited information about soft tissues or lateral structures; and the technique is not a dynamic imaging modality.

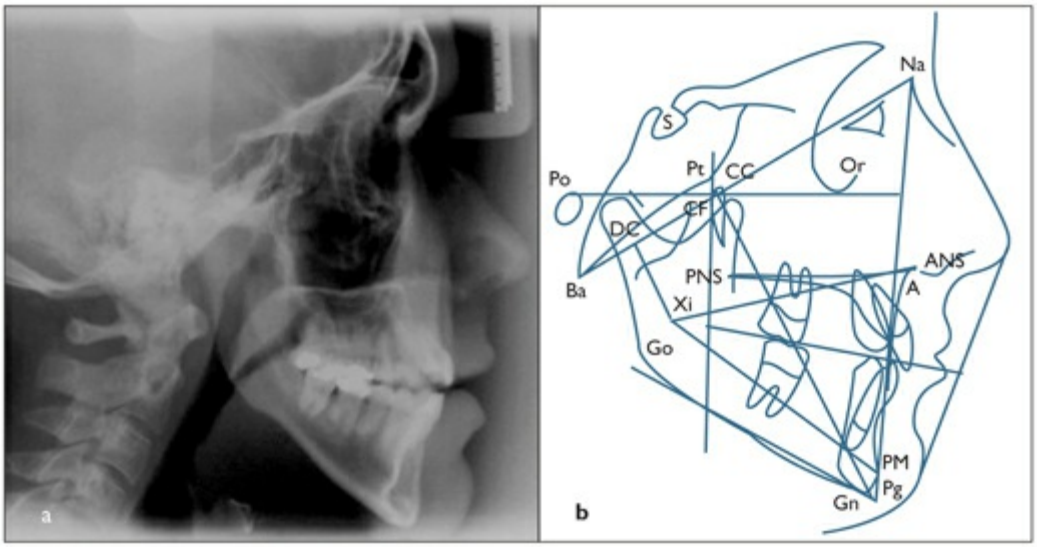


**Fig 8-1** *(a)* Lateral radiograph of the head and neck. *(b)* Initial cephalometric analysis. (Na) Nasion: anterior limit of the nasofrontal suture; (ANS) anterior nasal spine; (point A) deepest point of the curve of the maxilla between the anterior nasal spine and the dental alveolus; (PM) suprapogonion (protuberance menti): where the curvature of anterior border of the symphysis changes from concave to convex; (Pg) pogonion: most anterior point on the midsagittal symphysis; (Gn) gnathion: intersection of the tangent to the most inferior point on the inferior border of the symphysis and the most inferior point of the gonial region and the line Na-Pg; (Go) gonion: intersection of the line connecting the most distal aspect of the condyle to the distal border of the ramus (ramus plane) and the line at the base of the mandible (mandibular plane); (Po) porion: most superior point of the external auditory meatus; (Ba) basion: most inferior posterior point of the occipital bone at the anterior margin of the occipital foramen; (point Pt) pterygoid: intersection of the inferior border of the foramen rotundum with the posterior wall of the pterygomaxillary fissure; (point CF) center of face: intersection of the line Po-Or and a perpendicular line through Pt; (point CC) center of cranium: intersection of the two lines Ba-Na and Pt-Gn; (point DC) center of the neck of the condyle; (point Xi) geometric center of the ramus; (PNS) posterior nasal spine; (Or) orbitale: lowest point on the external border of the orbital cavity; (S) sella.

Studies using cephalometrics have demonstrated craniofacial differences between patients with sleep apnea and normal control subjects,[2] but the definitive results are often difficult to compare because there is no consensus regarding the optimal cephalometric variables that distinguish control subjects from individuals with apneas. The most commonly reported craniofacial characteristics of nonobese patients with sleep-disordered breathing include a small (corpus length) retrognathic, mandible; a narrow posterior airway space; enlargement of the tongue and soft palate; an inferiorly positioned hyoid bone; and a retrognathic maxilla.[3,4]

## Acoustic Reflection

Acoustic reflection is a noninvasive imaging technique based on the analysis of sound waves reflected from upper airway structures. The phase and amplitude of the reflected sound waves can be used to determine the cross-sectional area of the airway. The technique is generally performed through the mouth, is free of radiation, and, because it is both fast and reproducible, permits dynamic imaging of the upper airway. However, acoustic reflection does not provide direct information on airway structure or anatomy or show the soft tissue structures; it only indicates the size of the airway lumen. In addition, it is performed while the awake patient is in the sitting position and using an oral mouthpiece, even though mouth opening alters the upper airway geometry. Studies using acoustic reflection have demonstrated that the upper airway area of apneic subjects is smaller than that of nonapneic controls, but thus far the technique has been used primarily as a research tool.[5]

## Fluoroscopy

Fluoroscopy has been used to assess dynamic closure and sites of obstruction in the upper airway of patients with OSA. Somnofluoroscopy (fluoroscopy performed while the patient is asleep) has demonstrated that upper airway closure occurs in the retropalatal region for most patients with OSA.[6] Although fluoroscopy provides a dynamic evaluation of the upper airway during wakefulness and sleep, high radiation exposure, superimposition of the upper airway soft tissue structures, and the possible need for sedation to attain sleep make this technique impractical for routine

use.[6]

## Optical Coherence Tomography

Optical coherence tomography is another technique that can be utilized to generate quantitative, real-time images of the upper airway. This technique involves the insertion of a 3-mm-diameter optical probe in the nose. Rotation of this probe provides a 360-degree profile of surrounding tissue, and longitudinal movement allows the upper airway to be scanned at multiple sites. A similar technique has been used to examine microscopic tissue anatomy in other disciplines, including ophthalmology, dermatology, vascular medicine, gastroenterology, and urology.

In addition to the capacity to continuously measure changes in the airway dimensions under a variety of conditions, other advantages of optical coherence tomography include patient comfort, minimal effects on sleep quality or architecture, and the lack of radiation. Limitations include the inability to view the complete circumference of the airway at all sites in all subjects and the inability to track changes in airway caliber when the patient's breathing is rapid.[7] In addition, this imaging modality examines the airway lumen; it cannot evaluate craniofacial or soft tissue structures that are not directly adjacent to the airway.

## Nasopharyngoscopy

Nasopharyngoscopy is an accessible and inexpensive method used to evaluate the nasal passages, oropharynx, and vocals cords of patients in multiple positions and in awake and asleep states (during spontaneous sleep or under sedation). Although it is invasive and requires nasal anesthesia, nasopharyngoscopy does not involve radiation exposure.

This technique has been used in numerous studies to evaluate the site of airway obstruction, state-dependent airway changes in patients with OSA, and the effects of mandibular repositioning devices, weight loss, and uvulopalatopharyngoplasty (UPPP) on airway caliber. Nasopharyngoscopy, however, examines only the lumen of the upper airway and does not provide measurements of the surrounding soft tissue structures. The combination of nasopharyngoscopy with the Müller maneuver

(thought to simulate the upper airway collapse that occurs during an apnea) has been shown to add important information on possible sites of upper airway obstruction.[8,9]

Some studies suggest that patients with predominantly retroglossal obstruction identified during a Müller maneuver are not ideal candidates for UPPP, and for those patients other types of surgical procedures should be considered (sliding genioplasty or maxillomandibular advancement). For the patient with predominantly retropalatal collapse during the Müller maneuver, UPPP should be considered the surgical option of first choice.[10] However, strong data showing an improved surgical outcome in patients selected for UPPP using the combination of nasopharyngoscopy and a Müller maneuver are lacking. Nonetheless, current studies show that sleep endoscopy might be a promising tool to identify sites of obstruction and to guide surgical procedures[11] and oral appliance treatment (see chapter 10).

## Dynamic and Cone Beam CT

CT scanning is widely available and is performed while the patient is in the supine position. It is ideal for imaging craniofacial structures and the lumen of the upper airway. Three-dimensional volumetric reconstructions can be obtained by reconstruction of axial CT images or directly by using helical CT scanners. Ultrafast or dynamic CT can be performed with electron beam CT, which provides excellent temporal (50-millisecond) and spatial resolution to assess dynamic changes of the upper airway dimensions during a respiratory cycle.[12] CT scanning can be used during wakefulness or during sleep to identify the site of upper airway obstruction.

Most studies using CT to assess airway caliber during wakefulness and sleep have demonstrated narrowing in the retropalatal region of patients with OSA.[13] CT has also been used to evaluate patients undergoing UPPP. The site of obstruction identified with CT scan only partially predicts the success rate of UPPP.[14] Patients with retropalatal obstruction identified by CT scanning have better results with UPPP than do patients with retroglossal obstruction. Nevertheless, CT scanning has not become a part of the routine evaluation of OSA patients because this technique has a limited soft tissue contrast resolution (in particular for adipose tissue in the upper airway), it is still relatively expensive, and it exposes the patient to radiation.

Cone beam (CBCT) scanners are also used for the evaluation of the upper airway. CBCT uses the same principle as conventional CT but presents three major differences: *(1)* it uses a low-energy fixed anode tube; *(2)* the scanner rotates around

the patient only once, capturing the data using a cone-shaped x-ray beam (approximately 20% of the regular radiation); and *(3)* the patient is in the sitting position, although some machines have the ability to perform scanning while the patient is in the supine position. Their small size makes installation of CBCT scanners within a dental clinic feasible, but image interpretation requires training and expertise. Studies are needed to determine if CBCT has value in diagnostic evaluation of and treatment planning for patients with OSA.

## Magnetic Resonance Imaging

MRI may be the technique of choice for studying patients with OSA because it provides excellent resolution of upper airway soft tissue structures (including adipose tissue), accurately measures cross-sectional airway area and volume, allows multiplanar imaging (axial, sagittal, and coronal), provides data for three-dimensional upper airway reconstructions, can be performed while patients are awake or asleep, and does not expose patients to radiation. With the development of ultrafast or dynamic imaging, MRI can evaluate motion of the upper airway and provide information to determine the level of collapse.[12] Magnetic tagging and magnetic resonance spectroscopy may lead to a better understanding of the pathophysiology, tissue characteristics, and biomechanics of the upper airway in patients with OSA.

However, MRI is expensive, is not available in all hospitals, and can be difficult to perform if patients are claustrophobic. Also, MRI cannot be performed if patients have ferromagnetic implants such as pacemakers or patients weigh significantly more than 150 kg. Finally, patients may have difficulty achieving spontaneous sleep in the MRI scanner because of the noise associated with the procedure.

Regardless of these limitations, research and clinical studies[15,16] using MRI have significantly improved the current understanding of the pathogenesis of OSA (level of airway obstruction) and have started to provide insight into the mechanisms underlying the efficacy of continuous positive airway pressure, oral appliances, weight loss, and surgery for patients with sleep-disordered breathing. MRI is also a powerful tool to quantify intermediate traits (phenotype of the upper airway) for genetic studies in OSA patients.[17] Studies have already successfully utilized volumetric MRI to identify the upper airway soft tissue risk factors for OSA: enlargement of the tongue, lateral pharyngeal walls, and total soft tissue surrounding

the upper airway (Fig 8-2).

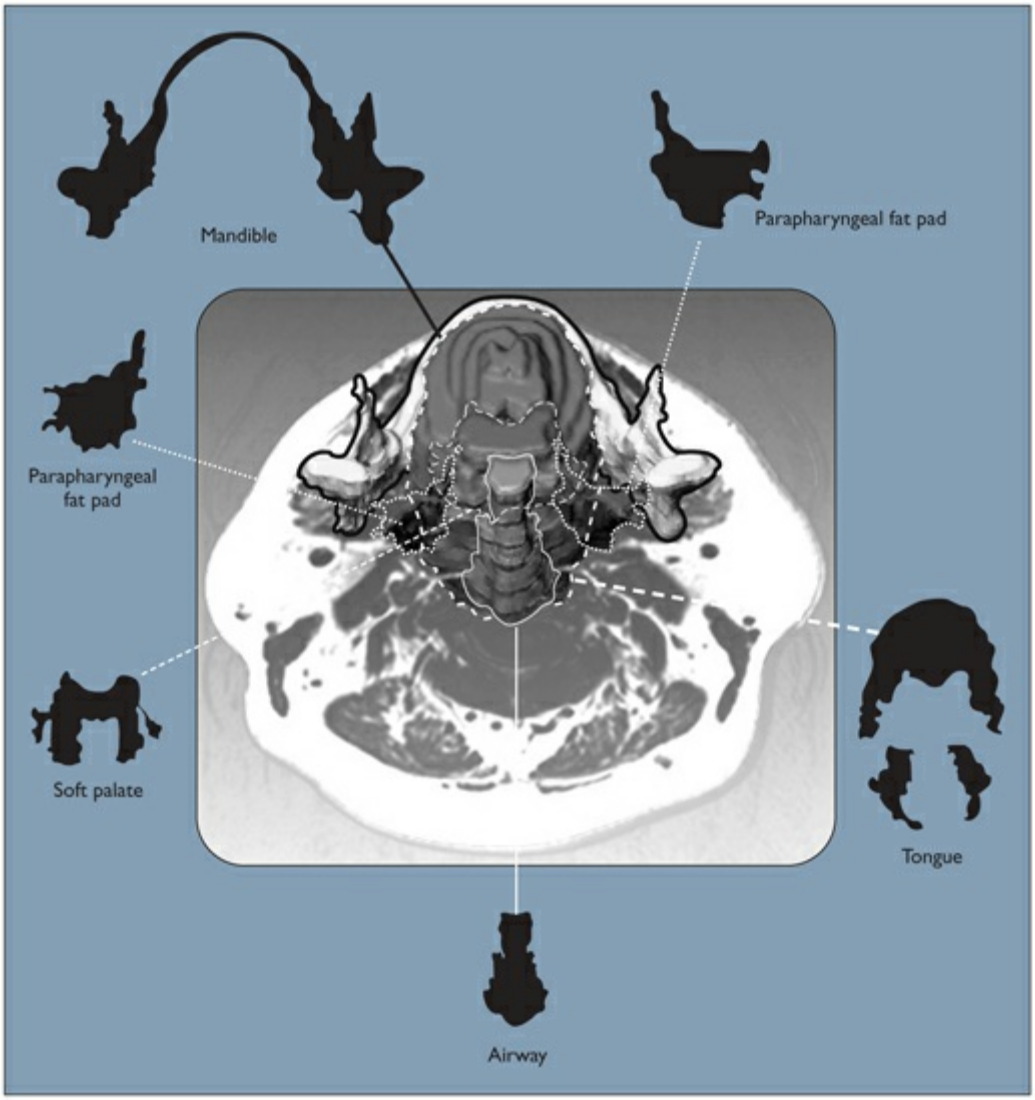


**Fig 8-2** Three-dimensional reconstruction of the upper airway and surrounding soft tissue structures from axial MRIs in a patient with sleep apnea.

Clinical indications are being developed for the use of MRI in the treatment of the upper airway, notably in the determination of the type of therapy, especially surgical (eg, patients undergoing UPPP). However, no data so far have demonstrated that the detection of the site of airway obstruction with this method improves the patient selection for surgery or the surgical outcomes for UPPP patients.[12] MRI is a powerful, noninvasive research tool that has substantially improved scientific understanding of sleep-disordered breathing, but the technique is not yet indicated for the routine evaluation of patients with sleep apnea.

## State-Dependent Upper Airway Imaging

State-dependent imaging clarifies the pathophysiology of OSA in a way that cannot necessarily be achieved during wakefulness. Changes in upper airway caliber and the surrounding soft tissue structures during sleep do not always correlate with the findings during wakefulness. Trudo et al[18] studied differences in airway structures in the sleeping and awake states in normal subjects. They found that the narrowest portion of the airway was in the retropalatal area in most subjects. The volume of the retropalatal airway was reduced by 19% during sleep, but there was no significant reduction of retroglossal airway volume. The finding that the airway does not narrow uniformly in the retropalatal and retroglossal regions during sleep indicates that the upper airway does not function as a homogenous tube. The retropalatal airway narrowing was secondary to a reduction in both the anteroposterior and lateral airway dimensions (Fig 8-3). The reduction in the lateral dimension was related to the thickening of the lateral pharyngeal walls, whereas the anteroposterior narrowing was primarily related to posterior movement of the soft palate.[18]

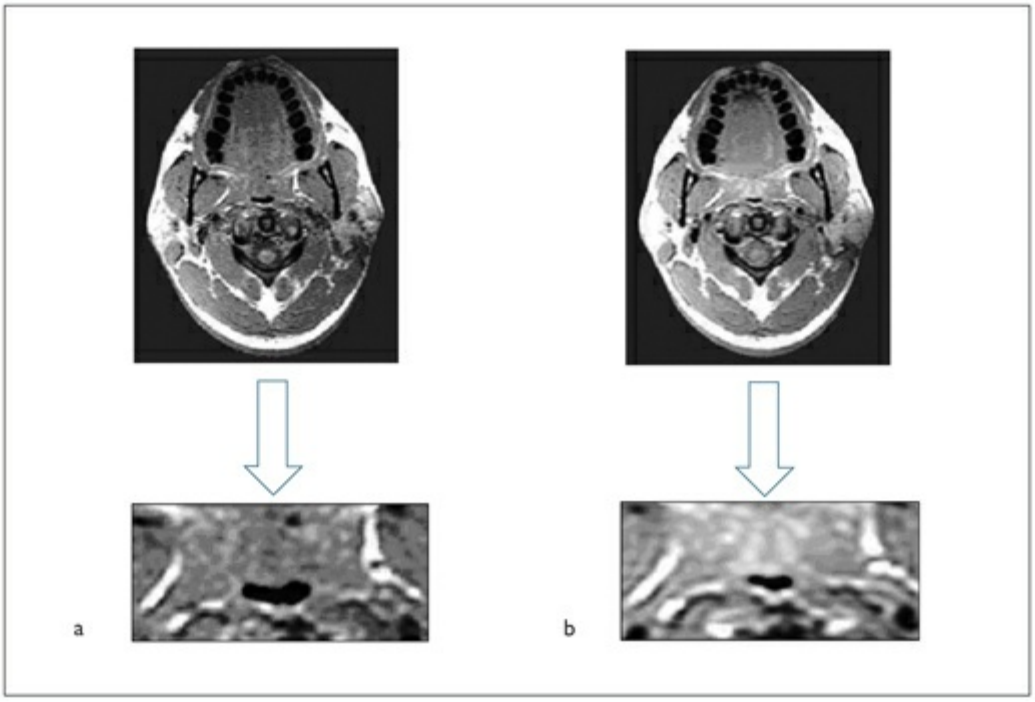


**Fig 8-3** T1-weighted axial MRIs of a normal subject during wakefulness *(a)* and sleep *(b)* showing a reduction, during sleep, in the anteroposterior and lateral dimensions of the upper airway.

Other studies have investigated the alterations in upper airway caliber in apneics during sleep. Horner et al,[13] using conventional CT imaging in patients with apneas, demonstrated that airway obstruction during sleep is caused by posterior displacement of the soft palate and tongue and lateral displacement of the pharyngeal walls. Suto and colleagues,[19] using sagittal ultrafast MRI, also found retropalatal airway closure in normal and apneic subjects during sleep. The state-dependent retropalatal narrowing resulted from reductions in the anteroposterior and lateral airway dimensions.

These state-dependent changes to upper airway conformation have also been illustrated with nonradiographic imaging techniques. Badr et al[20] used nasopharyngoscopy to study the upper airways of sleeping normal subjects and patients with central sleep apnea and demonstrated retropalatal and retroglossal narrowing in all the subjects, although retropalatal narrowing was more common. Upper airway imaging during sleep is a valuable tool for understanding the biomechanics of airway closure. State-dependent imaging may also be helpful in identifying appropriate candidates for upper airway surgery because it can provide a thorough evaluation of the site of occlusion during sleep.

## Conclusion

Both static and dynamic imaging techniques have been used to examine the structure and function of the upper airway during wakefulness and sleep. The data from these studies have emphasized the importance of the lateral pharyngeal walls in addition to the tongue and soft palate in modulating changes in upper airway caliber. At present, upper airway imaging techniques such as MRI with three-dimensional reconstruction and nasopharyngoscopy should be considered for patients who are to undergo UPPP or other types of upper airway surgery. For patients who will undergo maxillomandibular advancement, sliding genioplasty, or oral appliance treatment, CT scanning with three-dimensional reconstruction and cephalometric analysis is the imaging modality of choice. Although these different imaging modalities have significantly improved the profession's understanding of sleep apnea syndrome, they are not indicated for routine diagnostic evaluation of or treatment planning for most patients with sleep-disordered breathing.

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CHAPTER 9

# AN OVERVIEW OF OBSTRUCTIVE SLEEP APNEA TREATMENT

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Continuous positive airway pressure (CPAP) therapy is the treatment option of first choice for most patients with symptomatic and significant obstructive sleep apnea (OSA) (Fig 9-1). There is a strong evidence base to support prescription of CPAP for symptomatic (eg, sleepy) patients with moderate and severe OSA, and such treatment usually has positive neurobehavioral and cardiovascular outcomes if patients can use CPAP effectively and consistently. However, it is less clear how to manage patients with all disease severities who are relatively asymptomatic or sleepy patients who are not compliant with CPAP therapy. For these patients, a range of other options may be considered, including lifestyle modification, sleep positional modification, oral appliances, and upper airway surgery. At this time, there is no reliably effective pharmacologic therapy for OSA.

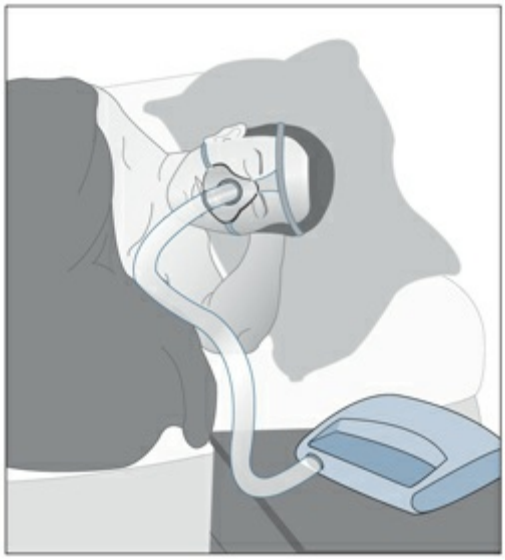

**Fig 9-1** Typical CPAP machine.

## Continuous Positive Airway Pressure

CPAP therapy for OSA was developed in the early 1980s [1] and subsequently became the first-choice therapy for symptomatic OSA. It remains the first option to be considered in this context by most sleep medicine practitioners. CPAP works by counteracting the sleep state–induced negative transmural pressure that promotes collapse and narrowing of the floppy-toned upper airway pharyngeal musculature; it does so by pneumatically splinting open the upper airway via the application of a positive pressure across the airway walls and so preventing the narrowing (hypopnea) or complete collapse (apnea) of the breathing conduit during sleep.[2]

The acute effectiveness of CPAP therapy has been repeatedly demonstrated physiologically in sleep laboratories during countless titration sleep studies (Fig 9-2); this improvement is often subsequently recognized by patients and their families when the treatment is used at home. CPAP therapy can and should render the usual metric of OSA severity, namely the apnea-hypopnea index, to within the normal range, usually considered to be fewer than 5 events per hour.

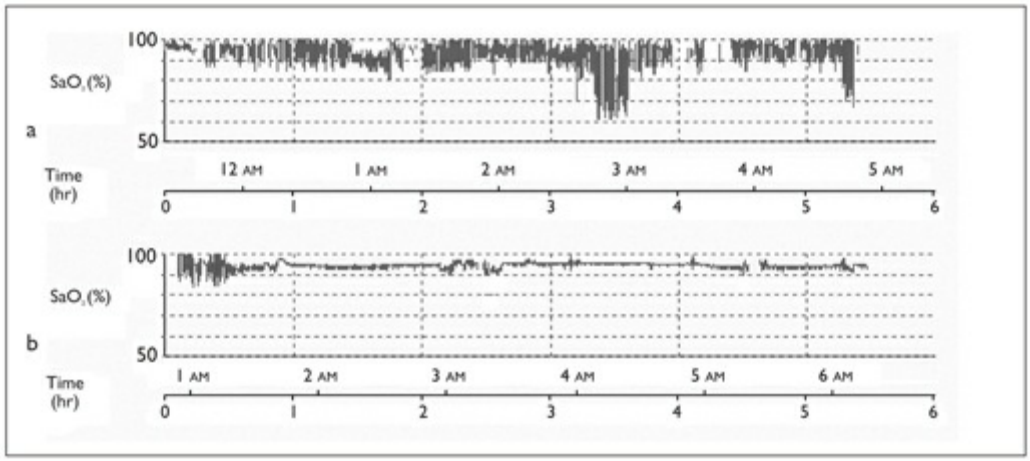


**Fig 9-2** All-night recordings of arterial hemoglobin saturation ($SaO_2$) in a patient with severe OSA on a control night *(a)* and a CPAP trial night *(b)*, highlighting the dramatic improvement with CPAP.

The diagnosis of clinically significant OSA is established by a combination of clinical assessment and diagnostic study, the latter is most often a polysomnogram (see chapter 7). This examination should be followed by a discussion between the practitioner and the patient (and often the patient's sleep partner) that focuses on the individual's risk factors for the occurrence and perpetuation of OSA as well as on the presence of significant comorbidities that may be exacerbated by and complicate the patient's OSA. Such potentially modifiable risk factors include excessive weight, obesity, and metabolic syndrome; nasal and other upper airway pathology; marked facial skeletal dysmorphia; and aggravating lifestyle issues such as smoking and excessive alcohol consumption.[3] Metabolic syndrome incorporates a range of comorbidities commonly associated with OSA: abdominal obesity, insulin resistance, dyslipidemia, and essential hypertension[4] (see chapter 6). These factors must be addressed in parallel with direct therapy (usually CPAP) used to abolish the pathophysiologic events of OSA. Interdisciplinary clinics that draw together practitioners of diverse clinical backgrounds (such as sleep, metabolism and nutrition, otorhinolaryngologic, and dental specialists) into a single, focused site for such care may form part of the future of best practice in the management of OSA.

Introduction of patients to CPAP requires explanation of the medical reasons for its use and the benefits that are likely to accrue; assistance with the choice of interface (mask) and attendant aids such as the chinstrap, humidification, and machine type (fixed-pressure, autoadjusting, or expiratory pressure relief); and even

psychologic techniques (such as cognitive behavior therapy) that may promote more successful compliance with CPAP therapy over the short and longer term. This approach usually involves a supervised in-laboratory sleep titration study, during which the technician or physician documents the optimal CPAP pressure setting. This setting is defined as the pressure that not only abolishes apneas, hypopneas, and snoring in all sleep stages and positions but also eliminates episodes of airflow limitation that do not meet the criteria of apnea or hypopnea but can contribute to arousals. The nighttime study is also used to troubleshoot any immediate adaptation issues.

Following the titration study, a prescription for the mask interface and CPAP pressure setting is given to the patient to acquire the equipment. Early follow-up by telephone, clinic attendance, and/or home visits enables confirmation of effective treatment use and troubleshooting of any ongoing or evolving difficulties and has been demonstrated in some studies to augment compliance.[5]

In a variation of the protocol, titration of optimal pressure is achieved in the patient's home (or unattended by a technician in a health care facility) with the use of an autoadjusting CPAP device set across a pressure range and used over an appropriate interval such as 1 or 2 weeks. Such devices deliver appropriate but varying positive pressure from breath to breath and have electronic data storage cards that can be analyzed to determine the average pressure delivered most frequently across the observation period (95th percentile pressure). This value can then be utilized as the optimal setting for a fixed-pressure CPAP machine.[6,7] The superiority of autoadjusting CPAP over fixed-pressure CPAP is not yet proven, and autoadjusting CPAP devices are more expensive.[8]

Good evidence has accumulated that effective CPAP improves the neurobehavioral and cardiovascular consequences of OSA (see chapter 6). Studies confirm that sleepiness and some of its consequences, such as the incidence of sleepiness-related motor vehicle accidents, are diminished with CPAP.[9,10] In many studies, general measures of quality of life in sleepy OSA patients are also improved by use of CPAP.[11,12] Adverse cardiovascular consequences of untreated significant OSA, in particular systemic hypertension but also some other measures of cardiovascular morbidity and mortality, appear to be lessened by patients' use of CPAP.[13]

Not all patients with OSA will accept or are able to tolerate CPAP. Even among sleepy patients who have moderate or more severe OSA, there is a significant level of noncompliance with prescribed therapy—between 46% and 83%, if more than 4

hours of average nightly use is used as a definition of compliance.[14] A number of individual factors or combination thereof may indicate the likelihood that a patient will not comply adequately with CPAP therapy, and these limiting factors may manifest prior to the initiation or early in the course (often in the first week) of attempted CPAP therapy.

Although many such factors have been explored as potential limiters to adequate CPAP compliance, studies suggest that much noncompliance remains to be explained. Increased nasal resistance,[15] outright claustrophobia,[16] and other psychologic factors are among the short list of limiting issues for which evidence of significant contribution to noncompliance exists. Mask leaks can be problematic, although there are now many varieties of masks that can be used to optimize treatment. Heated humidification may help individuals who experience nasal stuffiness with CPAP, and psychologic approaches, including cognitive behavioral therapy, to improve patient compliance are being applied with encouraging early results.[17]

There is scope for use of other treatments (eg, oral appliances; see chapter 10) as an adjunct to CPAP, and this is particularly relevant when patients travel to remote areas where CPAP usage is impractical or impossible.

# Other Treatments

## *Conservative treatment*

Conservative approaches involving weight loss, smoking cessation, and alcohol moderation are encouraged and useful in selected patients with OSA. Weight loss has been shown to be beneficial in reducing the severity of OSA,[18] and, at least anecdotally, major weight loss such as may occur over time after bariatric surgery can result in resolution of OSA.

Positional therapy (eg, using a backpack that prevents the subject from sleeping in the supine position) is most beneficial when OSA is predominantly supine in its occurrence, but studies suggest only a partial response to such therapy.[19]

A large range of pharmacologic approaches to treating OSA have been explored over many years, but these have been shown to be minimally or not at all effective[20]; research continues in this area.

Oral appliances such as mandibular repositioning devices (see chapter 10) and dentofacial orthopedic approaches (see chapter 11) in the management of OSA are discussed elsewhere in this volume. A comparison of OSA treatments, including surgery, is shown in Fig 9-3.

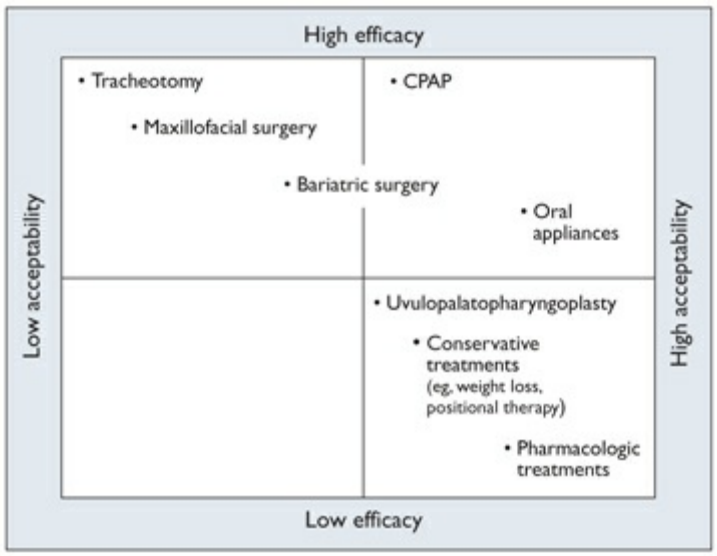


**Fig 9-3** Positioning of various OSA treatment classes in a matrix comparing efficacy and acceptability of treatments. Efficacy refers to the impact of the treatment on the apnea-hypopnea index and symptoms. Acceptability encompasses issues related to side effects, ease of use, cost, impact on others (eg, spouse), and compliance. To be a viable treatment option for the majority of patients, the therapy has to be both efficacious and acceptable (top right-hand quadrant). (Adapted from Cistulli and Grunstein[21] with permission.)

## *Upper airway surgery*

There are many well-described surgical approaches to the treatment of the upper airway in OSA (Table 9-1). Generally such surgery is reserved for patients who have snoring with minimal OSA or who have failed or are unwilling to use other effective OSA treatments (usually CPAP). The goal of such surgery is tissue reduction or reconstruction of the upper airway at any or all levels of anatomic narrowing: nasal, (retro-) palatal, and hypopharyngeal (base of tongue). Surgical management of the upper airway in OSA often involves a combination of these procedures, performed in phases. The selection and adequate performance of the procedures that will lead to the best outcomes require an experienced surgeon and

careful preoperative and perioperative multidisciplinary assessment.

| Table 9-1 | Upper airway surgical procedures for snoring and OSA* |
|---|---|
| **Procedure** | **Indications** |
| Nasal reconstruction | This approach may be used in patients with nasal septal and/or bony deviation, collapse of the alar valve or rim, and turbinate hypertrophy. (Turbinate reduction may also be achieved by radiofrequency ablation techniques.) |
| Tonsillectomy and/or adenoidectomy | This approach may be used in patients with tonsillar and/or adenoidal hypertrophy. |
| Uvulopalatopharyngoplasty | Palatal surgery aims to enlarge the collapsible retropalatal space by removing the elongated and swollen uvula and posterior portion of the soft palate and by refashioning the lateral pharyngeal pillars. |
| Mandibular osteotomy with genioglossus advancement; hyoid myotomy suspension; tongue base surgery (laser or radiofrequency vaporization approach or by linguoplasty) | The hypopharyngeal (base of tongue) space may be enlarged by surgical techniques that advance the position of the tongue itself or its supporting structure or by techniques that reduce the volume of tongue tissue directly. |
| Maxillomandibular advancement osteotomy | This approach may be used for patients with significant OSA who cannot or will not use CPAP or who have frank mandibular deficiency. |
| Tracheotomy | Nowadays, this option is used only rarely in severe cases of OSA that are not responsive to other treatments; tracheotomy bypasses the upper airway obstruction. |

*Adapted from Cistulli and Grunstein[21] with permission.

The appropriate definitions of surgical "success" are controversial, and recent critiques of surgery for treatment of OSA have documented the clear need for higher quality evidence and adequate definition of therapeutic effectiveness.[22] Although rarely leading to elimination of OSA, the improved patency resulting from nasal surgery may enhance effective use of and compliance with CPAP or reduce oral breathing. A recent meta-analysis has found that the pooled success rate for phase 1 procedures (eg, uvulopalatopharyngoplasty, laser-assisted palatopharyngoplasty,

radiofrequency ablation of soft palate or tongue base, genioglossus advancement, and hyoid myotomy suspension) is 55% when success is defined as a 50% reduction in the apnea-hypopnea index; the success rate falls to 31.5% when defined as a reduction in the apnea-hypopnea index to 10 or fewer events per hour. For phase 2 procedures (maxillary and/or mandibular advancement), the success rate is 86% when the more liberal definition is used but falls to 45% with the more rigorous definition.[22]

Many of these surgical procedures are associated with adverse effects, including bleeding, infection, permanent tooth anesthesia, and neuropathic pain.[23] Thus, it is important to establish more precise data about their effectiveness and the types of patient who might benefit from such treatment.

## Conclusion

CPAP remains the mainstay for effective treatment of significant symptomatic OSA. Recent evidence confirms the objective benefits. There remain difficulties in establishing CPAP treatment in some patients; further research is required to define effective remedies for factors that limit higher overall levels of compliance. There is growing evidence of the beneficial role of alternative therapies, and further research is required to define the subsets of patients for whom such therapies are useful.

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# CHAPTER 10

# ORAL APPLIANCES

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Snoring and obstructive sleep apnea (OSA) are common in the adult population, and oral appliances represent an easy and noninvasive treatment option for many of these individuals.[1–4] Mandibular repositioning appliances (MRAs) move the mandible forward to improve the upper airway patency and are the most evaluated type of oral appliance (Fig 10-1), while use of the tongue-retaining device (TRD) that produces suction of the tongue into an anterior bulb is less common.

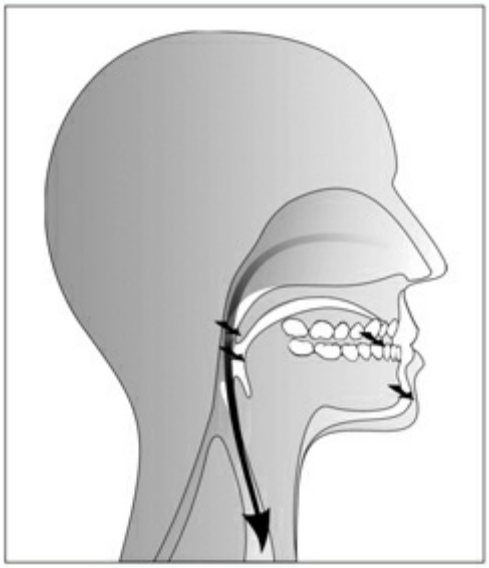

**Fig 10-1** Upper airway with *(arrows)* and without the MRA. (Illustration courtesy of Drs Marie Marklund and Michael Munkholm.)

## Mechanism of Action

The primary mechanism of action of an MRA is generally considered to relate to the anterior movement of the tongue and consequent increase in the anteroposterior dimensions of the oropharynx (see Fig 10-1). However, based on a number of studies using various imaging modalities, including computed tomography, magnetic resonance imaging, and nasopharyngoscopy,[1,2] it appears that the cross-sectional area of the velopharynx increases in both the lateral and anteroposterior dimensions, while the oropharynx increases in the lateral dimension during mandibular advancement in awake patients (Fig 10-2). These changes are thought to be mediated through mechanical stretching of the palatoglossal and palatopharyngeal arches, through which exist intricate linkages among the muscles of the tongue, soft palate, lateral pharyngeal walls, and the mandibular attachments. Notably, the changes in airway configuration produced by these appliances seem to show interindividual variability, which is likely a major factor in the inconsistent clinical response associated with this treatment modality.[1–3]

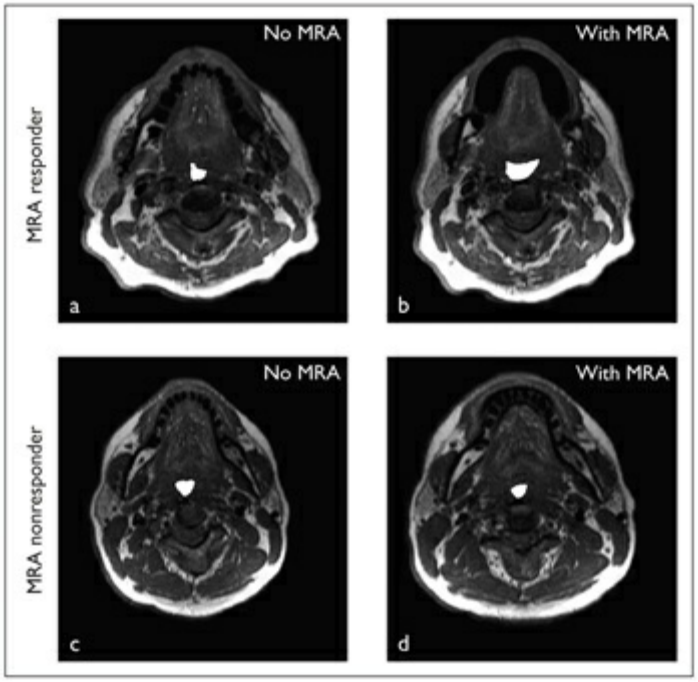


**Fig 10-2** Axial magnetic resonance imaging sections at the retroglossal level in two patients with OSA, taken with and without an MRA. The MRA responder *(a and b)* shows an increase in lateral airway dimensions with the MRA, whereas the nonresponder *(c and d)* does not (airways are highlighted).

The mechanism of action of a TRD is likely to be a little different from that of an MRA. The forward movement of the tongue out of the oral cavity tends to be greater with a TRD than that achieved with an MRA, and this movement may produce more favorable changes in the retroglossal region. It is also possible that a TRD counteracts the effect of gravity on the tongue in the supine position, although this remains to be proven.

## Clinical Outcomes

The majority of patients treated with MRAs report reduced daytime sleepiness, and snoring and sleep apnea measurements confirm fewer apneic and hypopneic events. Complete treatment success, defined as an apnea-hypopnea index (AHI) of fewer than 5 events per hour and resolution of symptoms, has been reported to occur in 19% to 75% of patients with mild-to-moderate OSA; the use of a more liberal definition of success, namely an AHI of fewer than 10 events per hour, has demonstrated higher success rates[5–8] (Table 10-1). Persistent snoring and daytime sleepiness during MRA treatment indicate a subtherapeutic effect.

**Table 10-1** **Effects of MRAs as reported in randomized controlled studies**

| | | AHI or RDI* | | AHI < 10 | | | AHI < 5 | |
|---|---|---|---|---|---|---|---|---|
| **Study** | **N** | **MRA** | **CPAP** | **Control** | **MRA** | **CPAP** | **MRA** | **center** |
| Ferguson et al[10] | 20 | 25 [15]<br>14 [15] † | 24 [17]<br>4.0<br>[2.2]†§ | | 55% | 70% | | |
| Engleman et al[9] | 48 | 31 [26]<br>15 [16] | 31 [26]<br>8.0<br>[6.0]§ | | 47% | 66% | 19% | 34% |
| Gotsopoulos et al[6] | 73 | 27 (2)<br>12 (2) †‡ | | 27 (2)<br>25 (2) | | | 36% | |
| Barnes et al[5] | 80 | 21 (1.3)<br>14 (1.1)<br>†‡ | 21 (1.3)<br>4.8<br>(0.5)†§ | 21 (1.3)<br>20 (1.1) | 49% | | | |
| | | | 24 (1.9) | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Lam et al[11] | 101 | 11 (1.7)<br>†‡ | 2.8<br>(1.1)†§ | 19 (1.9)<br>21 (2.5) | | | | |

(RDI) respiratory disturbance index.
*Results are presented as mean and (standard error of mean) or [standard deviation] before intervention (upper row) and after intervention *(lower row)*.
†Lower AHI or RDI with treatment than without treatment.
‡Lower AHI or RDI with MRA than with control.
§Lower value AHI or RDI with CPAP than with MRA.

There is as yet little good evidence of any beneficial clinical effects from TRDs, and they tend to be more cumbersome than MRAs.

Continuous positive airway pressure (CPAP) more effectively reduces sleep-related breathing disturbances than do oral appliances, particularly in patients with more severe disease.[5,7,9–11] Nevertheless, patients usually prefer MRAs over CPAP when both treatments are effective.[10] A comparison of MRA and CPAP is presented in Table 10-2.

**Table 10-2** **Relative treatment effects of MRA and CPAP on a range of clinical outcomes in OSA**

| Treatment effect | MRA | CPAP |
|---|---|---|
| Reduction in snoring | ++ | +++ |
| Improvement in sleep architecture | ++ | ++ |
| Reduction in sleep fragmentation | ++ | ++ |
| Improvement in sleep breathing indices (eg, AHI, minimum oxygen saturation) | ++ | +++ |
| Improvement in subjective and objective measures of daytime sleepiness | ++ | ++ |
| Improvement in cardiovascular function (eg, blood pressure and endothelial function) | ++ | ++ |
| Improvement in neuropsychological function | + | + |
| Improvement in quality of life | + | + |
| Reduction in motor vehicle accident risk | ?/+ | + |

+ = small benefit; ++ = moderate benefit; +++ = large benefit; ? = unresolved.

The modification of the health risks associated with OSA is a key goal of treatment (see chapter 6). Recent studies demonstrate MRAs to have a blood pressure–lowering effect of a similar magnitude to that achieved with CPAP.[12] Similarly, some studies demonstrate improvements in quality of life and aspects of neurocognitive performance, such as psychomotor speed, when MRAs are used.[13]

## Side Effects

Initial, transient side effects from MRAs are common; these include excessive salivation or dryness in the mouth, tenderness in the teeth and cran-iomandibular system, and the perception of an abnormal occlusion in the mornings. In the longer term, the occlusal changes become more prominent. The overjet and the overbite diminish, and the occlusion may open laterally.[14–16] Patients with normal or mesial occlusion will risk unfavorable occlusal changes, while patients with distal occlusion may benefit from the treatment.[14] The smallest occlusal changes may be expected in patients with initially deep bites and from devices that reduce the forces on the anterior teeth.[14,16] Nevertheless, the adverse effects of MRAs are generally considered to be negligible among most patients.

## Clinical Protocol

### *Multidisciplinary approach*

MRA treatment requires a multidisciplinary collaboration among the physicians who have the diagnostic, therapeutic, and overall medical responsibility for the patient. Dentists who are specialized in the treatment of sleep apnea have the main responsibility of selecting the best oral appliance for the given conditions (eg, whether the complaint is jaw pain or temporomandibular limitations and lack of protrusive movement; whether the dentition and periodontal tissue are healthy or unhealthy; and whether the patient is fully or partially edentulous). They also have to monitor the efficacy of the chosen oral appliance over time, with the assistance of

appropriate. The clinical approach to medical diagnosis is covered in chapter 7.

## *Indications and contraindications*

The decision to prescribe an oral appliance requires an understanding of all therapeutic options in the context of the individual patient's circumstances (see chapter 9). According to published practice guidelines, oral appliances are indicated for patients with mild-to-moderate OSA who prefer this form of treatment over CPAP or who do not respond to or are unable to tolerate CPAP.[3] The guidelines also recommend that, whenever possible, CPAP be considered for patients with severe OSA in preference to oral appliances, given its greater efficacy. At present, CPAP has no known role in treating nonobstructive forms of sleep-disordered breathing (see chapter 4).

A major clinical limitation of oral appliances is the time required to achieve the desired effect, especially when there is an imperative to commence treatment quickly. This includes situations involving severe symptomatic OSA (eg, leading to a concern about driving risk), with or without coexistent medical comorbidities such as ischemic heart disease.

## *Prediction of treatment response*

Clinical features and cephalometric variables reported to be associated with a better outcome of MRA therapy are listed in Box 10-1.[17] Imaging modalities such as computed tomography, magnetic resonance imaging, and endoscopy appear to provide predictive information, although their role in routine care is limited by cost and convenience factors (see chapter 8).

**Box 10-1 Clinical and cephalometric predictors of successful treatment with an MRA**

**Clinical predictors**

- Younger age
- Lower body mass index
- Supine-dependent OSA

- Supine-dependent OSA
- Smaller oropharynx
- Smaller overjet
- Shorter soft palate
- Smaller neck circumference
- Lower AHI

**Cephalometric predictors**

- Shorter soft palate
- Longer maxilla
- Decreased distance between mandibular plane and hyoid bone

Notably, enlargement of the velopharyngeal airway during mandibular advancement appears to predict a good clinical outcome (see Fig 10-2). There are reports that measurement of nasal resistance and spirometry have moderate predictive value.[18,19] The clinical application of these findings will require prospective validation of these methods.

## *Initial dental assessment*

The dentist conducts an odontologic examination, including the patient's history and documentation of oral diseases and occlusal conditions. Caries, periodontal disease, or craniomandibular disorders may delay or preclude MRA treatment. The presence of 8 to 10 teeth in each arch and a minimum 5-mm protrusive capacity of the mandible are usually required for optimal results from MRA treatment.

After the assessment is completed, the dentist gives the patient an individual estimate about the chances of treatment success in relation to the risk for side effects; the explanation should include a long-term treatment plan. Written consent is valuable for the future management of the treatment.

## *Appliance selection*

Several types of MRAs have been evaluated. The clinician's judgment is required to determine the most appropriate design for each patient. Information about

by the national and international dental sleep medicine societies.

Dual-block appliances consist of maxillary and mandibular plates that are coupled by one of several modes, including elastic or plastic connectors, metal pin and tube connectors, hook connectors, acrylic resin extensions, or magnets. Dual-block adjustable MRAs are most convenient because these facilitate the incremental adjustment of mandibular position over time. The influence of these appliance design features on treatment outcome remains uncertain, although studies suggest that they may impact efficacy and tolerance.[8,20]

Monoblock devices take more time to adjust and require the support of a dental technician. The TRD has primarily been suggested for patients with an insufficient dental support to retain an MRA.

## *Appliance adjustment*

The dentist prepares plaster casts of the teeth and an occlusal registration to estimate a comfortable and effective jaw position. An initial mandibular advancement of about 5.0 mm or 50% to 60% of maximal protrusion is recommended, with successive increases in relation to the achieved treatment effects over a period of weeks or months, as tolerated.[1] The final extent of jaw repositioning depends on the patient's ability to protrude, the severity of OSA, the occlusal diagnosis, the type of appliance, and the patient's ability to breathe through the nose.

During the initial stages (weeks to months), the patient and, if possible, the sleep partner assess the improvement in symptoms. Patients who have achieved the desired subjective therapeutic response are referred for follow-up. Incremental advancement in steps of 0.5 to 1.0 mm is implemented for patients with a subtherapeutic response.[21] Advancement sometimes must be diminished to alleviate tenderness in the craniomandibular system.

## *Follow-up*

Once titration is complete and the optimal subjective therapeutic response has been achieved, the patient is referred back to the sleep clinician for medical evaluation of the treatment outcome. A follow-up sleep study is recommended, particularly for patients with moderate-to-severe OSA at baseline because improvement in symptoms is not always accompanied by an adequate reduction in AHI.

symptoms is not always accompanied by an adequate reduction in AHI.

The exact regimen for long-term follow-up has to be individualized based on the patient's OSA severity, general health, type of occlusion, and oral health. During the follow-up visits, the dentist monitors the usage, symptoms, weight increase, side effects, dental and oral health, degree of jaw repositioning, and condition of the appliance. Ongoing contact with the sleep clinician is important because the treatment effects on OSA may vary over time, which may necessitate a renewed sleep study or consideration of an alternative treatment modality because of side effects or medical concerns.

Currently there is no objective method to monitor compliance in clinical practice, and evaluation relies on self-report. Although compliance is highly variable, studies suggest that patients use the treatment most nights for the entire sleep period, at least in the short term. Over the first year of treatment, the median use is approximately 77% of nights.[1] These results may be dependent on attributes of the appliance and the follow-up protocol employed. Long-term adherence, up to 5 years, also seems to be acceptable, although some patients abandon treatment for a variety of reasons, including development of side effects, appliance wear and tear, and attenuation of the efficacy of treatment.[22]

## Conclusion

MRAs are indicated as the first line of treatment for snorers and patients with a mild-to-moderate OSA who are otherwise generally healthy. Patients who cannot tolerate CPAP therapy or who prefer MRA therapy may use this device provided that a sleep study has confirmed an adequate therapeutic response. Side effects are usually mild and transient but may influence the length of acclimatization required to complete the treatment. Minor occlusal changes are common, but these are acceptable for most patients. A multidisciplinary approach is obligatory to achieve accurate diagnosis and optimal treatment with oral appliances.

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CHAPTER 11

# DENTOFACIAL ORTHOPEDICS

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Children and adults who suffer from respiratory problems and obstructive sleep apnea (OSA) commonly exhibit disturbances in craniofacial morphology. This chapter explores the impact of respiratory alteration on the growth in the craniofacial region, the relationship between craniofacial morphology and sleep-disordered breathing, and the effect of orthopedic therapy on dentofacial morphologies and sleep-disordered breathing.

## Craniofacial Growth and Impact of Function on Craniofacial Form

The general consensus for craniofacial growth is that cartilage is the primary determinant of growth of the cranial base synchondroses. The growth of the dentofacial regions follows the functional matrix theory; that is, growth occurs in response to functional needs and possibly in response to the growth of the nasal cartilage. Linder-Aronson1 proposed the cause-and-effect pathway of reduced nasal breathing during wakefulness and resultant craniofacial abnormality (Fig 11-1). Mouth breathing leads to an altered pattern of muscle recruitment in the oral and nasal capsule, resulting in skeletal changes. Animal experiments have demonstrated that 3 months of partial fixed nasal airway reduction in infant rhesus monkeys

resulted in an increase in the facial height and a reduction in the maxillary width and length.[2] In children, mouth breathing associated with adenotonsillar hypertrophy is associated with extended posture of the head, a retrognathic mandible, larger anterior facial height, steeper mandibular plane, lowered position of the hyoid bone, and anteroinferior posture of the tongue compared to normal children.[3] This seems to be a physiologic response to the need for maintenance of a patent oropharyngeal airway. Adenoidectomy appears to facilitate mandibular growth over the subsequent 5 years.[3]

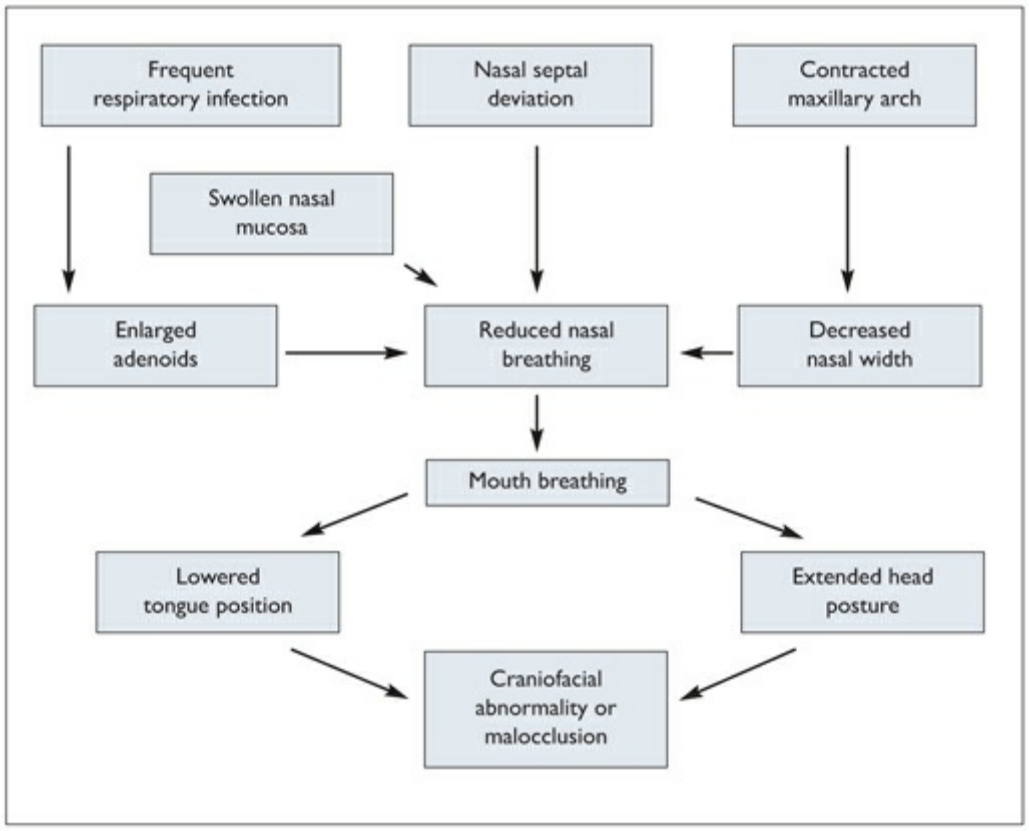


**Fig 11-1** Cause-and-effect relationship between increased airway resistance and craniofacial abnormality or malocclusion. (Adapted from Linder-Aronson[1] with permission.)

Solow and Kreiborg4 investigated the relationship of postural changes induced by airway obstruction and morphologic dentofacial changes in children and young adults and developed the soft tissue stretch theory. This postulates that mouth breathing leads to postural changes (3- to 5-degree extended craniocervical posture), an altered pattern of muscle function, and concurrent skeletal changes.[4] Nasopharyngeal obstruction is considered to be a trigger to extended craniocervical

posture because removal of the adenoids reverses this craniocervical angulation. A decreased craniocervical angulation decreases the dorsally directed pressure on the soft tissues, which improves the incisor proclination. This same change in posture and decrease in stretching of soft tissues should also generate an improvement in mandibular development.

A recent preliminary report, using data from the Third National Health and Nutrition Examination Survey conducted in the United States (encompassing 14,272 individuals from 8 to 50 years of age), has challenged the conventional view by casting doubt on the relationship between respiratory function and malocclusion.[5] Regression analyses in the population-based cross-sectional study did not reveal any significant difference in the prevalence of respiratory disease and/or allergy in individuals with posterior crossbite, negative overjet, open bite, or excessive overjet compared to the prevalence in control subjects without these occlusal traits, either before or after researchers controlled for age, race, gender, orthodontic treatment, and socioeconomic status.[5] Further work will be required to resolve this important issue.

## Dentofacial Morphology Associated with OSA

Numerous imaging studies have identified the facial characteristics associated with OSA (see chapter 7):

- Retruded maxilla and mandible in relation to cranial base
- Increased mandibular plane angle and anterior facial height
- Inferiorly positioned hyoid bone
- Reduced length of the mandible
- Narrowed posterior airway space and longer soft palate
- Increased tongue size
- Increased craniocervical angulation

Furthermore, it has been suggested that OSA patients have significantly narrower, shorter, and more tapered maxillary dentition and a more skeletally constricted maxilla than do nonsnoring, nonapneic control subjects.[6]

Genetic and ethnic variables must be considered in the understanding of the cause-

and-effect relationship of craniodental characteristics and risk of sleep-disordered breathing. Maxillomandibular prognathism is frequently found in African Americans; a large tongue and soft palate could reduce the patency of airway and predispose these individuals to OSA. The tendency to maxillomandibular retrusion in Hispanics and the tendency to a narrow cranial base angle in Asians predispose both groups to OSA. Hou et al[7] evaluated the dentofacial characteristics of Chinese men with OSA and found that those with severe OSA had a significantly longer soft palate, more inferiorly positioned tongue base, and a larger craniocervical extension than did those with mild OSA. This study also established body weight, lower posterior facial height, mandibular body length, craniocervical extension, and sella-hyoid distance as significant predictors for severity of apnea.[7]

A study of Japanese men using three-dimensional magnetic resonance imaging found greater mandibular divergence, smaller mandibular length, and smaller area at the mandibular base, but no differences in soft tissue volumes, between OSA patients and normal controls.[8] Such studies highlight the variable interactions between craniofacial and soft tissue factors in the development of OSA across different racial groups.

The effect of adenotonsillectomy on dentofacial morphology has been examined in children with OSA. In a study comparing OSA children with age-and sex-matched normal control children, the OSA group showed a more posteriorly inclined mandible, more anteriorly inclined maxilla, greater lower anterior facial height, shorter anterior cranial base, and reduced airway space prior to surgery. Five years after adenotonsillectomy, there was no significant difference in most aspects of dentofacial morphology between the study and control groups, except that the children in the OSA group exhibited a shorter anterior cranial base and shorter nose.[9] The results of the study *(1)* support the possibility that upper airway obstruction during childhood development contributes to the progressive evolution of OSA (Fig 11-2) and *(2)* lay the foundations for a therapeutic strategy that aims to halt this evolution. Considering the apparent association between childhood snoring and poor academic performance[10] and the reported improvements in neurobehavioral function in children undergoing adenotonsillectomy for OSA,[11] the potential role of dentofacial orthopedic treatment in the prevention of OSA is of public health interest. (The role of adenotonsillar hypertrophy in tooth grinding and sleep bruxism is discussed in chapter 16.)

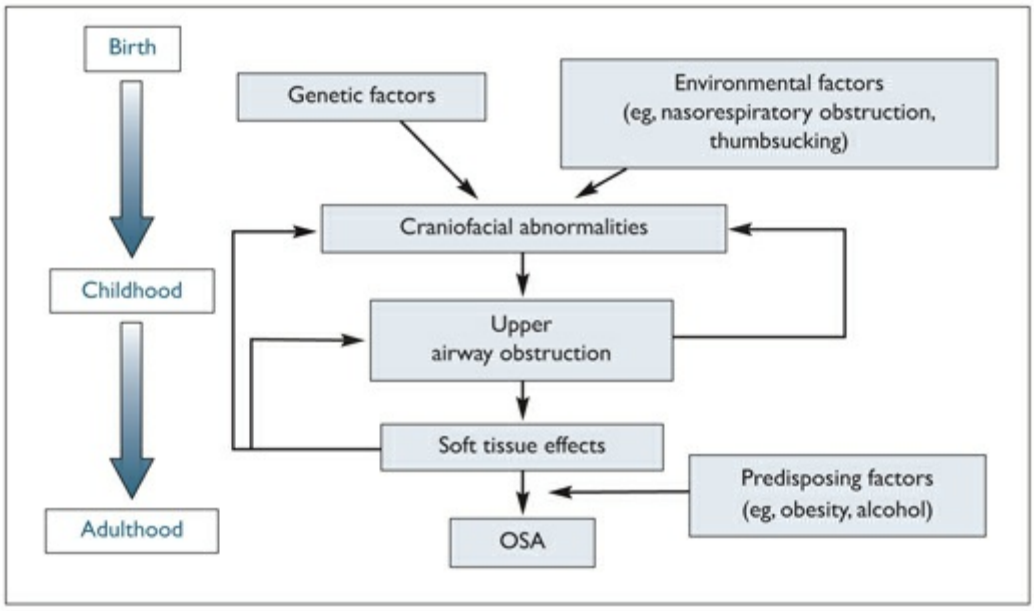


**Fig 11-2** Postulated evolution of OSA from childhood to adulthood, emphasizing the potential role of craniofacial abnormalities.

## Dentofacial Changes with Orthopedic Therapy

Improvement and normalization of the dentofacial morphology may have a positive impact on respiratory problems and OSA.

### *Maxillary expansion*

A significant number of children suffering from mild OSA have nasal obstruction (nasal septal deviation with or without turbinate hypertrophy) associated with a narrow maxilla. Maxillary constriction may increase nasal resistance and alter the tongue posture, leading to narrowing of the retroglossal airway and OSA.[12]

Maxillary expansion is a common orthopedic treatment for maxillary constriction. Several studies have shown an increase in nasal width and nasal cavity dimension following maxillary expansion. Pirelli et al[13] investigated the effect of rapid maxillary expansion (RME) on 31 children (19 boys and 12 girls) with narrowed maxillae and absence of adenotonsillar hypertrophy. Six to 12 months following RME retention, a resolution of sleep-disordered breathing was noted.

In a further study, 42 children with a history of mouth breathing, snoring, OSA, and evidence of maxillary constriction, but without adenotonsillar hypertrophy or obesity, were studied.[14] Patients underwent orthodontic and ear, nose, and throat assessments, including auditory and respiratory tests, a daytime sleepiness questionnaire, polysomnography, and radiologic investigations. All the investigations were carried out before orthodontic therapy, after 1 month while the expansion device was still in place, and 4 months after the end of the orthodontic treatment, which lasted for about 6 to 12 months. In all patients, opening of the midpalatal suture was achieved, as confirmed by both intraoral occlusal radiographs and posteroanterior cephalograms (Fig 11-3). RME was found to widen the nasal fossa and release the septum, thus restoring normal nasal airflow and resolving OSA.[14]

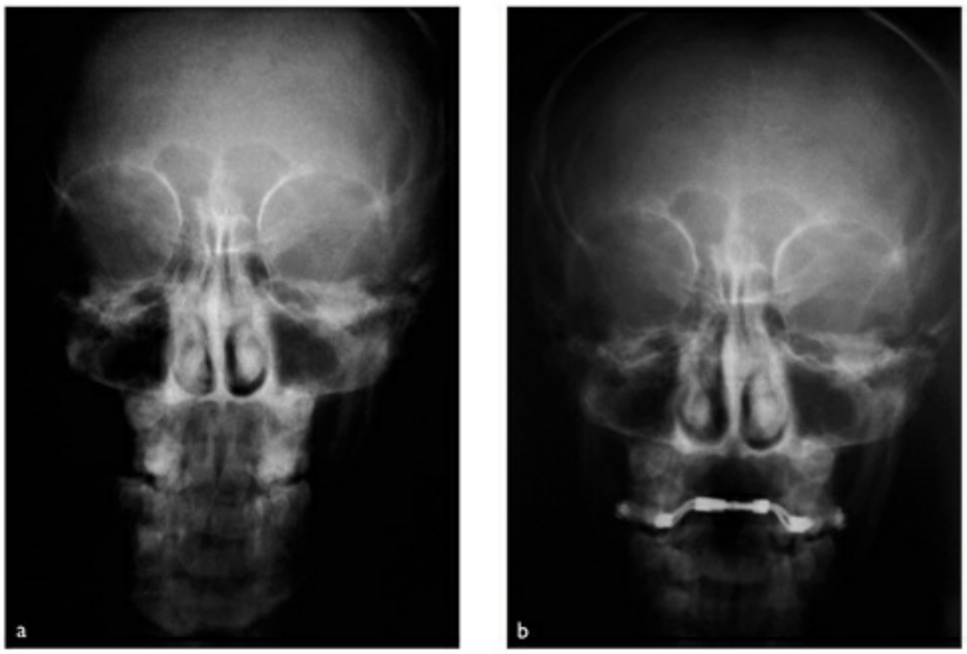


**Fig 11-3** Teleradiographs in posteroanterior view taken before *(a)* and after *(b)* RME, showing the widening of the nasal cavity and release of the septum.

More recently, the role of combined adenotonsillectomy and RME, and the best sequence of these treatments, was evaluated in prepubertal children who had OSA and adenotonsillar hypertrophy.[15] In the majority of such patients, both therapeutic approaches were required to resolve the OSA, and the order of treatments did not appear to be important.[15] These studies suggest an important role of RME in the treatment of OSA in children.

Furthermore, RME or surgically assisted RME can be used to widen the maxilla in adults. In a pilot study, Cistulli et al[16] revealed that 9 of 10 adult patients who had RME or surgically assisted RME had major reductions in snoring, OSA, and hypersom-nolence. However, further research is required to validate the cause-and-effect association of OSA with a narrow maxillary-palatal-nasal complex as well as to evaluate the long-term stability of maxillary and nasal expansion.

## *Maxillary advancement*

Maxillary retrusion can be diminished through dentofacial orthopedics as well as by surgery (see chapter 9). Very few studies have investigated the effect of maxillary advancement on the upper airway, either as a treatment for sleep-disordered breathing or as a preventative measure. It has been shown that the combination of RME and reverse-pull headgear therapy significantly increase the linear measurements and nasopharyngeal area of the upper airway.[17] Samman et al[18] performed cephalometric comparisons in 70 adults with Class III maxillomandibular relationships before and 6 months after surgery. In the maxillary advancement group, nasopharyngeal depth was increased. Because it is not known whether these subjects had OSA, the relevance of these findings to OSA warrants investigation.

## *Mandibular advancement*

Baik et al[19] reported that OSA patients with obstruction at the retropalatal and retroglossal regions showed the strongest tendencies for mandibular retrognathia. It is postulated that advancement of the mandible may decompress the pharyngeal airway and thereby reduce the symptoms of OSA (Fig 11-4). Mandibular advancement is achieved by functional appliance therapy, mandibular distraction osteogenesis, surgical mandibular advancement, or a combination of these techniques. Mandibular advancement is among the most frequently used approaches in the surgical management of OSA (see chapter 9).

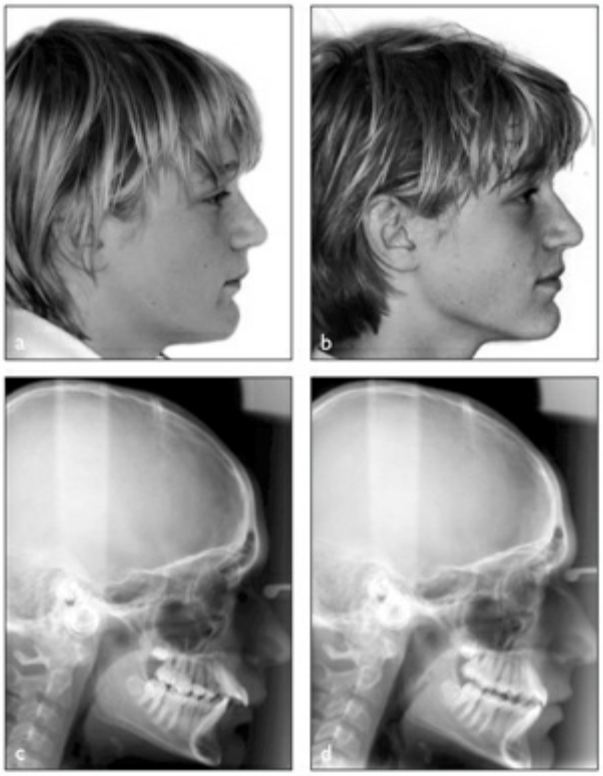

**Fig 11-4** Before *(a)* and after *(b)* profile views and before *(c)* and after *(d)* lateral cephalograms of mandibular deficiency treated with an orthopedic appliance.

The effect of a functional orthopedic appliance on oropharyngeal airway dimensions has been assessed in children with mandibular deficiency, and these appliances have been found to significantly increase the posterior airway space at the oropharyngeal and nasopharyngeal levels.[20] A more recent long-term study evaluated the stability of the changes in the pharyngeal airway area following activator-headgear treatment; the area of pharyngeal airway showed a significant increase during orthopedic treatment and remained stable at long-term evaluation.[21] However, neither study involved patients with OSA, and evaluations were performed with two-dimensional radiographs. Hence, further work is required to evaluate this approach by using three-dimensional imaging in prospective studies.

## Conclusion

Craniofacial morphology plays an important role in the pathophysiology of OSA.

Although the cause-and-effect relationship remains to be proven, upper airway obstruction during childhood development appears to contribute to the development of craniofacial abnormalities that result in further airway narrowing. Early identification and treatment of such abnormalities using dentofacial orthopedic techniques may be of benefit in children with OSA. Furthermore, treatment may have a potential preventive role.

Advanced imaging modalities such as cone beam computed tomography and magnetic resonance imaging can assist in the assessment of such patients (see chapters 7 and 8) and help to more clearly define the cause-and-effect relationships. However, more rigorous studies are required to clearly define the role of dentofacial orthopedics in the long-term treatment of OSA.

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# SECTION III

## SLEEP BRUXISM AND MOVEMENT DISORDERS

CHAPTER 12

# DEFINITIONS, EPIDEMIOLOGY, AND ETIOLOGY OF SLEEP BRUXISM

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Ghizlane Aarab, DDS
Jacques van der Zaag, DDS

Sleep bruxism (SB) is a common sleep-related movement disorder that is characterized by clenching or grinding of the jaws or teeth. Bruxism may also occur during wakefulness and is then primarily characterized by clenching or tapping of the teeth or jaw bracing without tooth contact. The present chapter deals with SB and not with awake-time bruxism. Other orofacial movement disorders during sleep, such as faciomandibular myoclonus and rapid eye movement behavior disorders, are the subject of chapter 13.

A detailed description of the clinical and instrumental techniques for diagnosing SB can be found in chapter 14. As discussed in that chapter, a final diagnosis of SB can only be established by sleep laboratory testing; oral history and/or clinical assessment may be inaccurate. SB is not always a harmless condition; its possible detrimental effects on orofacial structures range from dental problems (such as tooth wear [attrition] and fractures or failures of dental restorations or implants) to musculoskeletal problems (such as hypertrophied masticatory muscles and temporomandibular pain) and headache.

When any of these possible consequences is present, treatment of SB may be indicated.[1] Management of SB includes sleep hygiene instructions, occlusal stabilization appliances, and medication (see chapter 17).

In the present chapter, the definitions and epidemiology of SB in adults are elaborated first. While the physiopathology is discussed in detail in chapter 15, the present chapter includes a concise description of the etiology of SB. Readers are

referred to chapter 16 for a discussion of SB in children.

## Definitions

There are several current definitions of SB in the literature. The three most commonly used will be described.

In 2005, the American Academy of Sleep Medicine published the second edition of the *International Classification of Sleep Disorders, second edition (ICSD-2)*.[2] The revised nosology contains a new category, sleep-related movement disorders. Many of the disorders now classified as *sleep-related movement disorders*, including SB, were previously classified among the *parasomnias*, that is, undesirable behaviors that occur predominantly during sleep. However, although many parasomnias can be characterized as simultaneously complex, goal-directed, and purposeful, some of them lack purposeful goals. The latter disorders, including SB, are now listed in the new sleep-related movement disorders category. The *ICSD-2* defines *SB* as "an oral parafunction characterized by grinding or clenching of the teeth during sleep that is associated with an excessive (intense) sleep arousal activity."[2]

This definition is commonly used for research purposes as well as by sleep medicine clinicians. The operationalization of this definition requires the use of sleep (polysomnographic) recordings obtained either in the patient's natural home environment (ambulatory) or in a sleep laboratory using additional audio-video recordings.

A definition of bruxism for dental professionals can be found in the *Glossary of Prosthodontic Terms*, where *bruxism* is considered *(1)* "the parafunctional grinding of teeth" and *(2)* "an oral habit consisting of involuntary rhythmic or spasmodic nonfunctional gnashing, grinding, or clenching of the teeth, in other than chewing movements of the mandible, which may lead to occlusal trauma."[3] This definition is adequate for clinical dentistry because it clearly describes the characteristics of the disorder. In the context of the present chapter, however, the definition is less applicable because of the lack of a link to the sleep-wake state in which the oral parafunctions or habits are expressed. Wakeful and sleep-time bruxism probably have different etiologies and mechanisms.

Similar to the definition in the *Glossary of Prosthodontic Terms*,[3] the definition supplied by the American Academy of Orofacial Pain is "a diurnal or nocturnal

parafunctional activity including clenching, bracing, gnashing, and grinding of the teeth."[4] Unfortunately, the use of the terms *diurnal* and *nocturnal* instead of *wakeful* and *sleep-related* (the latter two better respecting the fact that being awake or asleep does not always coincide with daytime and nighttime, respectively) makes this definition less precise. Further, where clenching and grinding are commonly known phenomena in dentistry, the terms *bracing* and *gnashing* need further elaboration. Gnashing is not defined while bracing is considered synonymous with clenching. Finally, the most recent edition of guidelines from the American Academy of Orofacial Pain[4] states that current SB can only be diagnosed with direct measurements such as portable electromyography and polysomnography.

When the advantages and disadvantages of the three definitions are weighed against each other, the *ICSD-2* definition is preferred for its unequivocal and operational nature.[2]

## Epidemiology

SB is a common condition. However, prevalence studies of SB are complicated by the fact that case definition is usually based on self-report or on a combination of self-report and clinical findings (including difficult to interpret measures such as the degree of attrition; see chapter 14). This approach yields less accurate case definitions than those based on objective laboratory or ambulatory recordings. The issue is further compounded by the fact that many epidemiologic studies fail to distinguish wake-time from sleep-related bruxism. Nevertheless, because sleep studies in large numbers of individuals are not feasible, self-report currently reflects the best available data for epidemiologic surveys. Clinicians must recognize the limit of methods used to assess the epidemiology and/or to describe the etiology.

Accurate prevalence estimates are further complicated by the fact that many studies report rates of SB that derive from populations with medical comorbidities. Common comorbidities that may influence the prevalence of SB are anxiety and other psychiatric health issues, geriatric conditions, orofacial pain, Down syndrome, and cerebral palsy.

For example, Aggarwal et al[5] conducted a large-scale, population-based, cross-sectional study using self-report questionnaires. Of the more than 2,000 respondents, 34% of those with orofacial pain reported being aware of tooth grinding, while only 18% of those without orofacial pain reported grinding. Orofacial pain patients thus

had a significantly increased odds ratio of 2.4 (95% confidence interval = 1.7 to 3.4) of reporting tooth grinding. This suggests that study populations must be described in detail to unravel potential confounding comorbidities.

Two well-designed, large-scale epidemiologic surveys are worth elaborating and probably provide the best prevalence of SB estimate to date. In a survey comprising more than 2,000 personal interviews across Canada, the question "Do you very often, often, occasionally, or never grind your teeth during sleep?" was answered positively (ie, with "often" or "very often") by 8% of the adult respondents.[6] Men and women responded similarly, with prevalence estimates decreasing with age for both sexes. Figure 12-1 shows the drop in SB prevalence from approximately 13% in respondents 18 to 29 years of age to approximately 3% in those older than 60 years.

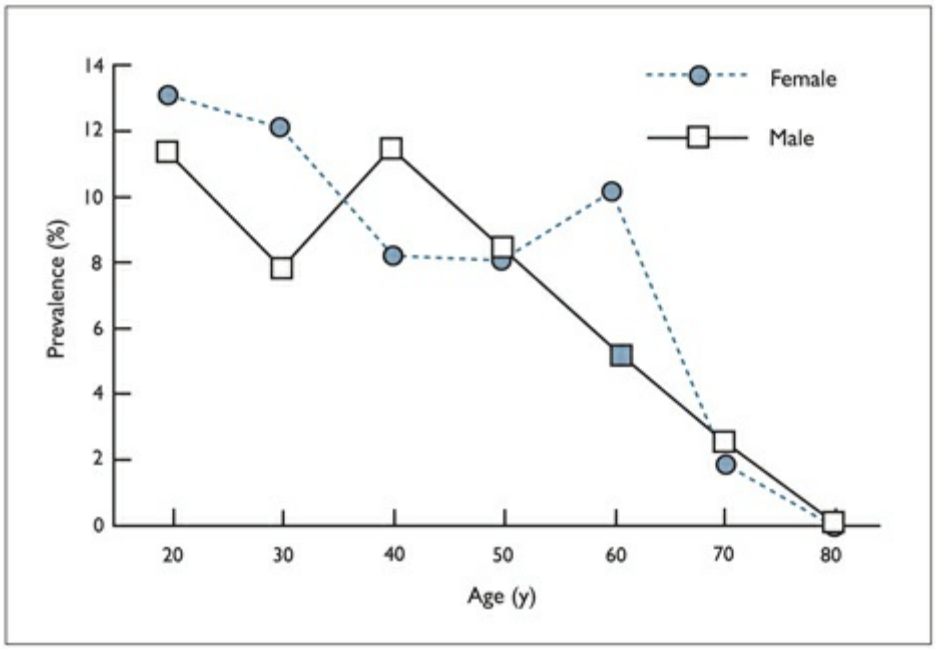


**Fig 12-1** Percentage of positive responses (ie, often or very often) to the survey question "Do you very often, often, occasionally, or never grind your teeth during sleep?," by age group and for both genders. (Reprinted from Lavigne and Montplaisir[6] with permission.)

In a large-scale, population-based, cross-sectional telephone survey in the United Kingdom, Germany, and Italy, Ohayon and colleages[7] found that tooth grinding during sleep occurred at least weekly in 8.2% of the more than 13,000 respondents. As in the study by Lavigne and Montplaisir,[6] Ohayon et al[7] did not observe

differences in SB prevalence by sex and found that prevalence declined with increasing age.

The consistency of the observations in these two epidemiologic surveys suggests that self-reported tooth grinding during sleep has a prevalence of approximately 8% in the general adult population, is equally present in men and women, and shows a decline with increasing age. This last conclusion, however, should be interpreted with caution because the higher prevalence of complete denture wearers among the elderly as well as the more frequent use of medicines that may suppress SB (eg, benzodiazepines; see chapter 17) in this age group may have reduced the awareness of SB in the older age groups.

## Etiology

Epidemiologic surveys not only provide insight into the prevalence of diseases or disorders but may generate insights into possible etiology. Because research on the etiology of SB has not yet produced large numbers of high-quality articles, however, the commonly made distinction between *risk factors* (ie, factors that are derived from longitudinal studies as part of a causal chain that directly increases the probability of a disease occurring) and *risk indicators* (ie, potential risk factors that are derived from cross-sectional studies and can only suggest associations) cannot be made for SB.[8] The lack of longitudinal studies on SB indicates that most etiologic factors for SB that are reported in the literature should most appropriately be considered risk indicators. Several in-depth review articles and book chapters address this issue.[9–11] A summary of SB risk indicators[11] can be found in Table 12-1.

**Table 12-1** **Overview of some risk indicators that are described in the literature in relation to SB, including an indication of the availability of evidence***

| Risk indicator | Evidence |
|---|---|
| *Morphologic* | |
| Anatomy of orofacial skeleton | Absent |
| Morphology of dental occlusion/articulation | Absent |

| | |
|---|---|
| *Psychosocial* | |
| Anxiety/stress | Growing |
| Personality (eg, competitiveness) | Growing |
| *Physiologic and biologic* | |
| Traumatic injury | Present |
| Genetics (heritable) | Growing |
| Sleep-related arousal | Present |
| Sleep-disordered breathing | Present |
| Neurochemicals (eg, catecholamines) | Present |
| *Exogenous factors* | |
| Medications (eg, serotonin reuptake inhibitors) | Present |
| Illicit drugs (eg, Ecstasy) | Present |
| Alcohol, caffeine, smoking | Present |

*Overview derived from Lobbezoo et al.[11]

SB risk indicators can be grouped as peripheral and central types. As reviewed previously,[9,11] peripheral indicators such as the anatomy of the orofacial skeleton and the morphology of dental occlusion and articulation may play a minor role (if any) in the etiology of SB. For example, in a sleep laboratory study, it was shown that the orofacial morphology of SB patients—quantified as 26 standard occlusal measures that were recorded clinically and from dental casts and as 25 standard angular and linear measures that were taken from cephalometric radiographs—did not differ from that of nonbruxers.[12]

Central indicators such as psychosocial problems and physiologic conditions, on the other hand, do seem to play a role in the etiology of SB.[11] For psychosocial problems such as anxiety, competitiveness, and stress, the evidence for a causal relationship with SB is growing, although it is not yet conclusive and sometimes still controversial.[10,13] For example, Pierce et al[14] showed that only 8 of 100 SB patients had a significant positive correlation between self-reported stress and electromyographically determined SB. These findings suggest, at least in this

sample, that the role of psychosocial problems such as stress in SB may be smaller than expected and may differ among individuals.

Recent scientific advances support the idea that some physiologic conditions may predispose some individuals to SB (see chapter 15). These include sleep-related cortical and autonomic arousal (eg, rapid and transient changes in brain, respiration, and cardiac activity) and neurochemical alterations (eg, catecholamines such as dopamine and norepinephrine). A number of substances, including medications (eg, amphetamines, neuroleptics, selective serotonin reuptake inhibitors), recreational drugs such as Ecstasy (3,4-methylenedioxy-*N*-methylamphetamine), alcohol, caffeine, and smoking, have also been linked to SB. Sleep-disordered breathing (eg, snoring, upper airway resistance, and apnea-hypopnea) has also been reported to increase the probability of SB. Additional evidence implicates trauma with brain damage and a host of diseases, particularly neurologic (eg, cerebral palsy) or psychiatric disorders. Posttraumatic stress disorder, for example, has been associated with SB. These associations have been described in detail in previous reviews.[9–11]

Besides data on the prevalence of SB, the large-scale epidemiologic survey by Ohayon et al[7] identified some risk indicators for SB self-reporting, including daytime sleepiness, snoring, obstructive sleep apnea syndrome, alcohol consumption, caffeine intake, smoking, living a stressful life, and anxiety. An overview of significant indicators and their odds ratios and 95% confidence intervals are provided in Table 12-2. Similarly, Lavigne et al[16] found smoking to increase the odds of SB nearly twofold (odds ratio of 1.9; 95% confidence interval = 1.4 to 2.6). The same report also demonstrated that smokers have more SB episodes associated with grinding sounds per hour of sleep than do nonsmokers.

**Table 12-2** **Overview of some significant risk indicators for self-reported SB: Odds ratios and their 95% confidence intervals (CIs)***

| Risk indicator | Odds ratio | 95% CI |
|---|---|---|
| Moderate daytime sleepiness | 1.3 | 1.1–1.6 |
| Snoring (not loud) | 1.2 | 1.0–1.4 |
| Snoring (loud) | 1.4 | 1.1–1.8 |
| Obstructive sleep apnea syndrome | 1.8 | 1.2–2.6 |
| Daily intake of alcohol (1 to 2 glasses) | 1.5 | 1.1–1.9 |

| | | |
|---|---|---|
| Daily intake of alcohol (≥ 3 glasses) | 1.8 | 1.4–2.4 |
| Daily caffeine intake (≥ 6 cups) | 1.4 | 1.2–1.8 |
| Daily smoking (≤ 20 cigarettes) | 1.3 | 1.1–1.5 |
| High life stress | 1.3 | 1.1–1.6 |
| DSM-IV anxiety disorder diagnosis[15] | 1.3 | 1.0–1.6 |

*Data derived from Ohayon et al.[7]

Finally, it remains unclear whether SB is genetically determined. Although some recent publications favor a role of genetics in the etiology of SB,[17] the exact mechanisms still must be unraveled (see chapter 15).

## Conclusion

SB is classified as a sleep-related movement disorder characterized by clenching and grinding of the jaws and teeth. SB has a prevalence of approximately 8% in both men and women, a rate that declines with increasing age. The etiology of SB is not well understood but is likely to involve concomitant behavioral and physiologic conditions. Some of the risk indicators for SB are anxiety, psychologic stress, traumatic brain injury, neurologic and psychiatric diseases, obstructive sleep apnea syndrome, snoring, daytime sleepiness, alcohol consumption, caffeine intake, and smoking. SB may also have a heritable component, although specific genetic variants have yet to be identified.

True risk factors for SB have not been clearly identified because of a lack of prospective and experimental investigations. Rigorous studies are necessary to determine whether currently identified risk indicators prevent or mitigate SB and its deleterious consequences.

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CHAPTER 13

# OROFACIAL MOVEMENT DISORDERS IN SLEEP

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Motor activities during sleep are divided into physiologic and pathologic types.[1,2] Several physiologic orofacial motor activities are known to occur during sleep.[3] They play a role in protecting and integrating oroesophageal functions and tissues during sleep.[4,5] However, their occurrence may become exaggerated in several sleep disorders.[3,5,6] Abnormal orofacial movements in patients with neurologic and psychiatric disorders can appear during sleep or wakefulness or both.[3,6,7] The terminology of orofacial movement disorders in sleep used in this chapter generally extends to conditions with exaggerated normal motor activities as well as conditions characterized by the presence of abnormal, aimless (nonpurposeful) movements.

This chapter overviews *(1)* physiologic orofacial motor activities and their relevance; *(2)* abnormal orofacial movements that occur in sleep disorders; and *(3)* concomitant movement disorders and other medical factors related to abnormal orofacial movements in sleep. Sleep bruxism (SB) covered in this chapter is viewed as a secondary type of orofacial movement disorder rather than a primary type, which is discussed in more detail in chapter 12.

## Usual Physiologic Orofacial Motor Activity During Sleep

A number of typical physiologic orofacial motor activities are present during sleep and usually do not disrupt sleep continuity in otherwise healthy subjects. However, exaggerated occurrences of these activities may disturb sleep in patients with sleep disorders[1–3] (Table 13-1).

**Table 13-1** **Usual physiologic oromotor activities**

| Oromandibular movement | Physiology in normal sleep | Functions | Associated sleep disorders when movements exaggerated |
|---|---|---|---|
| Swallowing | 6 to 10 times/h<br>Adults: Non-REM sleep stages 1 and 2<br>Children: REM sleep<br>Associated with arousals | Protection of airway<br>Protection and clearance of esophageal acid | Sleep-related gastroesophageal reflux<br>Sleep-related abnormal swallowing<br>OSA |
| Rhythmic masticatory muscle activity | 60% of population<br>1 to 2 times/h<br>Dominant in non-REM sleep stages 1 and 2<br>Associated with arousals | Unknown whether associated with salivation or an increase in airway patency | Parasomnias<br>Sleep-related gastroesophageal reflux<br>Sleep bruxism<br>OSA<br>Snoring |
| Sleep talking | Commonly observed<br>More frequent in children than adults<br>All sleep stages<br>Associated with arousals | Reflection of emotional states,<br>dreaming, cognition during sleep | Parasomnias |
| Facial expression | All sleep stages<br>Associated with arousals | Reflection of emotional states while dreaming | Parasomnias |
| Hiccup | All sleep stages<br>Rarely associated with arousals | Unknown impact of spasms in diaphragm | Sleep hiccup |
| Sigh | 1 to 25 times/h<br>All sleep stages | Increase of pulmonary compliance | OSA |
| Cough | Rare<br>Associated with arousals | Protection of lungs from aspiration | Sleep-related abnormal swallowing<br>Sleep-related gastroesophageal reflux<br>OSA<br>Asthma, chronic cough |
| | All sleep stages | | |

| | | | |
|---|---|---|---|
| Nonspecific jaw muscle jerk | Associated with arousals, body jerks, and movements | Orofacial manifestation of arousal motor response | Problems with fragmented sleep (eg, OSA, insomnia) |

(non-REM) non–rapid eye movement; (REM) rapid eye movement; (OSA) obstructive sleep apnea.

Swallowing is the most common orofacial motor activity during sleep.[3] A low frequency of swallowing during sleep can be associated with decreased salivation and reflex activity. Swallowing during sleep may prevent nocturnal aspiration or protect oroesophageal structures from acid reflux.

Rhythmic masticatory muscle activity (RMMA) is defined as chewing-like, rhythmic jaw movements at a frequency of about 1 Hz. It is also found in 60% of normal subjects.[8] Eighty percent of these events occur in light non–rapid eye movement (non-REM) sleep. It remains to be demonstrated whether RMMA contributes to the lubrication of oroesophageal structures or an increase in airway patency.[4,5] Patients with parasomnias and SB also exhibit increased and intense RMMA with tooth grinding during sleep. The pathophysiologic relation between RMMA and SB is discussed in chapter 15.

Many children and adults occasionally utter, groan, and speak during sleep. These events are not a medical concern unless they become very loud and frequent.[1,6] Facial expressions (eg, grimacing and smiling) can reflect emotional states during sleep. Hiccup, defined as repeated sounds in the throat caused by a sudden contraction of the diaphragm, can persist during sleep. Sighs are deeper breaths, bigger than average respiration, most of which are occasionally followed by a respiratory pause. Coughing, although rare in healthy subjects, protects the lungs from aspiration during sleep.

Nonspecific jaw jerks are defined as tonic orofacial muscle activities representing an orofacial manifestation of the physiologic gross body movements. They are observed in association with sleep stage shift, arousal, and awakening.[1,2] These jerks can occur more frequently in patients with fragmented sleep (eg, sleep apnea) and resolve when fragmented sleep is attenuated.[1]

When physiologic orofacial motor activities are disturbed or exaggerated during sleep (see Table 13-1), orofacial, pharyngeal, or esophageal symptoms may arise at night or in the morning. In addition, these symptoms can be found in patients who use intraoral devices during sleep.[8,9] Oral splints are used to manage SB and associated pain in jaw muscles and the temporomandibular joint. Some patients may have

secondary complaints of oral dryness and drooling while using oral splints (see chapter 17). Mandibular repositioning (advancement) appliances or devices are effective in reducing obstructive respiratory events, but orofacial symptoms (eg, tooth, muscle, or joint pain), oral dryness, and drooling can also be reported for a few weeks by the patients until titration is optimized to relieve respiratory obstruction and comfort (see chapter 10).

## Orofacial Movements in Sleep Disorders

The orofacial movements that may occur during sleep in patients with concomitant sleep disorders are summarized in Table 13-2.

**Table 13-2** **Sleep disorders related to orofacial movement disorders**

| Sleep disorder | Reported orofacial movements |
|---|---|
| *Sleep-disordered breathing* | |
| • OSA syndrome | SB, nonspecific jerks, sighs |
| *Insomnia* | SB |
| *Parasomnias* | |
| • Non-REM sleep parasomnias: Night terrors, confusional awakening, and somnambulism (sleepwalking) | SB, rhythmic masticatory muscle activity, talking, grimacing, laughing, shouting, swallowing, eating behavior |
| • REM sleep parasomnias: RBD nightmare disorders | OMM |
| • Other parasomnias: Sleep-related groaning | |
| *Sleep-related movement disorders* | |
| • Restless legs syndrome* | SB |
| • Periodic leg movements during sleep* | |
| *Other conditions associated with sleep abnormalities* | |
| • Sleep-related faciomandibular myoclonus | SB, tongue biting, RBD |

| | |
|---|---|
| • Sleep-related epilepsy* | SB, lip smacking, gagging, myoclonus, facial twitch, tongue biting |
| • Sleep-related abnormal swallowing | Swallowing, coughing, choking |
| • Sleep-related gastroesophageal reflux | RMMA, swallowing, choking, coughing |

*SB is seemingly no more prevalent in this group than in the general population.
(RBD) REM sleep behavior disorder; (OMM) oromandibular myclonus.

In patients with sleep-disordered breathing, mainly obstructive sleep apnea (OSA), it is reported that apnea-hypopnea events are occasionally terminated by tonic activation of masticatory, tongue, and pharyngeal muscles as well as body movements and jerks.[1,2,9] Tonic jaw muscle activities can be part of a general motor response to respiratory arousals for restoring breathing.[1,5,9] Although several studies have reported that tooth grinding in patients with SB is rarely directly associated with apnea-hypopnea events, tooth grinding has been reported to be more prevalent in patients with OSA.[10,11]

Morning oral dryness can be associated with frequent mouth breathing during sleep.[4] When SB and OSA occur in the same patient, possible adverse effects related to the use of mandibular advancement appliances include jaw muscle and joint pain, oral dryness, and a sensation of occlusal change.[9]

*Parasomnias*, defined as unpleasant or undesirable behavioral or experiential phenomena, involve complex, seemingly purposeful behaviors during sleep (see chapter 3).[6] Although most parasomnias are more prevalent in children than in adults (eg, somnambulism, sleep terrors, and confusional arousals), others are not (eg, rapid eye movement sleep behavior disorder [RBD]).[6] Various oromandibular movements associated with grimacing, talking, chewing, and clenching may concomitantly occur with grinding. Some parasomnias (eg, sleep talking, sleepwalking) reportedly share a genetic background with SB.[12]

Several sleep movement disorders are observed during sleep. Restless legs syndrome during wakefulness or periodic leg movements during sleep are sleep-related movement disorders primarily affecting the legs.[6] Their coexistence with SB has been reported to be low.[8]

Sleep-related faciomandibular myoclonus or oromandibular myoclonus (OMM), characterized by tapping-like vertical jaw movements during sleep, can be found in 10% of subjects aware of tooth grinding.[7] This condition can be distinguished from

SB[13] and may cause nocturnal tongue biting. Concomitant or secondary sleep conditions, such as sleep epilepsy, RBD, or insomnia, can be associated with sleep-related OMM. Thus, these conditions should be ruled out.

Patients with sleep-related gastroesophageal reflux experience the sensation of heartburn and a sour taste on waking from sleep.[6] Frequent reflux events disturb sleep and are associated with swallowing. The coexistence of sleep-related gastroesophageal reflux, tooth grinding, and hyposalivation or xerostomia may increase the risk of tooth erosion and wear.[4]

It is not uncommon for patients with chronic pain to complain of insomnia, long delays in falling asleep (more than 20 or 30 minutes), and/or difficulty in resuming sleep if they awaken during the night (see section IV). SB can also occur concomitantly with anxiety disorders, restless legs syndrome, and periodic leg movements during sleep.[14]

## Orofacial Manifestations of Movement Disorders in Sleep

Patients with movement disorders display a variety of motor disturbances characterized by abnormally increased (hyperkinetic) or decreased (hypokinetic) motor activities in the body.[15,16] Some abnormal orofacial movements that occur during wakefulness may persist during sleep (Box 13-1).[17] In addition, tooth grinding is often reported during sleep in patients with movement disorders.[3,7] Patients with orofacial movement disorders often present oromotor dysfunctions (chewing difficulty, dysphagia, dysarthria), orofacial pain, burning mouth, oral dryness, and tooth wear that may have to be managed by dentists.[15,16,18]

**Box 13-1 Movement disorders that persist during sleep or are associated with SB***

**Movement disorders**

*Hyperkinetic movement disorders:*

• Oromandibular dystonia

- Huntington disease
- Tics (Tourette syndrome)
- Hemifacial spasms

*Hypokinetic movement disorders:*

- Parkinson disease

**Drugs or substances**

- Alcohol, caffeine, nicotine (cigarette smoking)
- Antipsychotic drugs and other dopamine receptor–blocking agents
- Antiemetic drugs: Metoclopramide, prochlorperazine
- Calcium antagonists
- Selective serotonin reuptake inhibitors
- Lithium
- Psychostimulants: Cocaine, amphetamines (eg, Ecstasy)

**Other medical conditions**

- Olivopontocerebellar atrophy
- Shy-Drager syndrome
- Whipple disease
- Angelman syndrome
- Mental retardation

*Data based primarily on case reports.[15,16,18]

Evidence concerning the persistence of orofacial movement disorders during sleep has been gathered mainly from case reports. Moreover, few studies have used objective assessment methods for sleep and orofacial movements. Thus, the pathophysiology of abnormal orofacial movements during sleep in patients with movement disorders needs further investigation.

## *Hyperkinetic movement disorders*

Orofacial dyskinesia is characterized by various irregular, excessive, aimless movements in the face, tongue, and jaw. In edentulous individuals it can have a

peripheral origin to occur in a patterned (stereotyped) fashion during wakefulness and is presumably absent during sleep.[19] In most cases, however, oral dyskinesia has a central (extrapyramidal) origin and usually disappears during sleep.

Oromandibular dystonia is characterized by slow, twisting, repetitive muscle spasms affecting the mandible, tongue, and lips.[15,16] Dystonic orofacial activities, as well as SB, occur during sleep.

Huntington disease is a hereditary neurodegenerative condition characterized by irregular, unpredictable choreic body movements.[16] Some patients manifest tooth grinding during sleep.

Tics are repetitive, irregular, stereotyped, suppressible movements often involving the eyes, face, and neck.[18] They can occur during light non-REM sleep in association with microarousals, sleep stage shifts, and awakenings in patients with Tourette syndrome.

Hemifacial spasm is characterized by unilateral, nonepileptic twitches of the face that persist during sleep.[17]

Injection of botulinum toxin to jaw muscles is effective the short-term management of various types of oral dyskinesia and severe cases of bruxism, but the available evidence-based support is limited.

## *Hypokinetic movement disorders*

Parkinson disease is a multisystem neurologic syndrome characterized by a hypokinetic movement disorder involving degeneration of the dopaminergic system.[1,15,16] During sleep, swallowing difficulties and drooling persist, but resting orolingual tremor is absent. Tooth grinding and dystonic orofacial movements during sleep, related to levodopa therapy, have been reported in some parkinsonian patients.[7]

## *Drug-induced orofacial movement disorders and other medical conditions*

Neuroleptic-induced abnormal oromandibularmove-ments and secondary bruxism may be observed during sleep.[20,21] Delayed-onset (so-called tardive) dyskinesia induced primarily by long-term antipsy-chotic drug exposure usually disappears or

decreases during sleep. The type of orofacial movement observed may vary. Dystonic movements with tooth grinding also occur in patients using antiemetic drugs with dopamine receptor–blocking properties (metoclopramide and prochlorperazine), calcium channel blockers (cinnarizine and flunarizine), selective serotonin reuptake inhibitors, cocaine, lithium, and amphetaminic drugs such as Ecstasy (3,4-methylenedioxy-*N*-methylamphetamine).[20,21]

Bruxism and abnormal orofacial movements during sleep have been documented in case reports describing patients with epilepsy, olivopontocerebellar atrophy, Shy-Drager syndrome, Whipple disease (with characteristic oculomasticatory myorhythmia), Angelman syndrome, and mental retardation.[7,8,15,22]

## Role of Dentists in Diagnosis and Treatment

If a patient is aware of tooth grinding and associated orofacial symptoms, it is important for the clinician to check the history for the following items:

- Signs and symptoms of sleep disorders (eg, daytime sleepiness, sleep disturbances, frequent awakenings, sleep-related behaviors, snoring, and morning oral dryness
- Involuntary movements in orofacial regions and in the body or medical diseases associated with abnormal movements
- Use of medication that influences sleep and orofacial movements

When these characteristics are present, the dentist must refer the patient to a specialist in sleep medicine, movement disorders, or neurology. These specialists can play a major role in the diagnosis and treatment of abnormal movements. Dentists can be involved in alleviating orodental problems, but knowledge of the disorders and pharmacotherapy is required to manage these conditions appropriately. In the absence of concomitant medical disorders (responsible for secondary SB), dentists are responsible for the management of SB and the associated orofacial symptoms.

## Conclusion

This chapter has summarized the physiologic and pathologic orofacial motor activities that occur during sleep in healthy subjects and patients with medical disorders. There are several anecdotal reports of orofacial movement disorders in sleep, but information is limited about the prevalence, pathophysiology, and valid treatment strategies.

Several oral complications may occur, including traumatic injuries and tooth wear, requiring adequate preventive and corrective approaches. Dentists are involved in management of the various oral complications (eg, use of an oral splint for teeth protection).

The possibility of underlying toxic or medical disorders should be recognized. If any of these conditions are suspected, it is preferable for dentists to consult and work in collaboration with medical specialists to better manage orofacial movement disorders in sleep and their related complications.

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CHAPTER 14

# CLINICAL APPROACH TO DIAGNOSIS OF SLEEP BRUXISM

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Sleep bruxism (SB) is a motor activity that has drawn increasing interest in clinical dentistry in recent years. Although SB is not a life-threatening disorder, it can affect the patient's quality of life, especially through dental problems such as tooth wear, damage to tooth structures or dental restorations, pain in the orofacial region, and tension-type headache. There are various ways to assess the presence of SB (Box 14-1). This chapter summarizes the methods used to measure SB-related symptoms (eg, tooth grinding and pain on waking) and signs (eg, tooth wear) for clinical diagnosis and for monitoring in clinical trials to assess the mechanisms, effectiveness, and safety of SB management approaches.

**Box 14-1 Methods for assessing SB**

- Questionnaires
- Clinical examination
- Intraoral appliances:
  - Wear of intraoral appliance
  - Detection of occlusal force
- Masticatory muscle electromyographic (EMG) recording:
  - Portable (ambulatory) EMG recording device
  - Miniature self-contained EMG detector and analyzer

- Polysomnography (sleep laboratory)

A status diagnosis is generally based on a combination of the patient's self-reports and a clinical examination.[1,2] A confirmed diagnosis is only possible using tools such as audio-video and electrophysiologic recordings, but these methods are not likely to be routinely used in clinics, as is explained later in the chapter.

## Questionnaires

Self-reports of jaw clenching and tooth grinding are useful to assess the presence or absence of SB. Questionnaires are generally used in both clinics and research. The main advantages of questionnaires are their capacity to gather subjective information efficiently over large populations.[3,4]

However, questionnaires have some limitations. SB-related signs and symptoms and awareness of bruxism fluctuate substantially over time,[5] and underestimation and overestimation of the prevalence of SB via questionnaires have been reported.[6] The occurrence of tooth grinding sounds, as observed longitudinally in a laboratory, is highly variable over time.[7,8] It has also been reported that most muscle episodes of SB, whatever the type of jaw muscle contraction (phasic [rhythmic], tonic [sustained], or clenching), may be unaccompanied by noise.[9] Consequently, a large percentage of patients are unable to identify themselves as bruxers, especially those who sleep alone. Reports of tooth grinding are usually associated with the sleep partner's complaint of a disturbing grinding noise. Therefore, questionnaires, which consist of subjective self-assessments, have limited validity. Nevertheless, they can at least guide the clinician in the diagnostic process[3,10,11] (Box 14-2).

**Box 14-2 Examples of questions* used to assess SB[3,10,11]**

- Do you very often, often, occasionally, or never grind your teeth during your sleep?
- Has anyone said you grind your teeth at night?
- Do your teeth, gums, or jaw muscles feel sore when you wake up?

- Has anyone heard you grinding your teeth at night?
- Is your jaw ever fatigued or sore on awakening in the morning?
- Are your teeth or gums ever sore on awakening in the morning?
- Do you ever experience temporal headaches on awakening in the morning?

*The questions are meant to guide the clinician in the diagnostic process and do not necessarily elicit "yes or no" answers. Other questionnaires on sleep and respiratory disorders can be used in combination.

## Clinical Examination

Currently, a clinical diagnosis of SB is generally based on a report of tooth grinding sounds by the sleep partner and the presence of tooth wear (Fig 14-1), tooth mobility, and damage to teeth (eg, chipping), dental restorations, or prostheses. Other clinical symptoms may include pain and dysfunction in the temporomandibular joint, jaw muscle pain, fatigue or stiffness on waking, and additional signs such as masticatory muscle hypertrophy or tongue and cheek indentation. Because these subjective symptoms or signs are secondary, they should not be used as sole confirmation of clinical SB.

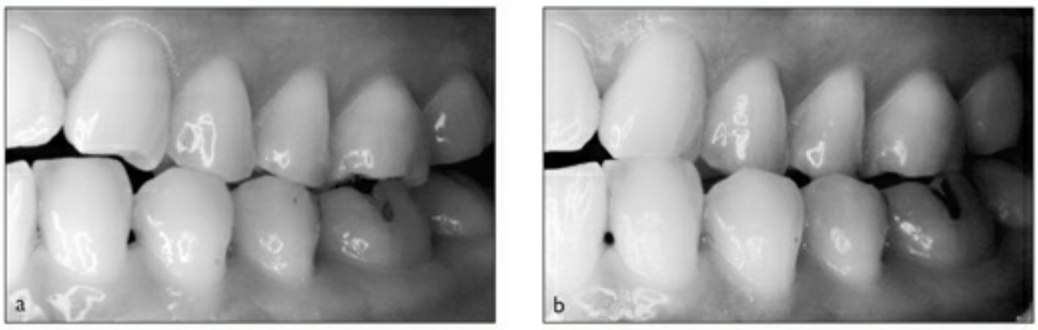


**Fig 14-1** *(a)* Tooth wear is apparent on the maxillary and mandibular canines in intercuspal position. *(b)* The facets of these canines fit perfectly in the lateral occlusal position. Tooth wear can be observed on the incisors, canines, premolars, and molars.

Because of its variability over time, SB is difficult to diagnose. Some helpful diagnostic criteria have been proposed by the American Academy of Sleep Medicine[12] (Box 14-3). They consist of anamnestic and clinical indicators and serve

as practical descriptors of SB for both clinical and research purposes. Again, these criteria are not considered perfect or definitive for diagnosis of SB.

**Box 14-3 Clinical diagnostic criteria of SB[12]**

- The patient reports or is aware of tooth grinding sounds or tooth clenching during sleep.
- One or more of the following signs is present:
  - Abnormal wear of the teeth.
  - Discomfort, fatigue, or pain of the jaw muscles and locking of the jaws on awakening.
  - Hypertrophy of the masseter muscles on voluntary forceful clenching.
  - Jaw muscle activity cannot be better explained by another current sleep disorder, medical or neurologic disorder, medication use, or substance use disorder.

In fact, the primary symptom is the sleep partner's report or the patient's awareness of tooth grinding sounds and/or tooth clenching during sleep. However, these criteria may not be very accurate, as explained earlier. Excessive tooth wear, an indirect indicator of SB, is the most common observable clinical sign of the presence of SB.[4] Nonetheless, the clinician should keep in mind that tooth wear may have occurred months or years before the examination. Tooth wear is a cumulative consequence of both functional and parafunctional wear. It does not prove ongoing or current bruxism activity, nor can it indicate whether the subject has static tooth clenching. In addition, a number of factors, including age, gender, occlusal condition (eg, subject occluding on only a few teeth because of a malocclusion), diet, amount and type of fluid intake, oral dryness resulting from medications or health conditions (gastroesophageal reflux, anxiety), and tooth consistency (wear resistance) are all associated with various degrees of tooth wear.[13] Therefore, evaluation of tooth wear to establish a diagnosis of current bruxism activity and its severity is still controversial.[13,14]

Although the clinical diagnostic criteria of the American Academy of Sleep Medicine have limitations, they are still useful, and their clinical validity will probably improve with modifications in the coming years. For instance, greater

accuracy concerning tooth wear would be achieved if time aspects or temporal profiles (eg, period, frequency, duration, and fluctuation over time) were considered, with correction for the influence of the multiple factors described above (eg, diet, age, and enamel density).

## Devices and Recording Systems

A variety of tools to assess SB activity are now available for clinical and research purposes, including intraoral appliances and muscle activity recorders (see Box 14-1). However, a lack of standardized SB scoring criteria and evidence-supported validity (eg, reliability, accuracy, and reproducibility) limits the predictive value of these tools for clinical application.[8,15,16] The outcomes obtained with most of the available tools may not truly reflect the status of SB at a given time because of the variability across nights and the discomfort and disturbances associated with recording methods (eg, home versus laboratory, wire on the face, or an appliance in the mouth that may reduce or exacerbate SB motor activity).

Overall, recognition of SB is based mainly on clinical findings, and the tools that will be described are more useful in clinical research setups. Diagnosis of SB is based on the clinician's judgment of the aforementioned signs and symptoms. There is currently no simple and valid device or tool that can provide an accurate diagnosis.

### *Intraoral appliances*

SB activity has been estimated using intraoral appliances.[17–21] Briefly, the results obtained with these tools have been based on either observation of wear facets (presence, distribution, and progression over time) on the intraoral appliance[17,18] or measurements of occlusal force using a sensor embedded in the intraoral appliance to count the number and duration of tooth contacts via an extraoral computerized system.[19,20] Although observation of occlusal wear on the appliance is helpful in assessing wear patterns (eg, anterior, posterior), quantifying the wear requires sophisticated methods.[18,21] One simple method uses different-colored layers in the appliance to assess wear over time.[17] However, the thickness of the device may be uneven in relation to the shape of the dental arch or tooth position (eg,

malocclusion), which affects the accuracy of the estimation.[17,21]

One major problem with the use of an intraoral device is the possible lack of correlation with natural SB activity. The presence of the oral appliance may affect the extent of activity. Before the validity and value of intraoral devices as a diagnostic tool can be determined, well-designed comparative studies must be conducted to evaluate the potential influence of such an intraoral device on natural bruxism activity.

## *Masticatory muscle EMG recording systems*

Portable electromyographic (EMG) measurement systems were developed in the early 1970s to measure SB. These tools were innovative because they enabled multiple-night recordings of SB in the patient's home at minimal expense[7,17] These systems can now estimate masticatory muscle activity over time, that is, the number, duration, and magnitude of SB events, with acceptable accuracy.[22,23]

Specific criteria for the detection and scoring of SB activity with portable EMG recording systems have been proposed[22] (Box 14-4 and Fig 14-2), but their validity in a large population has not yet been confirmed. One significant limitation is that, in the absence of audio and video scorings, portable measurement systems tend to overestimate SB-related activity because of the presence of other confounding orofacial activities such as sighing, coughing, or somniloquy.[16,2 5] It was recently reported that up to 30% of jaw muscle activity is not specific to SB in bruxism patients.[26] Dentists using these systems should be aware that the presence of concomitant sleep disorders (eg, periodic limb movement, sleep breathing) cannot be excluded.[16,25]

**Box 14-4 Polysomnographic and SB scoring criteria[9,12,15,22_24]**

**Ambulatory criteria**

- EMG:
  - Amplitude: At least 10% of maximum (voluntary clench while awake)
  - Duration: More than 3 seconds
  - Periodicity: Interval of 5 seconds between events

• Heart rate change: Rise of 5% in beats per minute when an SB EMG event is present

**Sleep laboratory criteria**

• Mean SB EMG amplitude: At least 10% of maximum clenching activity while awake (masseter muscles)

•Three types of SB contractions scored within an SB episode:

- Phasic: More than three EMG bursts; each burst ≥ 0.25 and ″ 2.00 seconds
- Tonic (similar to awake clenching): One EMG burst of > 2.00 seconds (representing 10% of EMG SB–related activity during sleep)
- Mixed: Both phasic and tonic types

• Sleep laboratory diagnostic criteria based on frequency of EMG episodes per hour of sleep (see Fig 14-2):

- Low frequency: Two to four episodes (phasic, tonic, or mixed) per hour of sleep*
- Mild to high frequency: More than four episodes (phasic, tonic, or mixed) per hour of sleep or 25 bursts per hour

*These patients have an increased risk of reporting morning pain or headache; it is important to monitor respiration to exclude sleep-disordered breathing.

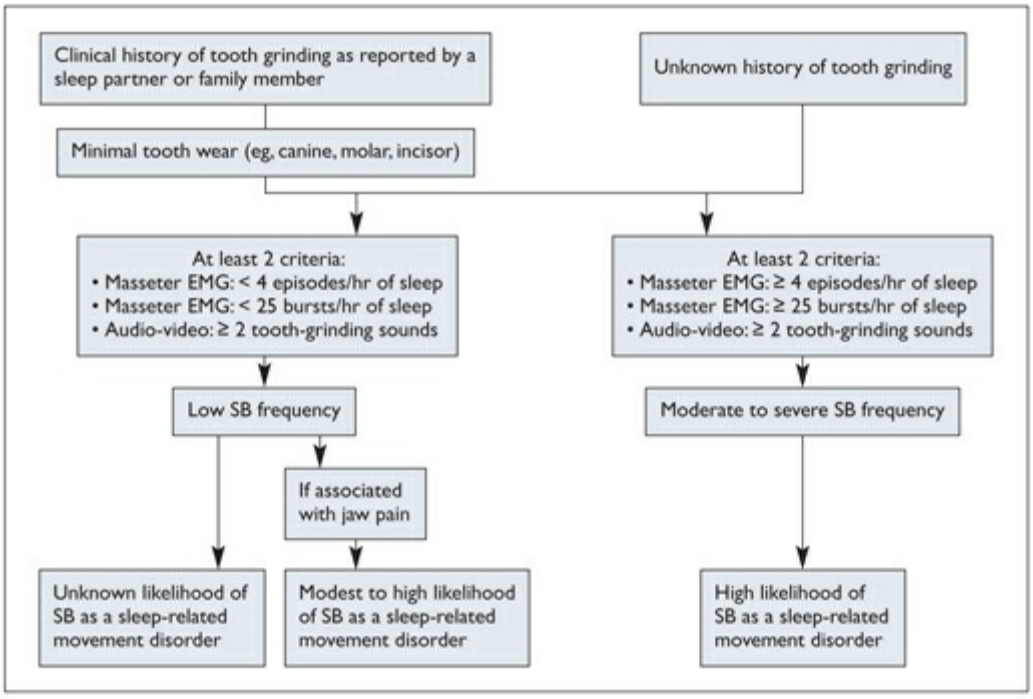

**Fig 14-2** Suggested criteria for including SB as a sleep-related movement disorder based on scoring of polysomnographic and audio-video recordings.[9,12,15]

A miniature self-contained EMG detector and analyzer was recently developed.[27] The special feature of this device is that the number of jaw muscle activity events is readily estimated by simply attaching a recorder to the skin over the masseter muscle. The system collects EMG activity over 5 to 6 hours, and the clinician can extract a motor activity score the next morning. As with the other tools described, the scoring algorithm does not discriminate nonspecific motor activity that is unrelated to SB.

More recently, another miniature self-contained EMG detector and analyzer was developed, incorporating a biofeedback function (electric stimulation) that may alter SB ongoing activity.[28] It enables online recording of EMG activity of the anterior temporalis muscle and processing of EMG signals to detect tooth grinding and clenching.

The diagnostic validity of these miniature systems in populations of patients with and without SB and tooth grinding history remains to be demonstrated by independent studies. If these devices can provide an acceptable approximation of SB and can discriminate nonspecific oromotor activities from SB, they could be useful tools in large-sample studies, although their accuracy in chairside diagnosis has not yet been confirmed.

## *Polysomnography*

Polysomnographic (sleep laboratory) recordings for SB generally involve electroencephalography to measure brain activity, EMG to measure muscle activity, electrocardiography to assess heart rate variability, oximetry to measure blood oxygen levels, and the use of oronasal thermistors and nasal cannula pressure transducers with abdominal and chest belts to monitor respiratory changes and detect sleep-disordered breathing. To assess SB specificity against normal or atypical oromandibular activities (eg, coughing, swallowing, somniloquy), the aforementioned signals must be recorded simultaneously with audio-video data.[15,16,26] More precisely, SB activity is scored based on EMG activity in the masticatory muscles (mostly the masseter and occasionally the temporalis muscles) using specific criteria to recognize the SB-related pattern (see Box 14-4 and Fig 14-2).

One strength of the sleep laboratory setting is the highly controlled recording environment to identify concomitant sleep disorders (eg, sleep apnea and periodic limb movement disorder) and the capacity to exclude non-SB–related orofacial activities (eg, myclonus, swallowing, and coughing) that occur during sleep.[26,29] In medically complex patients, such as those presenting with pain, cardiorespiratory problems, sleep epilepsy, or violent parasomnia (see chapter 3), SB-related physiologic changes such as microarousal, tachycardia, or sleep stage shift can be monitored as well. Therefore, a polysomnographic study allows multidimensional analyses of sleep-related physiologic behavior.

Polysomnographic sleep laboratory EMG-based assessments are reported to be very reliable.[24,30] However, a major limitation is that some patients may not tolerate changes in their sleep environment. This may influence the natural occurrence of SB. Another limitation of the use of polysomnography for SB diagnosis is that multiple-night recordings are very expensive, and the generated data take hours to score. Sleep laboratory recordings are useful for research purposes, but for clinical diagnosis, they are only recommended for medically complex SB patients when unexplained findings are present (eg, frequent breakage of teeth or dental restorations) or when tooth tapping suggests sleep-related epilepsy.[16]

A future direction for the assessment of bruxism would be to establish a method that can directly, reliably, and rapidly measure ongoing bruxism activity. Clinical diagnosis would benefit from a simple, handy device that patients could use routinely with features such as rapid placement, noninterference with sleep, and rapid extraction of valid data. In this regard, miniature self-contained EMG detectors and analyzers show great potential, as long as they are scientifically validated (algorithms to assess specificity over nonrelated SB motor activity and to discriminate concomitant complex medical sleep disorders). They should be used routinely only after validation in a large population and determination that they are both diagnostically sound and cost effective.

## Conclusion

A collection of signs and symptoms related to SB in conjunction with complaints by a sleep partner is still the most efficient and reasonable way to assess SB in a clinical setting. Special appliances and recording methods have proven valuable as research tools but have limitations in clinical practice. As yet, no simple device can

provide a definitive diagnosis of SB.

However, EMG recording can be used in some patients presenting concomitant sleep or medical disorders such as sleep apnea-hypopnea syndrome, periodic limb movement, and epilepsy. In such cases, close collaboration with the patient's physician would be mandatory.

To date, there are no rapid and reliable clinical diagnostic methods that combine reasonable diagnostic validity, technical validity, strong guidance for therapeutic decisions, and cost effectiveness. Clinicians must be very cautious when interpreting the results of questionnaires and clinical examinations because of the possibility of overestimation. Clinicians and patients will benefit from the development of intelligent and valid systems that are able to discriminate and recognize oromotor activity and have simplified signal processing for SB assessment.

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CHAPTER 15

# PATHOPHYSIOLOGY OF SLEEP BRUXISM

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The aim of this chapter is to outline the physiologic events linked to the sudden onset of tooth grinding during sleep and to revise the various hypotheses proposed to explain sleep bruxism (SB). The discussion specifically highlights recent work utilizing quantitative analysis of jaw muscle activity in relation to brain, cardiac, and respiratory function that more fully describes SB and its accompanying sleep arousal–related patterning.

During the second half of the 20th century, the causes of SB were believed to be stress and anxiety, occlusal interferences, dopamine activity in basal ganglia, and, in children, hypertrophy of tonsils or allergies[1–3] (Fig 15-1). Most previously existing concepts or hypotheses that attempted to explain the genesis of SB are now supported by some scientific evidence, with the exception of the role of occlusal interference, which will not be described in this chapter.[3–5] It is likely that the genesis of SB cannot be explained by a single or simple mechanism.

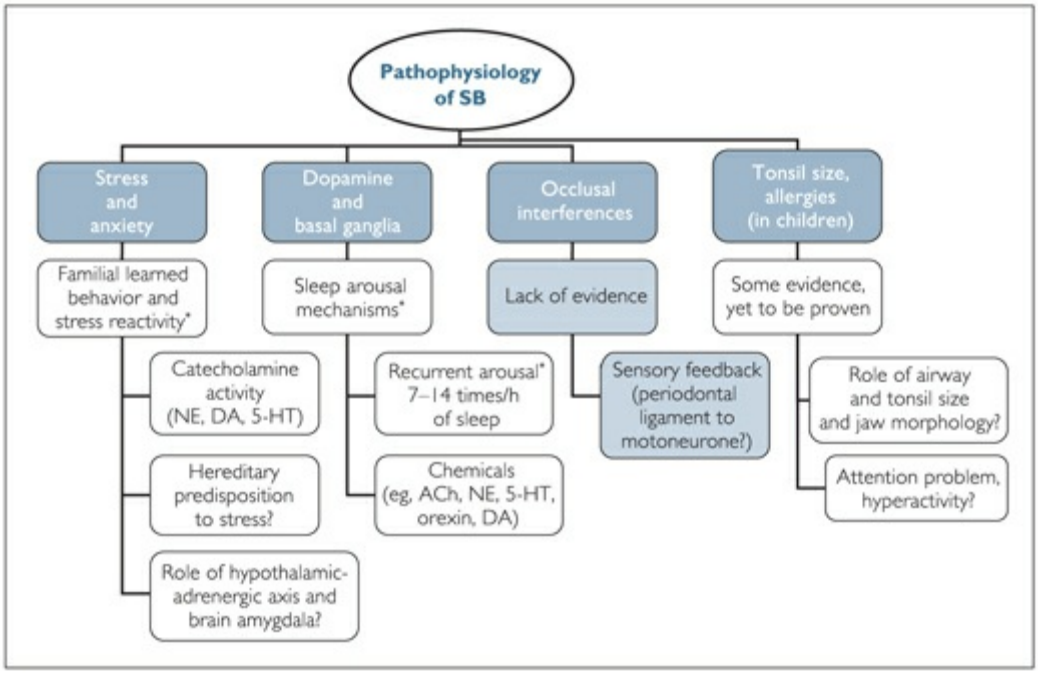


**Fig 15-1** Historical evolution of SB pathophysiology, from discoveries during 1960 to 1980 *(gray squares)* to current understanding *(white squares)*. (ACh) acetylcholine; (NE) norepinephrine; (DA) dopamine; (5-HT) serotonin. *Rise in cardiac, respiratory, and muscle activity (see Fig 15-2).

## Oromotor Activity During Sleep

Several types of motor activity of the mouth and the face can be present during sleep. These activities can be normal phenomena, clinical manifestations of an underlying disease, or the principal component of an abnormal condition. These oromotor activities include swallowing; sleep talking; coughing; grunting; head, lip, or jaw movements; and the rhythmic recurrence of co-contractions of both closing (eg, masseteric and temporalis) and opening (eg, suprahyoid) jaw muscles.[6,7] Such activities often occur concomitantly with other body movements.[6]

Differentiated from the aforementioned oromotor activities, a distinct masticatory muscle activity pattern has proven to constitute the basic pattern of SB. This unique and complex motor pattern is called *rhythmic masticatory muscle activity (RMMA)*[5,6,8] when electromyographic (EMG) activity reaches a specified individual threshold and is repeated at a particular frequency, as described below (see also

chapter 14). Three types of SB episodes have been classified:

1. Phasic: Brief, repetitive jaw muscle contractions with three or more consecutive EMG bursts, lasting 0.25 to 2 seconds each
2. Tonic: Sustained activity lasting more than 2 seconds
3. Mixed: Both types of episode

Nine of every 10 episodes of SB are either the phasic or mixed type. In young and otherwise healthy patients who have reported a recent history of tooth grinding, two major subgroups of SB patients can be identified: *(1)* a group with a low frequency of RMMA episodes (about 2 per hour of sleep) and *(2)* another with a high frequency of RMMA episodes (more than 4 per hour of sleep).[8] Some subjects will have 1 or 2 tooth grinding episodes per night, while others will present up to 80 episodes. Bruxers also exhibit other orofacial activities during sleep, which can constitute up to 30% of the entire set of oromotor events.[7] It is important to be aware that up to 60% of the normal population, ie, subjects not reporting sleep-related tooth grinding history, exhibit RMMA episodes but at a low frequency (about an episode per hour of sleep).[5,6]

## Genesis of SB: Sleep Arousal and Autonomic Activation

As described earlier in this volume (see chapters 1 and 2), sleep occurs in cycles and is divided into non–rapid eye movement (non-REM) and rapid eye movement (REM) sleep. Non-REM sleep consists of light stages (1 and 2) and deep stages (3 and 4). Most of the oromotor events in bruxers are observed in stages 1 and 2 and, more rarely, in REM sleep. SB occurs at a higher rate during REM sleep in patients suffering from psychiatric and/or neurologic diseases and in subjects who use medication that affects the central nervous system.[1,5,6]

The distribution of oromotor events is nonuniform across a given sleep cycle. During the transition periods from deep sleep toward light or REM sleep, bruxism episodes occur in clusters. They are characterized by the presence of brief sleep arousals (ie, a transient, 3- to 10-second reactivation of brain, heart, and respiratory activities with a rise in muscle tone; these brief arousals are also called *microarousals*). Sleep arousals are natural and recurrent physiologic events, grouped in a pseudocyclic fashion termed the *cyclic alternating pattern*.[9]

It was recently shown that close to 85% of SB events are observed within these naturally occurring arousals and in a specific ascending sequence of physiologic activity[5,6,10,11] (Fig 15-2):

1. At –8 to –4 minutes, a rise in autonomic sympathetic cardiac dominance occurs (acceleration-like effect) with a concomitant withdrawal of the parasympathetic influences (braking-like effect; Fig 15-3).
2. At –4 seconds, there is a rise in rapid-frequency cortical activity (EEG activity).
3. At –1 second, there is a concomitant rise of about 25% in heart rate as well as a greater than 100% increase in amplitude of inspiratory effort (nasal air flow) and a concomitant rise in suprahyoid muscle tone (jaw- and airway-opening muscles).
4. These increases are followed by the onset of RMMA in jaw-closing muscles (masseter and temporalis) and concomitant tooth grinding.

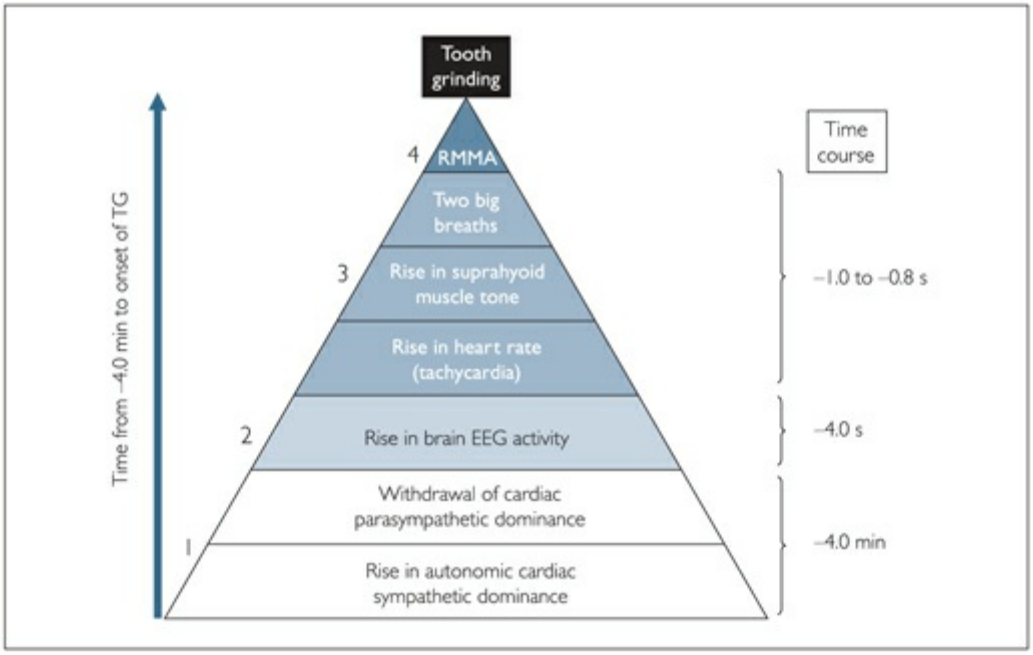


**Fig 15-2** Ascending sequence of physiologic events within arousal-related RMMA preceding tooth grinding (TG). (EEG) electroencephalographic.

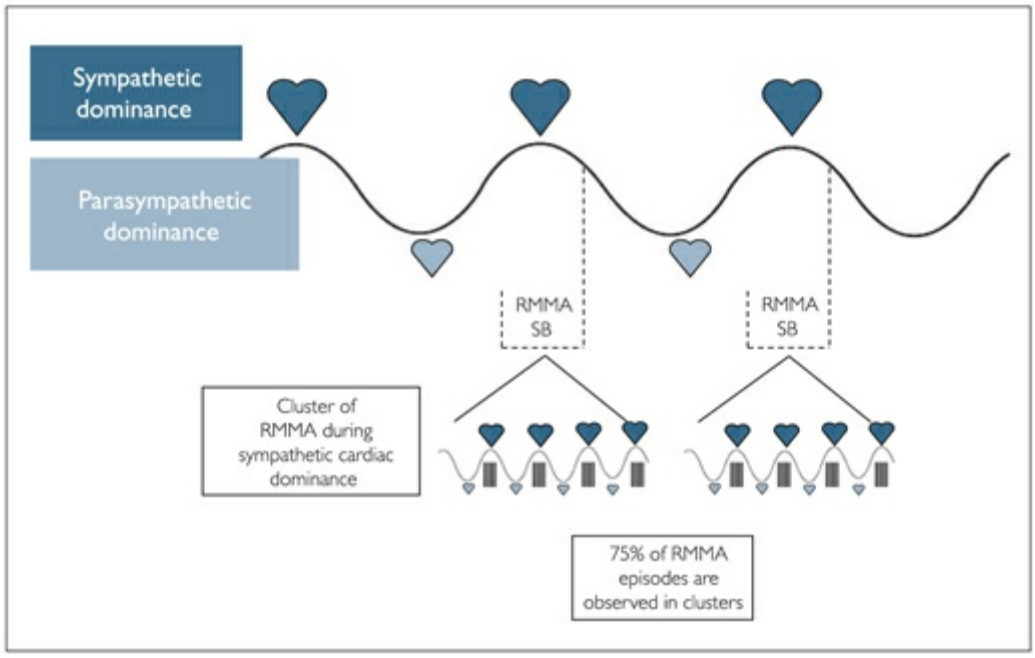


**Fig 15-3** Cyclic fluctuations during non-REM sleep of the cardiac autonomic activity in parallel to episodes of RMMA. SB does appear in clusters.

The exact cerebral source generators of RMMA are still unknown.[10] The control of rhythmic masticatory movements during the awake state occurs under a complex interaction among networks in the brainstem (trigeminal and facial motor nuclei, the lateral part of the reticular formation, the nucleus pontis caudalis, premotor interneurons, and the main sensory nucleus). *Central pattern generator* is the global name for the "masticatory" network located in the rostral pole of the trigeminal nucleus.[12] The amplitude and duration of masticatory movements are driven by the central pattern generator in close interaction with sensory feedback from receptors located in the oral mucosa, periodontium, jaw muscle spindles, and possibly temporomandibular joint receptors. However, there is yet no direct evidence to support the involvement of the central pattern generator of mastication in the genesis of RMMA.

Nevertheless, during sleep, the rhythmic contractions of jaw muscles related to SB are probably initiated in the brainstem.[5,10] The magnitude of sleep arousals may activate some type of masticatory motor pattern. A recent study using transcranial magnetic stimulation suggested that jaw motor activity in SB patients is probably of subcortical origin because no difference was noted in cortical evoked responses between SB patients and control subjects during wakefulness, a finding that must be replicated during sleep.[13] Although mechanisms linked to bruxism events have been

described, this does not constitute an identification of the cause that generates the phenomenon in otherwise healthy subjects. The following section of this chapter updates and revises existing evidence concerning the putative factors possibly associated to the genesis of SB.

## *Stress, anxiety, and the hypothalamic-adrenal axis*

The concept of stress became popular during the 20th century following the discovery that individuals under acute threat (eg, surgery, car accident, or the fight-or-flight reaction) or chronic work load may show an increased level of catecholamine release (norepinephrine, epinephrine, and dopamine). The hypothalamic-pituitary axis was described as controlling the release of catecholamines from the adrenal glands. High levels of catecholamines have been found in the urine of both children and adults who exhibit tooth grinding during sleep.[5] Such findings have been interpreted as the consequence of stress factors in subjects with SB. More recently, findings from a questionnaire-based survey have suggested that bruxism patients tend to have a deficit in their coping strategies when confronting stress.[14] This is congruent with a large population study in which Europeans, 15 years of age and older, who were aware of sleep-related tooth grinding also reported a highly stressful life and increased symptoms of anxiety.[15]

However, the aforementioned studies were based on questionnaires: They should be interpreted cautiously given the absence of an objective confirmation of tooth grinding during sleep. In fact, two studies performed in North America, using EMG recordings, failed to show a strong association between stress and SB-related tooth grinding. One study used parallel 24-hour self-reports of life stress during the day preceding the recorded sleep. Only 8% of the subjects showed a relationship between life stress and EMG-recorded SB. The subjects reporting high life stress were more likely to report anxiety, irritability, and depression.[16]

This finding was supported by a study in which the number of RMMA episodes per hour of sleep was used to define SB. No difference in the percentage of individuals reporting either life stress or anxiety the day before the recording was found between groups of SB subjects with a low or high frequency of RMMA or normal subjects.[8] Interestingly, subjects in the low-frequency group were actually more likely to report current stress related to sleep-laboratory conditions and morning jaw pain, data that contradict the hypothesis that increased stress causes increased SB activity.

## *Neurochemistry*

The behavioral and physiologic dimensions of sleep and wake states are regulated by a complex network of several neuronal pathways and neurochemical systems that drive either ascending or descending inputs from the reticular formation toward the thalamus, hypothalamus, and cortex or toward the spinal cord, muscles, and heart or lungs, respectively[17–19] (see Fig 15-1 and chapter 2 for more information). Among the main neurochemical substances that have a role in the genesis and maintenance of wakefulness and sleep, there is little evidence to support a link between dopamine, serotonin, norepinephrine, and γ-aminobutyric acid (GABA) and the genesis of RMMA[5,6,17] (see chapter 17). At this time, no evidence exists to support a role for acetylcholine, histamine, or orexin (also known as *hypocretin*)—substances involved in vigilance—in the genesis of RMMA. Nevertheless, it would not be surprising to discover in the future that most of these substances have such a role.

In the middle of the 20th century, following recognition of the importance of dopamine in neurodegenerative movement disorders, particularly Parkinson disease, it was proposed that dopamine might be related to the genesis of tooth grinding. A similar low level of evidence, based on case reports of patients with either neurodegenerative or mental disorders, also suggested that serotonin- and norepinephrine-related medications might be of therapeutic benefit to individuals with SB.[5,6,20] However, subsequent randomized experimental controlled trials in young and healthy subjects reporting sleep-related tooth grinding failed to confirm a a dominant role for dopamine in the genesis of RMMA.[5,6] Levodopa, a catecholamine precursor (ie, a dopamine, epinephrine, and norepinephrine precursor) had a modest effect in reducing the number of RMMA events per hour of sleep. Bromocriptine, a dopamine agonist, had no effect.

The evidence supporting the role of serotonin in the genesis of RMMA in patients with SB is also low. Most studies were designed to test a potential therapeutic benefit of either tryptophan (a serotonin precursor) or the tricyclic antidepressant amitriptyline. These medications were found to have no marked effect on RMMA.[5,6,20]

Just as sleep and wakeful states are governed by a complex network, the change in muscle tone from wakefulness to non-REM sleep and REM sleep also occurs under a series of interactions among noradrenergic and cholinergic and GABAergic neurons.[10,19,21] The role of norepinephrine in maintaining wakefulness and high vigilance (eg, stress) is well known.[17] Furthermore, norepinephrine is a potent

mediator of muscle tone during sleep, ie, dominant in the loss of muscle tone characterizing REM sleep.[21] The probable influence of norepinephrine on the genesis of RMMA in patients with SB is supported by recent randomized experimental controlled studies showing that clonidine, an α-agonist with central effects, reduced the frequency of RMMA.[22] However, the results were hampered by the fact that administration of clonidine was associated with severe hypotension in 20% of young and healthy normotensive subjects.

GABA is a major inhibitory neurochemical substance in the brain that is important for the genesis of sleep. However, its role in the genesis of SB is probably indirect because GABA acts on almost all neuronal systems related to wake, sleep, and motor control. Among its closest clinical analogs, diazepam and clonazepam both reduce SB. However, they also have significant side effects such as sleepiness, dizziness, and a risk of addiction.[1,5,23]

One case report of three elderly patients suggests that the limbic system (which plays a major role in emotion and motivation) may have a function in the genesis of bruxism.[24] The authors further suggest an interaction between the prefrontal cortical area and ventral tegmental area (both limbic structures) with noradrenergic, dopaminergic, and cholinergic interactions. Such findings need further investigation, but they may contribute to the link drawn between autonomic arousal reactivity and RMMA (as noted earlier). A recent immuno-chemistry study done in animals illustrated synaptic connectivity among the masticatory, limbic (amygdala), and autonomic pathways, providing indirect evidence linking rhythmic jaw movement to stress reactivity.[25]

## *Genetic factors*

To date, the first evidence of a genetic basis explaining a hereditary pattern of bruxism and related tooth wear has been drawn from questionnaire-based studies or from twin population analysis.[5,6,26] These surveys revealed that 20% to 50% of subjects aware of tooth grinding had a direct relative who was also a tooth grinder. Identical (monozygotic) twins share the highest probability of presenting bruxism with a high concordance.[26]

Further characterization of the specificity of the movements, etiology, and pathophysiology of SB is mandatory to establish a solid phenotype (including risk factors, clinical signs, and symptoms) before a search is initiated for one of several genes and proteins that could be expressed in relation to SB. The outcomes of such

studies will probably conclude that SB is linked to the expression of several genes (ie, polymorphism).

## Conclusion

The exact pathophysiology of SB is not known, but current evidence from experimental studies does suggest that RMMA and tooth grinding are secondary to the overactivation of the natural and ongoing physiologic activities linked to repetitive brief arousals during sleep. Evidence supporting an association between SB and stress, anxiety, and the hypothalamic-adrenal axis, however, is mixed at best, particularly when objective measures of RMMA are used. SB has been shown to be preceded by a sudden shift in autonomic cardiac and respiratory activity, in addition to brain activity, suggesting that a brief and intense overactivation of the autonomic nervous system may be more closely tied to the pathophysiology of SB. Although some modest evidence suggests that SB may have a hereditary component, it remains to be clearly demonstrated whether some individuals have a genetic predisposition to SB.

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CHAPTER 16

# SLEEP BRUXISM IN CHILDREN

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Bruxism, a stereotypical movement characterized by tooth grinding or clenching, can be observed while awake or when sleeping. Sleep bruxism (SB) is characterized by episodes of rhythmic masticatory muscle activity (RMMA) with or without tooth grinding (see chapter 14). Among adults, 60% of normal individuals also present episodes of RMMA in the absence of tooth grinding during sleep.[1] SB can cause concomitant jaw muscle pain, hypertrophy of the masticatory muscles, temporomandibular dysfunction, tinnitus, and headaches. The reported consequences of SB in children are tooth fracture, increased tooth sensitivity, mild-to-severe tooth wear, tooth hypermobility, injury to periodontal ligament and periodontium, hypercementosis, fractured cusps, pulpitis, pulpal necrosis, recession and inflammation of the gingiva, resorption of alveolar bone, and noncarious cervical lesions.[2–4]

## Epidemiology

In children, the onset of SB can occur as early as 1 year of age, with the eruption of the primary incisors. The prevalence estimates of SB, based on reports of tooth wear awareness, suggest a higher rate in children (14% to 38%) than in adults (estimated at 8%).[5–7] However, a longitudinal questionnaire-based study in which parents were questioned on the history of frequent SB reported a prevalence of 10.4% in 2.5 year olds and 32.6% in 6 year olds.[8] The likelihood of children having tooth clenching and grinding is 1.8 times higher if parents are aware of the signs and symptoms of

bruxism. The likelihood of reported bruxism is 3.6 times higher if children have a concomitant psychologic disorder, 1.7 times higher if they drool during their sleep, and 1.6 times higher if they are sleepwalkers. Interestingly, parental bedtime presence and separation anxiety at bedtime were both significantly higher in children with SB than in those without SB.[8] No gender difference in SB prevalence was noted.

Bruxism (while awake or during sleep) can also be seen in persons with Down syndrome, with an overall estimated prevalence of 42% in children between 3 and 14 years of age.[9] However, others have reported no difference in prevalence between children with Down syndrome and unaffected children.[10] Children with cerebral palsy may also have a higher prevalence of bruxism (36.9% to 69.4%) at clinical evaluation.[11,12]

These studies suggest that bruxism in children may be underdiagnosed because of a lack of parental awareness about the condition or the behavior of the sleeping child.

## Pathophysiology

The pathophysiology of SB in children is yet unknown (for more information on the pathophysiology, see chapter 15). In a recent pediatric study, no significant relationship was found between occlusal factors and the presence of bruxism,[13] but the diagnosis of SB was based only on clinical examination and self-report, without confirmatory polysomnographic and audio-video recordings, thus limiting the impact of the findings.

### *Stress and psychosocial influences*

There is a paucity of data on the relationship between stress and the psychologic factors often mentioned as being present in adult bruxism. A case-control study, however, revealed that pediatric bruxers have a 16 times greater probability of being anxious.[14] In comparison to control subjects, children with bruxism have higher urinary concentrations of epinephrine and dopamine.[15]

## *Findings in sleep*

In children between 5 and 18 years of age, 66% of SB episodes are associated with electroencephalographic arousals; these occur more often in stage 2 of non–rapid eye movement sleep and in rapid eye movement sleep.[16]

A sequence of events preceding onset of an SB episode has been defined in adults but needs confirmation in children: *(1)* increased sympathetic activity 1 minute before, *(2)* increased electroencephalographic frequency 4 seconds before, *(3)* increased respiratory amplitude associated with tachycardia 1 second before, and *(4)* increased electromyographic (EMG) activity of the suprahyoid muscle 0.8 seconds before, and *(5)* finally RMMA with or without tooth grinding.[17,18]

## *Pharmacology and neurochemistry*

Dopamine and norepinephrine may play a role in the pathophysiology of adult SB (see chapters 15 and 17), but their role is unknown in children.

However, children with attention-deficit/hyperactivity disorder (ADHD) who are treated pharmacologically with central nervous system stimulants have a higher prevalence of bruxism (considered to be secondary SB) than do children with untreated ADHD and control children without SB.[19]

## *Genetics and familial predisposition*

SB is a persistent trait: More than 86% of adults with SB report having been bruxers as children.[20] No clear pattern of genetic transmission has been found. A study of twins showed that monozygotic twins ($r$ = 0.58) were more likely to be tooth grinders than heterozygotic twins ($r$ = 0.20).[20,21] Another study showed that a child with one parent who exhibits bruxism is 1.8 times more likely to be a bruxer.[7] However, environmental factors are also critical in the development of SB, as shown in the twin study.[21] Polymorphism is the most likely genetic heritability pattern.[20]

# Risk Factors

Various risk factors for SB have been listed in Table 16-1. In a pilot sleep study with 10 children, 40% of the subjects scored high on attention and behavioral problem checklists.[16] Other studies have also reported that children with persistent bruxism presented with a trend toward a higher prevalence of ADHD.[8] Children with other psychologic disorders are also at increased risk for bruxism.[7]

**Table 16-1 Risk factors for SB**

| Concomitant condition | Strength of evidence base |
|---|---|
| *Parasomnias* | |
| Enuresis | +++ |
| Sleep talking | +++ |
| Sleepwalking | +++ |
| *Medical and psychologic conditions* | |
| Sleep-disordered breathing or snoring | +++ |
| Morphology of the tonsils and adenoids | +++ |
| Allergies | + |
| ADHD | ++ |
| Anxiety | ++ |
| Headaches | ++ |
| Separation anxiety at bedtime | ++ |
| *Medications* | |
| Methylphenidate | |
| (eg, Ritalin [Novartis Pharmaceuticals]) | ++ |
| Selective serotonin reuptake inhibitors (eg, paroxetine, fluoxetine, fluvoxamine, and sertraline) | +++ |
| Norepinephrine-serotonin reuptake inhibitors (eg, venlafaxine) | ++ |
| Antipsychotics (eg, haloperidol) | ++ |
| *Concomitant oral habits* | |

| | |
|---|---|
| Nail biting, pen biting, etc | ++ |

+++ = Solid evidence; ++ modest evidence; + = low evidence.

### *Airway patency*

A significant increase in breathing amplitude occurs just prior to an SB episode, suggesting that SB may help to reinstate airway patency in some patients.[22] A relationship between SB and sleep-disordered breathing has been reported previously. In one study, 16 of 17 pediatric patients with SB were also snorers, according to parental reports.[23] Furthermore, children with nasal obstruction had a 65.2% prevalence of bruxism.[24] In two pediatric studies in patients with sleep-disordered breathing, the prevalence of bruxism and tooth grinding decreased after tonsillectomy or adenotonsillectomy, from 45.5% to 11.8% and from 25.7% to 7.1%, respectively.[25,26] A cross-sectional study done at the Université de Montréal (n = 604, aged 7 to 17 years) showed higher odds ratio for bruxism and Class II classification (skeletal 2.2 [1.3 to 3.7] and dental 1.9 [1.1 to 3.0]). Furthermore, snoring was observed more often in children with narrow palates (odds ratio 2.2 [1.0 to 4.7]).[27]

## Diagnostic Evaluation

The diagnosis of SB is based on clinical interview, clinical evaluation, and objective polysomnographic testing (see chapter 14). The interview investigates the history of clenching and tooth grinding. This history of SB is usually corroborated by a sibling or by parents who have heard grinding noises while the patient is sleeping. Parents who keep their bedroom door open report bruxism 1.7 times more often than those who do not.[7]

The interview should include questions about medications used, such as antidepressants or antipsychotics, and recreational drugs (eg, 3,4-methylenedioxy-*N*-methylamphetamine, known as *Ecstasy*). Reported tooth fracture or increased tooth sensitivity can also be associated with jaw clenching while awake and SB. Moreover, drooling during sleep and sleep talking are 1.7 and 1.6 times, respectively, more likely to be associated to bruxism.[7]

The clinician must enquire about concomitant jaw muscle pain, temporomandibular dysfunction (eg, limitation of jaw movement or the presence of joint sounds), and headaches (mostly temporal), particularly those experienced in the morning after awakening, all of which have been associated with jaw clenching while awake and SB. The prevalence of bruxism is higher in children with headaches (23.3%) than in children without headaches (16.5%).[28]

The clinical evaluation should include palpation of the head and neck to rule out pain from either temporomandibular disorders or other joint pain; examination of the buccal mucosa (tooth grooving or ridging inside the cheeks or on the sides of the tongue); assessment of salivary secretion (increased risk for tooth wear in the absence of saliva or when salivation is low); and examination of the severity of tooth wear. Furthermore, the presence of hypertrophied masseteric muscles can be an indirect sign of tooth clenching or grinding.

## *Ambulatory and sleep laboratory monitoring*

To investigate and to confirm the presence of unusual oromandibular motor activity during sleep, ambulatory recording or in-laboratory polysomnography is helpful. Ambulatory recordings are made with portable EMG recording devices that can be used while the patient sleeps at home. However, these ambulatory recordings are not SB specific and cannot confirm diagnosis of SB in the absence of audio-video recording, because approximately 30% of oromotor activities during sleep are not SB specific.

In-laboratory polysomnography with simultaneous audio-video recordings under infrared lighting (with EMG recording of at least one masseteric muscle, electroencephalogram, leg electrode, and a full respiratory montage) rules out concomitant sleep disorders such as periodic limb movements during sleep, sleep apnea, insomnia, or sleep epilepsy.

There is a known night-to-night variability of EMG SB occurrence (approximately 25%) in adults, and the variability of SB episodes with tooth grinding noises is closer to 50%.[29]

## *Scoring and severity scale of SB*

Methods and criteria for SB scoring have been developed for adults (see chapter 14)

but have not been validated for children; however, some researchers have applied similar criteria to children.[16] It may be possible to revise adult criteria to make them applicable to children by using different cutoff values, as has been the case in revising adult criteria for sleep-disordered breathing (eg, the definition of obstructive sleep apnea is modified from more than five events of apnea-hypopnea per hour of sleep in adults to more than one event in children).

## Management

There is no known available treatment to prevent SB in children. As is the case for adults, behavioral approaches such as sleep hygiene and relaxation may be of interest, but there is an obvious lack of evidence-based studies. The efficient and safe use of medication or oral appliances, as described for adults in chapter 17, must be evaluated in children. Furthermore, the effects of orthodontic and surgical techniques used to improve respiration in children with sleep apnea on the genesis of SB are unknown, but the topic is of interest because the presence of large tonsils is reported to be a risk factor for tooth grinding.

The management of SB in children deserves to be the subject of long-term research and clinical commitment because of its persistence over time and over age,[8,20] its high night-to-night variability,[29] the cyclic presentation of the symptoms, the absence of a curative treatment, and the low level of long-term follow-up data (Box 16-1).

**Box 16-1 Management of primary complaints of pediatric SB***

**Tooth grinding noise or tooth damage and wear**

- *Behavioral modification:* The parents and patient should be educated about relaxation techniques and sleep hygiene. This is also applicable in cases of separation anxiety (for example, gradual separation and a reward system).
- *Dental appliances:* To date, dental appliances have only been studied in adults, and lack of evidence prevents firm and safe conclusions about their use in children. If oral appliances are worn, they should not interfere with growth and development. In adults, it was shown that within 4 weeks of use the SB

index returned to the baseline level after the initial drop.[30,31] Moreover, in adults, the overall compliance was estimated to be 50% after 1 year.[30] In the pediatric population, the burden would fall on the parents to maintain a higher level of compliance by and oral hygiene of their child.

**Jaw muscle pain or headaches on awakening**

- *Referral to a sleep specialist:* Patients should be sent to a specialist to investigate the possibility of upper airway resistance syndrome or sleep apnea. When patients' symptoms include daytime sleepiness, headaches on awakening, or gastroesophageal reflux, it is important to investigate whether either sleep apnea or upper airway resistance syndromes are concomitant. Children with migraine headaches reportedly experience more sleep disturbances, such as bruxism (29%) and snoring (23%), than controls.[32]
- *Medication history:* The history should include a list of all medications being used because some may exacerbate movements during sleep (eg, methylphenidate) or some respiratory disturbances (eg, opioids).
- *Medication:* In the adult population, various muscle relaxants (eg, meprobamate, diazepam, lorazepam, and clonazepam) and botulinum toxin have been used in SB treatment management. However, the effect and safety of these medications have not been studied in children. A recent pilot study showed that trazodone decreased the occurrence of SB in trauma-burned children aged 6 to 18 years.[33] Nevertheless, randomized controlled and longitudinal trials with polysomonographic and audio-video recordings of SB are needed in children.
- *Head posture:* It has been reported that bruxers have a more anterior and downward head tilt.[34] Another study suggests that cervical spine muscle–joint dysfunction could be an etiology of pediatric SB. Complete relief of the subjective symptoms was observed after vectored upper cervical manipulations, a finding yet to be confirmed.[35]

*All treatment approaches require caution because there is a lack of evidence-based validation in children

## Conclusion

Pediatric SB is underdiagnosed in sleep medicine because of parents' and

clinicians' limited knowledge of its characteristics and because of poor interdisciplinary communication among health care professionals. The condition is also poorly managed because of the lack of knowledge and evidence about its risk factors, pathophysiology, and consequences.

It is hoped that future research will determine that not all children with SB and tooth grinding require intervention. At the present time, because of the paucity of studies supporting preventive or management approaches, only children with severe tooth malocclusion or damage and those presenting with concomitant medical problems (eg, pain and respiratory disturbances) are actually directed to care.

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# CHAPTER 17

# MANAGEMENT OF SLEEP BRUXISM

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Generally, the ideal treatment approach for sleep bruxism (SB) would be based on a clear etiology and intended to repair damage caused by the disorder and eliminate etiologic factors to prevent recurrence. Unfortunately, the pathophysiology of SB is not comprehensive, and some aspects remain controversial (eg, role of sensory feedback and occlusion). Therefore, definitive treatment and prevention remain elusive. For these reasons, the word *management* is preferred instead of *treatment*. More information on etiology and pathophysiology is found in chapters 12 and 15, on the interaction between SB and pain in chapter 21, and on the pharmacology of pain and sleep in chapter 23.

Common management modalities are best categorized as *supportive*, a term that refers to methods directed toward altering or alleviating the patient's symptoms rather than directly controlling or eliminating etiologic factors or pathologic causes underlying the disorder. In general, management approaches are most often initiated to prevent possible damage to the stomatognathic apparatus or to prosthetic restorations. Several approaches to intervention target masticatory muscle hyperactivity related to SB and potential harmful consequences, such as damage to teeth, discomfort and pain in the jaw muscles or temporomandibular joints, and headaches. However, management of muscle hyperactivity does not address other factors, such as tooth wear, oral dryness or xerostomia secondary to stress and changes in the lubricant properties of saliva, headache, and sleep-disordered breathing (eg, snoring, upper airway resistance, hypoventilation, and apnea-hypopnea). Before deciding which therapeutic measure is required, the clinician should seek a definitive diagnosis with special emphasis on contributing, initiating, and perpetuating factors.

Generally, bruxism activity during sleep is transient or episodic. Expected

treatment results should be estimated by weighing the benefit for the patient (such as relief and quality of life) against possible adverse effects. Oral and occlusal interventions, pharmacotherapy, botulinum toxin (BT) injections, and behavioral and psychologic therapy are common therapeutic approaches briefly reviewed in this chapter (Table 17-1). The final section focuses on pediatric SB issues.

**Table 17-1** **Palliative management for SB***

| Management | Effect | Level of evidence | Notes |
|---|---|---|---|
| *Orodental management* | | | |
| • Oral appliances: | | | |
| – Mouthguard/tooth protection | Neutral | Weak | For short-term use |
| – Occlusal appliance/tooth protection | Positive | Moderate | Risk of aggravating sleep-disordered breathing |
| – Mandibular repositioning appliance | Positive | Moderate | For short-term use |
| – Anterior tooth appliance (eg, NTI splint) | Positive | Moderate | For short-term use |
| • Dental treatments: | | | |
| – Dental occlusion (ie, tooth equilibration and orthodontic occlusal corrections) | Questionable | Low | Should be avoided |
| *Pharmacologic management*† | | | |
| • Sedative and muscle relaxants: | | | |
| – Clonazepam | Positive | Moderate | Risk of dependence |
| – Diazepam, buspirone | Positive | Case report | Risk of dependence |
| • Serotonin-related: | | | |
| – Tryptophan | No effect | | |
| – Amitriptyline | No effect | | |

| | | | |
|---|---|---|---|
| • Dopaminergic: | | | |
| – Levodopa | Modest | Moderate | |
| – Pergolide | Positive | Case report | |
| – Bromocriptine | No effect | | |
| • Cardioactive: | | | |
| – Clonidine | Positive | Moderate | Severe risk of hypotension in morning |
| – Propanolol | No effect | | |
| *Behavioral management*‡ | | | |
| • Explanation of causes and exacerbation factors for SB | Questionable | Weak | |
| • Elimination of clenching teeth and bracing jaw during daytime in reaction to life pressures | Questionable | Weak | |
| • Lifestyle changes; introduction of sleep hygiene, relaxation, autohypnosis, and winding down before sleep | Questionable | Weak | |
| • Biofeedback | Questionable | Weak | |
| • Physical therapy and training in relaxation and breathing | Questionable | Weak | |
| • Psychologic therapy to manage stress and life pressure | Questionable | Weak | |
| *Other management* | | | |
| • Botulinum toxin | Questionable | Weak | |

* Data from Lavigne et al.[1] †Short-term management for acute or severe condition. ‡None supported by strong evidence. (NTI) nociceptive trigeminal inhibition.

# Oral and Occlusal Interventions

Two different approaches should be distinguished in this category: *(1)* irreversible treatments (eg, selective occlusal adjustments, oral rehabilitation, and orthodontics) and *(2)* reversible, temporary occlusal modalities (eg, interocclusal appliances). The current state of the art regarding the pathophysiology of SB conceptualizes the disorder as primarily related to centrally regulated phenomena. SB is not, as historically considered, primarily driven by peripheral factors, such as activation of periodontal receptors, once thought to contribute to either the onset or persistence of this parafunctional behavior (see chapter 12). Irreversible occlusal adjustments can cause serious, unjustified damage to the dentition and should be avoided. Evidence-based data supporting the use of oral rehabilitation and orthodontic treatment in managing SB, a transient condition across the life span, are lacking.

Interocclusal appliances are the most common modality used to manage SB and associated orofacial pain or temporomandibular symptoms. Despite their benefits and wide usage, the mechanism of action of interocclusal appliances is one of the more controversial issues in the scientific literature.[5]

The nociceptive trigeminal inhibition (NTI) tension suppression system has been lately cleared by the US Food and Drug Administration (FDA). This system is based on the assumption that an anterior bite stop reduces electromyographic (EMG) muscle activity during both clenching and grinding. This statement is partially confirmed by a study that found that the anterior bite stop had a significant effect in decreasing EMG activity during both clenching and grinding for the anterior and posterior temporalis and masseter muscles when compared to the EMG measured without the anterior bite stop.[2] A recent investigator-blinded randomized controlled crossover study that compared the efficacy of the NTI with an occlusal appliance (OA) indicated a strong inhibitory effect on EMG activity in jaw-closing muscles during sleep when using the NTI but not the OA.[3] However, the EMG activity was not directly related to clinical outcome. In contrast, a randomized controlled trial that compared the effects of the NTI and an OA on signs and symptoms of temporomandibular disorders (TMDs) found the OA superior for all variables registered.[4] One subject treated with a NTI splint exhibited an impaired occlusion at the 6-month follow-up.[4] Since the NTI does not cover all the teeth in an arch, there is a possibility of developing posterior dental over eruptions and/or anterior dental intrusion; NTIs should be recommended for short-term use only.

The most studied and apparently safest interocclusal appliance is the OA, also known as a *stabilization appliance*. This is a removable, hard acrylic resin device that fits over the teeth of one dental arch and provides optimal static and dynamic occlusion to the patient. In a crossover randomized controlled study, the effect of an

OA and a palatal appliance (PA) on SB was examined.[6] Both appliances have the same design, but the PA eliminates occlusal coverage. Both splints were found to reduce the SB-associated EMG activities of the masseter muscles; however, the effect was transient (2 to 3 weeks).

In a similar double-blind parallel controlled randomized clinical trial, neither appliance (OA or PA) had an influence on SB activity or on standard sleep parameters.[7] The researchers recommended that the application of appliances "be considered at the individual patient level."[7] Guidelines for indications and contraindications for OA are needed.

The effectiveness of OA in the management of patients with TMDs remains particularly controversial. One critical review, for example, found that TMD symptoms were reduced 70% to 90% with the use of an OA,[5] whereas a more recent review found insufficient evidence either for or against the use of OA therapy in treating TMDs.[8] Use of a maxillary OA may also have deleterious effects in patients suffering from sleep-disordered breathing such as apnea and hypopnea. Gagnon et al[9] found that OA may actually increase the risk of aggravation of respiratory disturbances and recommended that clinicians question patients regarding snoring and sleep apnea before using OA therapies. For more information on sleep-disordered breathing, see chapters 4 and 7.

In a recent randomized controlled experimental study, the short-term use of an occlusal stabilization appliance (for 6 consecutive nights) reduced the frequency of SB-related events by 42%.10 The use of a double-arch appliance without any mechanism in place to move the mandible forward produced a similar reduction (approximately 40%). However, the reductions in SB motor activity obtained when a temporary mandibular repositioning appliance (MRA)—commonly used to manage snoring and sleep apnea—was set in a 25% or 75% protrusive position nearly doubled the reductions found with the other appliances (77% and 83%, respectively). At the end of the study, however, when subjects were asked about their personal opinion regarding the two oral devices, a significantly greater number preferred the OA over the MRA; patients reported that the MRA was too cumbersome because of its size. A recent study replicates these findings using a smaller MRA that was specifically made for each patient.[11]

This issue notwithstanding, the superior efficacy of the MRA may inform etiologic perspectives of SB. It has been hypothesized that SB may play a functional role in reestablishing airway patency during sleep, which may be compromised as a result of the posterior displacement of the mandible, tongue, and the soft tissues during

sleep.[12,13] This theory suggests that SB may be a response to sleep-related hypoventilation or upper airway resistance in the absence of frank obstructive sleep apnea. Appliances and treatments designed to improve breathing during sleep theoretically should reduce SB; however, this hypothesis has yet to undergo rigorous scientific scrutiny.

Despite these controversies, when SB is suspected based on early morning masticatory muscle pain, reports by a sleep partner, or by any other clinical or laboratory diagnostic means, interocclusal appliance therapy should be considered. If a clinical decision to deploy an OA is made, the most prudent approach would be to require frequent and regular follow-up visits to monitor effectiveness, evaluate the development of iatrogenic factors, and reevaluate the cost-benefit analysis. Moreover, if the patient does report the apparition of snoring, cessation of breathing, choking during sleep (suggestive of obstructive sleep apnea), morning headache, or an increase in awake-time sleepiness, it would be wise to request a sleep medicine consultation to exclude secondary sleep-disordered breathing.

## Pharmacotherapy

Since modern etiologic theories of SB focus on central factors (see chapters 12 and 15), a curative pharmacologic treatment should at least be possible. At present, however, no safe and/or definitive medication has been identified. A critical review of drugs and bruxism concluded that:

> *There is insufficient evidence-based data to draw definite conclusions concerning the effects of various drugs on bruxism. Although certain substances related to the dopaminergic, serotonergic, and adrenergic systems suppress or exacerbate bruxist activity in humans and animals, the literature is still controversial and based mostly on anecdotal case reports. More controlled, evidence-based research on this under-explored subject is needed.*[14]

Recently, several promising studies have been published on possible pharmacotherapy for SB. In a placebo-controlled polysomnographic study, clonazepam, a long-acting benzodiazepine, significantly improved the SB motor index and subjective sleep quality in a large age group population.[15] Clonazepam, however, may lead to tolerance and physiologic dependence, particularly with long-term use. Fatigue, somnolence, and occasionally muscular hypotonia (contraindicated in patients with sleep apnea-hypopnea) and movement coordination disturbances are possible side effects of clonazepam. For these reasons, the

clinician should take a judicious and cautious approach when contemplating prescribing clonazepam for long periods.

In another randomized experimental control study (ie, the aim was to challenge the mechanism of SB genesis, not drug safety), a midlevel dose of clonidine (an α-adrenergic receptor agonist) was found to reduce SB motor activity by decreasing cardiac sympathetic tone in the minutes preceding the onset of SB, preventing the sequence of autonomic sleep arousal that leads to motor activation in the genesis of SB.[16] Because morning hypotension was observed in 20% of the patients using clonidine, it was concluded that further dose-dependent research was required to assess its safety for the management of SB.

At the present time, no definitive pharmacologic approach to management of SB can be recommended. Needless to say, more controlled, evidence-based research on this underexplored subject is essential because it promises a potentially etiology-based cure.

## Botulinum Toxin Injections

Among pharmacologic agents that have a potential use in the management of SB is BT, a neurotoxin produced by the anaerobic bacterium *Clostridium botulinum*. When injected intramuscularly, BT prevents the release of acetylcholine from presynaptic vesicles localized at the neuromuscular junctions. The result is a temporary (3- to 4-month), reversible block of some of the motor fibers that have weakened muscle contraction. BT type A is now widely used to manage, but not cure, a broad range of clinical problems characterized by muscle activity that could be too tonic (sustained) or too intense.

The primary clinical indication for BT use in medicine is for movement disorders such as focal dystonia or torticollis.[17] A meta-analysis indicated that patients suffering from cervical dystonia and blepharospasm (sustained eye-blinking activity) benefit from BT use.[18] BT has also become the therapy of choice for oromandibular dystonia; its use in jaw-opening, jaw-closing, and jaw deviation dystonia has been documented.[19]

Although BT injections appear to be a safe and efficient method to temporarily relieve patients afflicted with severe oromandibular dystonias (including secondary medical disorder–related tooth grinding and bruxism), providing positive effects on patients' quality of life, BT injections cannot be considered a definitive or curative

treatment but rather are a palliative and transitory procedure. Furthermore, many issues and concerns about this agent remain unresolved. These include complications such as occasional local weakness (that can interfere with speech and mastication) and systemic effects of BT, which is known to be transported backward to the central nervous system (retrograde transport within nerve to cell body of neuron).[17] In 2008, the FDA issued an early communication about an ongoing safety review regarding a commercially available preparation of BT (Botox, Allergan). The FDA has received reports of systemic adverse reactions including respiratory compromise and death following the use of BT types A and B for both FDA-approved and unapproved uses. The reactions reported are suggestive of botulism, which occurs when BT spreads in the body beyond the site where it was injected.[20] The high cost of BT also reduces its usefulness for large groups of the population with lower income or without health insurance.

Clinical reports suggest that BT may be an agent of interest in the management of severe bruxism and tooth grinding. In a recent randomized controlled pilot study, muscle pain associated with bruxism was reduced following BT type A injection; however, it is unclear if awake or sleep-related bruxism was studied because no polysomnography was done to diagnose and quantify the motor activity.[21]

The effect of BT injections in the management of jaw muscle pain or orofacial pain is also extremely controversial.[22–25] Randomized controlled trials should be performed; these must incorporate a valid tool to confirm the presence of SB (see chapter 14) in order to assess the relative safety and efficacy of BT in the management of SB and related chronic orofacial pain.[24]

## Behavioral and Psychologic Therapy

Behavioral modalities used to manage SB include biofeedback, psychoanalysis, hypnosis, progressive relaxation, meditation, sleep hygiene, habit reversal, and massed practice. Recently, a randomized study compared the efficacy of an OA against that of cognitive-behavioral treatment.[26] Cognitive-behavioral treatment consisted of problem solving, progressive muscle relaxation, nocturnal biofeedback, and behavioral activation training to increase recreational activities and enjoyment. Both groups demonstrated significant reductions in SB activity, self-assessment of SB activity, and psychologic impairment, and increases in the use of positive stress-coping strategies. However, the effects were relatively small, and no group-specific

differences were observed in any dependent variable. The authors concluded that their findings do not readily confirm early assumptions that a combination of biofeedback and stress-coping counseling would be the most probable therapeutic means to obtain a long-term effect in SB patients and recommended "further controlled evaluations to verify treatment effects."[26] It also remains to be determined whether combining an OA with cognitive-behavioral therapy would yield additive or synergistic benefits relative to single therapy.

In an extensive review of principles for the management of bruxism, Lobbezoo et al[27] concluded that the value of behavioral approaches to SB is questionable because the modalities tested to date largely lack a sound scientific basis. This author's clinical and scientific experience, however, suggests that controlling stress can be helpful.[28] Well-designed studies regarding behavioral treatments, such as sleep-restriction therapy that are designed to promote better sleep (eg, more time in deeper non-REM stages, less arousal), are particularly promising and should be encouraged. Such approaches would be grounded in recent data demonstrating that SB is strongly associated with sleep-related arousals. Behavioral sleep medicine interventions have demonstrated robust long-term efficacy in managing insomnia and poor sleep quality (eg, Smith et al[29]; also see chapter 24).

## Pediatric Considerations

SB is a common phenomenon in children that can be alarming to parents (see chapter 16).[1] With respect to pediatric SB and its association with TMD, however, at least one study found no statistically significant association between primary dentition wear facets and clinical signs of TMD.[30] This report concluded that "wear facets in young children do not appear to warrant TMD evaluation or treatment." In the absence of direct evidence supporting behavioral and oral therapies for SB in children, the literature on pediatric SB suggests that anxiety, hyperactivity, and airway obstruction can be risk factors for SB.

The role of emotional and stressful states, measured indirectly by the concentration of urinary catecholamines in children, revealed that epinephrine and dopamine levels were positively associated with reports of SB-associated tooth grinding.[31] It was further suggested that psychologic techniques may be effective in reducing signs of SB in children with a primary dentition.[32] Strong evidence is needed, however, to guide clinicians in the use of behavioral approaches to manage

pediatric SB.

Children affected by attention-deficit/hyperactivity disorder (ADHD) who are receiving medication are reported to be at risk of tooth grinding. A comparative study, with healthy age- and gender-matched controls, revealed that pharmacologically treated ADHD children had a higher occurrence of bruxism than either ADHD children without medicines or control subjects.[33] Within the ADHD medication group, children receiving central nervous system stimulants (eg, methylphenidate) were associated with more frequent SB-related tooth grinding complaints from parents; it remains to be determined if this finding is the result of the higher level of vigilance of parents to their child's behavior and disorder.

The best strategies to adopt for ADHD children who are damaging their teeth through SB are yet unknown: a change in medication, a modification of the dosage, or the use of a soft splint replaced on a regular basis to preserve harmonious oropharyngeal growth development.

In the search for a somatic etiology for pediatric SB, it has been suggested that allergies or airway obstruction must be excluded in children with severe tooth grinding. It also has been suggested that SB in children can be initiated by an increase of negative pressures in the tympanic cavities from intermittent allergic edema of the mucosa of the eustachian tubes.[34] A positive correlation between sleep-disordered breathing and bruxism has also been hypothesized.[35] This theory is supported indirectly by the observation that bruxism decreased after adenotonsillectomy.[36] Vélez et al[36] further conjectured that head posture could affect airflow in children and could be part of the etiology of SB because SB was correlated with hypopnea and increasing airway patency. These authors recommend further studies to explore these mechanisms of bruxism (see chapter 16).

Given the relative paucity of systematic research related to the etiology and prevention of pediatric SB, a multimodal assessment, in addition to a dental evaluation, is recommended, including evaluation by an appropriate mental health professional, a physiotherapist, and an otolaryngologist to prevent further damage (not only dental). In children with a mixed dentition, when dental wear is suspected to be the result of SB, a soft splint may be recommended. However, the practitioner must proceed cautiously and reassess frequently to prevent growth and occlusal consequences.

More randomized controlled trials using quantitative measures of outcome (eg, polysomnography for muscle activity) will be necessary to guide clinicians in the management of SB. Tooth grinding in childhood may persist into adulthood, and no

direct evidence supports the concept that reduction of SB in children and management of related damage to primary dentition will prevent or alter the risk of tooth grinding in adult life.[1,37]

## Current Recommendations

Huynh et al[38] suggested incorporating two approaches with corresponding metrics to weigh the evidence on SB management. The first, the number needed to treat, allows several randomized clinical studies to be compared to derive a general conclusion. The second, effect size estimation, permits evaluation of the impact of treatment relative to a placebo using different studies of similar design. When number needed to treat, effect sizes, and the power of the available evidence are considered, it can be concluded that MRAs, clonidine, and OAs reduce, for a short-term period, SB in adults. However, the use of MRA and clonidine may be linked to potentially significant adverse effects: Possible morphologic changes can be expected with long-term use of MRA, and severe hypotension when the patient awakens can result from clonidine. Moreover, the risk of dependency limits the use of the drug clonazepam over long periods.

Based on these considerations, Huynh et al[38] argued that the OA is so far the treatment of choice to protect the patient from tooth damage and alleviate grinding sounds. No cure of SB can be expected with OA therapy because the reduction of muscle activity does not last more than a few weeks. Moreover, caution is suggested if OAs are to be used in patients suspected of suffering from sleep-disordered breathing (eg, obstructive sleep apnea-hypopnea syndrome).

When tooth grinding in children is reported by parents, airway patency must be assessed. Behavioral lifestyle suggestions may help and, for children with a mixed dentition who have severe tooth damage, use of a soft splint may be recommended.

## Conclusion

Several management strategies, ranging from OAs to pharmacology and psychotherapy, have been proposed to reduce the consequences of SB-associated tooth grinding (eg, tooth damage, orofacial pain, and headache). Before deciding the

most appropriate management strategy for SB for a given patient, the clinician should consider the actual or expected damage related to SB, the concomitant problems (eg, anxiety, airway patency, and the risk of sleep-disordered breathing), and the side effects of or contraindications to OAs and medication. More systematic research is awaited to guide the clinician seeking to apply an evidence-based approach to determine the best current management strategies for SB.

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# SECTION IV

## SLEEP AND OROFACIAL PAINS

# CHAPTER 18

# PATHOPHYSIOLOGIC CONCEPTUALIZATIONS OF CHRONIC PAIN

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*Pain* has been defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage," by the International Association for the Study of Pain.[1] The quality and characteristics of the pain experience convey valuable information. For example, a well-localized pain (eg, a toothache that does not extend over another trigeminal nerve branch) is a different phenomenon from diffuse pain (eg, fibromyalgia, more recently termed *musculoskeletal chronic widespread pain*).

Although the sensation of pain is important from an evolutionary standpoint, a warning system signaling injury or further damage, pain can transform a beneficial sensory phenomenon to a pathologic and intractable state known as *chronic pain*. In such cases, pain is less a symptom than a proper disease of the nervous system. Chronic pain has sometimes been described as pain that persists beyond the expected time of healing, but this definition is unsatisfactory because rates of healing and the factors associated with it are poorly understood. Furthermore, pain disorders are not necessarily linked to specific injuries. Some chronic pain conditions, such as fibromyalgia (widespread pain), myofascial and temporomandibular disorders (TMDs), and irritable bowel syndrome, for example, do not often involve identifiable peripheral insult and are increasingly described as central sensitivity syndromes (see chapter 21).

In a most general sense, chronic pain is sometimes simply described as pain that persists for 3 to 6 months or more. Through this simple descriptive definition,

chronic pain has become an epidemic with staggering economic and psychosocial consequences. The financial burden alone is astounding, estimated to cost in excess of US $1 trillion annually in developed countries.[2] Recent research surveys on the prevalence of chronic pain among the general population report numbers to vary from 11.0% to as high as 46.5%.[3] Chronic pain diminishes quality of life, often causes physical disability,[4] and is a serious risk factor for suicide,[5] rendering pain management an essential component of medical and dental care. Further, approximately two of three chronic pain patients suffer from comorbid conditions such as clinical insomnia (see chapter 3), mood alteration, and depression, which can be associated with a variety of negative health consequences (see chapter 22).

Although pain is the primary reason individuals seek health care, and dental care in particular,[6] few providers are specifically trained in pain management. Dental practitioners are increasingly called on to treat chronic syndromes in which pain is a central component, including facial pain, headache, and TMDs. Given the detrimental impact of pain, including increased mortality rates,[7,8] improvement in the understanding of the phenomenon of chronic pain and the identification of groups at high risk for chronic pain are becoming increasingly important.

In this review, some of the mechanisms and processes that underpin the development of chronic pain syndromes are outlined in broad terms and individual differences that potentially contribute to the development, persistence, and exacerbation of chronic pain conditions are discussed, all with a focus on the use of quantitative sensory testing (QST) to assess various aspects of pain perception. For example, a recent prospective study of TMD risk factors suggested that individuals with elevated acute pain sensitivity, revealed by QST (ie, tools and methods to assess pain threshold and tolerance using mechanical, thermal, or chemical pain sensory triggers, as described later in the chapter), may be at greater risk of developing persistent orofacial pain.[9] Readers who want more information about orofacial pain are invited to read the recent book by Sessle et al.[10]

## Mechanisms of Persistent Pain

The pain system (nociceptive processing) is composed of ascending and descending systems that function in parallel. Ascending pain transmission is the process that provides the brain with information about potential tissue damage once the cascade of neural signals is set in motion. Peripheral transmission of nociceptive signals

occurs via two distinct groups of peripheral fibers, generally termed *primary afferent fibers*. Cold and well-localized pain sensations are mediated by fast-conducting myelinated A-δ and A-β fibers. Unmyelinated, more slowly conducting C fibers transmit nociceptive signals produced by noxious heat, mechanical stimuli, or by poorly localized stimuli.[11] In general, A-δ fibers are thought of as contributing to first-pain sensations, which are often described as "sharp" or "pricking." In contrast, activation of C fibers tends to produce diffuse "aching" or "burning" sensations. Sensory receptors such as these are common to almost all multicellular animals and work together in shaping the conscious experience of pain.

These ascending signaling systems do not operate in isolation, of course, and they are subject to many local modulatory factors. For example, when tissue damage occurs, an inflammatory response is mounted, with release of factors such as potassium ions, substance P, prostaglandins, histamine, leukotrienes, and bradykinin (see chapter 19). These substances all have the potential to induce changes in peripheral receptors and primary afferent fibers; such alterations include a reduced activation threshold, expansion of receptive fields, generation of spontaneous activity, and recruitment of normally inactive, or silent, nociceptors. These and other similar changes constitute peripheral sensitization, which results in an increased nociceptive signal to the spinal cord.

## *Peripheral and central sensitization*

Peripheral sensitization is the reduced pain threshold (eg, increasing the probability of perceiving pain) brought about by increased responsiveness of peripheral nerve endings, or nociceptors, such as those in skin, muscle, or joints. Most people have experienced this sensation; for example, normally nonpainful touch may become quite painful on sunburned skin. This is termed *allodynia* (which can be either peripherally driven, centrally driven, or both). Such peripheral sensitization occurs because of the release of inflammatory chemicals and transduction proteins at the site of tissue damage, which in turn alters pain sensitivity through increased responsiveness of the peripheral nociceptors and fibers.

The sustained or repetitive activation of pain fibers associated with chronic pain can be approximated under controlled conditions in the laboratory. It is hypothesized that repetitive activation of pain fibers in states of chronic pain may alter the function and activity of central pain pathways and central processing of sensory information linked to nociception. This process is termed *central sensitization*. It is

produced and maintained by neuromodulators that augment transmitter and receptor activity or efficacy in the spinal cord and brain, producing an enhanced excitability of neurons in the central nervous system (CNS). For example, prolonged afferent nociceptive input induces an increase in N-methyl-D-aspartate activity in the dorsal horn of the spinal cord, induces A-β fibers to establish functional connections with pain pathways in the spinal cord, and induces glial cells to release proinflammatory cytokines throughout the CNS.[12]

Collectively, the multidimensional process of central sensitization produces hypersensitivity, tenderness, and pain in an enlarged area beyond the site of tissue damage. There is growing evidence that central sensitization plays a role in chronic pain syndromes, including fibromyalgia, widespread musculoskeletal pains, irritable bowel syndrome, and myofascial and TMD pains (see chapter 21).

## *Ascending and descending influences on nociception and pain*

The integration of nociception in the perception of and reaction to pain is dependent on the activation of parallel ascending pathways from spinal cord to the upper brain. The two main pathways are *(1)* the spinothalamic tracts for sensory processing of nociception, which include various thalamic relays and project to the sensory cortex, and *(2)* the spinolimbic tracts for emotional assessment of the emotional dimension of the pain experience, which project to the accumbens, amygdala, hypothalamus, insular cortex, cingulate cortex, and frontal cortex. In acute or experimental conditions, the activation of such pathways (Fig 18-1, *right side*) is concomitant with the activation of descending influences to alleviate nociception and reduce the emotional burden of pain; in chronic pain states, such mechanisms may be altered.

Under normal conditions, the overexcitement of spinal modulators is countered by local mechanisms and/or descending pain-inhibitory systems (see Fig 18-1, *left side*). In response to the perception of pain, multiple brain regions transmit descending signals to various regions of the spinal cord. However, dysregulation in this descending pain-modulatory circuitry is hypothesized to play an etiologic role in the chronic pain conditions of many patients. In part, this process constitutes the pain gate, which has been theorized (in the gate control theory[13]) to modulate transmission of pain-related signals at spinal and brainstem levels.

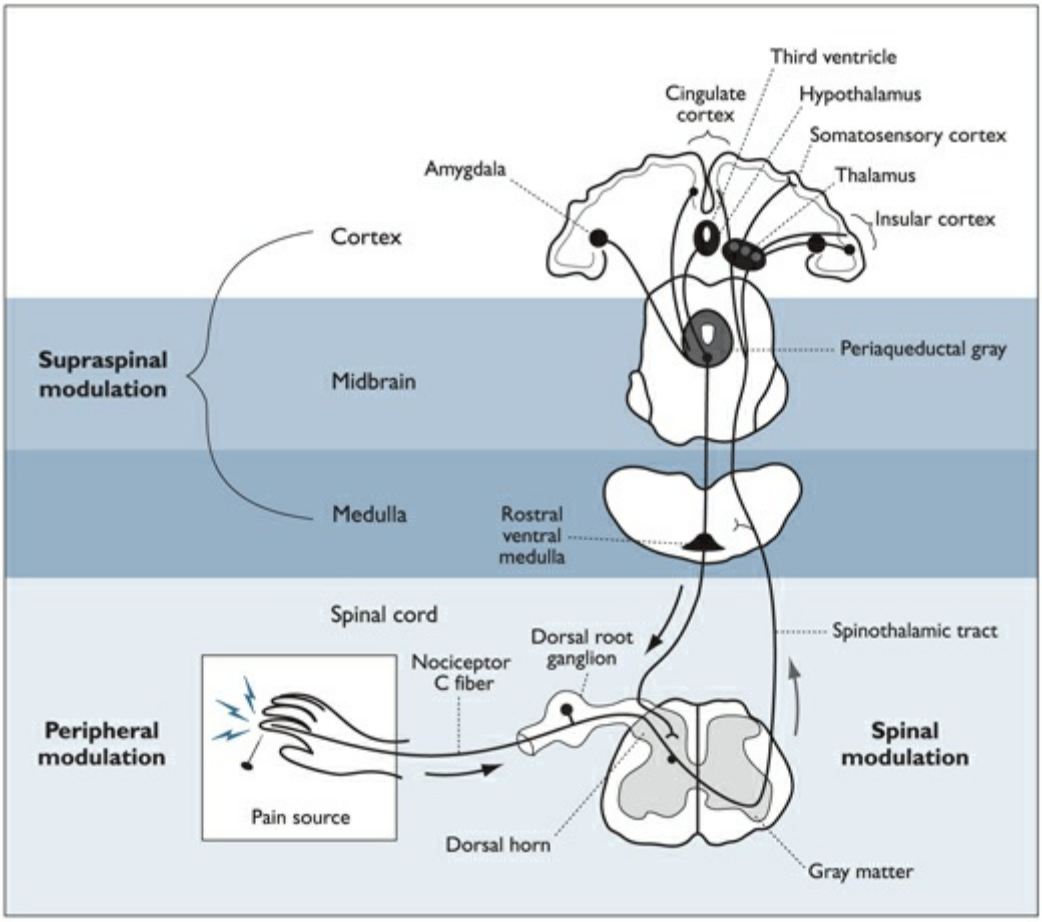


**Fig 18-1** Areas of pain processing. (Adapted from DeLeo[11] with permission.)

A discussion of the neuroanatomy and physiology of descending pain-modulatory systems is beyond the scope of this chapter (for more information, consult Sessle et al[10]), but it is clear that multiple cortical and subcortical structures play a role, and midbrain regions such as the periaqueductal gray and the rostral ventral medulla are heavily involved. Serotonergic and opioidergic neurotransmission are the mainstays of these descending systems (see Fig 18-1), although numerous neurotransmitters and neuromodulators are also implicated.

In addition to the processes of sensitization, chronic pain is also characterized by reductions in the effectiveness of pain-inhibitory circuitry in the brain and spinal cord. Indeed, many chronic pain syndromes are characterized by both above-average sensitivity to pain and below-average endogenous pain-inhibitory capacity.[14] Collectively, chronic pain conditions have been associated with alterations in central processing of noxious stimuli, and chronic pain is now classified as a CNS disease (eg, nerve signals transmitted from injured tissue lead to pathologic long-

term changes in the CNS).[14] The substantial comorbidity among many idiopathic pain-related conditions, such as TMDs, fibromyalgia and musculoskeletal chronic widespread pain, and irritable bowel syndrome, and their overlapping symptoms, including affective distress, cognitive deficits, and fatigue, suggest a common set of potentially CNS-related mechanisms.

## Assessment of Pain

In patients, direct assessment of activity in spinal cord or brain neurons is only possible by cell recording in patients undergoing elective surgery. Brain imaging offers an indirect method to assess brain cellular and metabolic activities in relation to pain perception. The integrity of nociceptive pathways and the pain-processing mechanism can be estimated with peripheral pain–related stimulations (eg, mechanical, thermal, or chemical) and *(1)* cortical recording of evoked potentials or brain imaging (millisecond to second processing); *(2)* sensory motor behavioral responses (eg, withdrawal reflexes in the second range); or *(3)* pain reports from patients (eg, numerical or visual analog scale and verbal state descriptors in the second to minute range).

### *Quantitative sensory testing*

QST, in which standardized noxious stimuli (eg, thermal: cold or heat; mechanical: pressure or vibration; chemical: infusion of noxious substances) are administered under highly controlled conditions, can reveal the presence of hypersensitivity to pain as well as dysfunction in descending pain-inhibitory systems. A complex method has been developed to assess the functional integrity of endogenous modulation of pain through CNS sensitization; this technique is termed the *temporal summation of pain*, or *windup*. Such tests are accomplished by administering repeated noxious stimuli in a short time period and measuring the resulting increase in pain response. Dramatically increased ratings with repetitive stimulation are thought to reflect CNS hyperexcitability.[14]

### *Diffuse noxious inhibitory controls*

Another assessment of endogenous pain-inhibitory systems is possible through the use of the paradigm of diffuse noxious inhibitory controls (DNIC).[14] In brief, DNIC refers to the phenomenon in which one pain inhibits the perception of a second pain applied to a distant body site. It can be captured by assessing responses to a phasic (ie, repetitive) noxious stimulus before and then during heterotopic (elsewhere on body; arm versus leg) application of a tonic (sustained) noxious stimulus. Generally, responses to the phasic noxious stimulus are reduced during concurrent administration of the tonic stimulus. Such experimental methods are used to evaluate normal pain-inhibitory functioning as a proxy for how clinical pain and nociception are processed and modulated. The magnitude of the reduction serves as a measure of the efficacy of central endogenous analgesic systems.

Although such experimental pain studies are utilized to model clinical pain processing, they do not necessarily capture the complexity of clinical pain pathophysiology. Abundant research, however, has suggested the relevance of experimental pain induction procedures in predicting clinical pain outcomes.[15] For example, imaging studies suggest that acute, standardized, noxious stimuli produced in the laboratory parallel the magnitude of CNS activity in brain regions associated with pain processing.[16,17] Thus, QST techniques, such as temporal summation and DNIC, provide a window to better understand how the human nervous system processes pain-related information.

### *Evidence for central hypersensitivity in chronic pain patients*

There is consistent and abundant evidence that many chronic pain syndromes, including somatic, visceral, neuropathic, and inflammatory chronic pain (see chapter 21), are characterized by generalized hyperalgesia (eg, an increased reactivity to pain) and diminished effectiveness of descending pain inhibition, which may result in hyperalgesia.[18] It is not at all surprising that pain conditions such as fibromyalgia, headache, TMDs, rheumatoid arthritis, complex regional pain syndrome, irritable bowel syndrome, and many others enhance pain sensitivity at the sites of pain complaints. However, this observation alone cannot distinguish between peripheral contributions to altered pain responsiveness and central hypersensitivity to pain. Currently, there is ample evidence that all of those conditions, and many others, are characterized by enhanced sensitivity to pain at anatomic sites that are distant from the site of pain and are not considered to be involved in the local pathophysiology of the condition. For example, patients with TMDs show reduced pressure pain thresholds at the finger, hand, and leg.[19,20]

Evidence of such globally enhanced pain sensitivity has been shown to predict the onset of diffuse, or widespread, chronic pain complaints,[21] which are relatively common both in the general population and especially in individuals with regional pain syndromes such as TMDs and irritable bowel syndrome. Diffuse chronic pain is associated with amplified negative pain consequences, such as increased distress, reduced function, and even early mortality.[7,22,23] Although the literature in this area is not definitive, features of maladaptive central pain processing, such as impaired DNIC, are hypothesized to be especially involved in the etiology of chronic diffuse pain, a concept elaborated further later in this discussion.

In addition, many chronic pain conditions are also associated with enhanced temporal summation of pain or impaired DNIC. For example, in examining responses to temporal summation, Staud and colleagues[24] found that patients with fibromyalgia had more rapidly increasing ratings than did controls, suggesting greater CNS sensitizability. Fibromyalgia patients also exhibited deficits in endogenous analgesic processes, examined through DNIC, when compared with controls.[25]

The list of conditions in which altered pain modulation has been demonstrated in both idiopathic and neuropathic pain disorders includes fibromyalgia, headache or migraine, irritable bowel syndrome, hip osteoarthritis, trapezius myalgia, vestibulodynia, and peripheral nerve injury (see Campbell et al[26] for review). It is also interesting that, in healthy subjects, DNIC activity or efficacy is inversely correlated with clinical pain.[27] These findings suggest that chronic pain conditions, broadly considered, are often characterized by central hypersensitivity and aberrant descending pain modulation and that such factors are likely to be most etiologically involved in syndromes characterized by persistent widespread pain, such as fibromyalgia. In general, the evidence for poorly functioning DNIC systems and amplified temporal summation of pain is strongest in studies of fibromyalgia (chronic widespread pain), which may be the quintessential disorder of deregulated CNS pain processing.[28,29]

## Who Develops Chronic Pain?

Multiple biopsychosocial factors (such as coping strategies or culture) are clearly associated with chronic pain, and recent evidence highlights the powerful role of individual variability in CNS processing, along with genetic and psychologic

factors, in determining the development and course of persistent pain. Edwards[14] hypothesized that an individual's pain sensitivity and pain-inhibitory capacity, reflecting natural CNS pain-processing variability, may influence the risk for development of chronic pain conditions. This theory postulates that highly pain-sensitive individuals with reduced endogenous pain-inhibitory functioning are at elevated risk for development and greater persistence of chronic pain states.

Several lines of research have substantiated this hypothesis, primarily through the use of laboratory pain induction procedures. Numerous studies, for example, have provided evidence that individuals with chronic pain conditions, such as TMDs, show greater sensitivity to noxious stimulation than do controls subjects.[30] Such findings, though, cannot distinguish between circumstances in which individual differences in pain processing increase the likelihood of developing chronic pain and circumstances in which the development of chronic pain is subsequently associated with altered pain processing. Of great interest, therefore, are prospective studies that follow individuals over time to evaluate individual differences in the development of pain.

A number of recent surgical studies have examined the relationship between basal pain sensitivity and acute postoperative pain. Among individuals undergoing limb amputation, laparoscopic cholecystectomy, anterior cruciate ligament repair, gynecologic surgery, lower abdominal surgery, prostate biopsy, and disk surgery, presurgical experimental pain responses were significantly correlated with the magnitude of postoperative pain up to a week after surgery (see Macrae[31] for review). In each case, individual differences reflecting greater sensitivity to pain (eg, lower pain threshold, lower pain tolerance, and higher ratings of pain in response to standardized noxious stimuli) were associated with the report of more intense acute postoperative pain. Several reports have indicated that preoperative QST responses predict acute pain after cesarean section.[32,33]

Only a few long-term studies evaluating the development or persistence of chronic pain have been performed. Of particular interest, Slade and colleagues[34] found that individuals with a greater sensitivity to noxious stimuli were at a greater than twofold increased risk, compared with those who were less sensitive, of developing TMDs. In another innovative, prospective study, Yarnitsky and colleagues[35] evaluated whether individual differences in endogenous pain-inhibitory capacity was predictive of risk of developing chronic postthoracotomy pain. Presurgically, the authors applied a noxious heat stimulus to the patient's arm and evaluated the degree to which this pain was reduced by immersion of the opposite hand in a hot

water bath, thereby analyzing DNIC (ie, the degree to which one pain stimulus activates endogenous analgesic systems and inhibits the pain from another stimulus, as described earlier). The authors found that both presurgical assessment of DNIC and the degree of acute postoperative pain independently predicted who was to develop chronic postthoracotomy pain. Patients with less effective DNIC systems were about twice as likely to experience long-term postthoracotomy pain as were patients who experienced above-average severity of acute postoperative pain. Figure 18-2 presents a probability plot representing the association between DNIC and development of chronic pain.

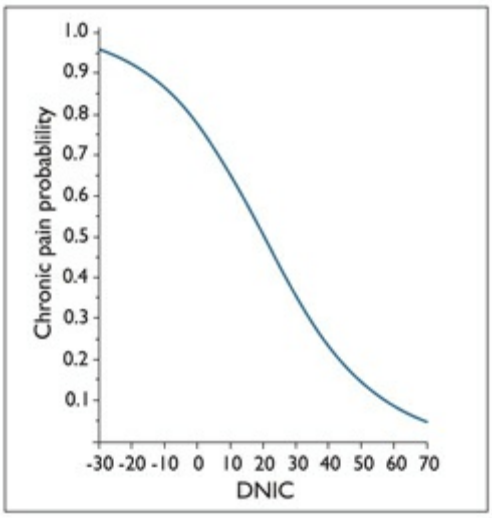


**Fig 18-2** Probability plot showing the association between DNIC and the probability of developing chronic pain. (Reprinted from Yarnitsky et al[35] with permission.)

## Pain Genes

Over the past several decades, a rapidly growing animal literature has documented the substantial contribution of genotype to pain sensitivity and pain susceptibility.[36] In human studies, the use of QST has been instrumental in facilitating the development of a parallel literature on the genetic aspects of pain perception; a recent report using three QST modalities estimated the heritability of pain sensitivity at between 22% and 46% across three types of noxious stimulation.[37] Human studies have now confirmed that certain single-nucleotide polymorphisms are associated with differing profiles of pain responses; many of these studies have utilized QST to demonstrate that genotype impacts both pain sensitivity and clinical pain responses,

including the development of a persistent pain condition.[38]

As one example of a recently identified "pain gene," several single-nucleotide polymorphisms have been studied on the gene coding for GTP cyclohydrolase (*GCH1*), the rate-limiting enzyme for tetrahydrobiopterin synthesis. Tetrahydrobiopterin is an essential cofactor for catecholamine, serotonin, and nitric oxide production and functions as a key modulator of peripheral neuropathic and inflammatory pain. Recent studies confirm that a particular *GCH1* genotype is associated with reduced postsurgical pain and with reduced sensitivity to mechanical, thermal, and chemical noxious stimuli.[39,40] Collectively, these studies all suggest a potentially strong influence of genetic factors in nociceptive processing and highlight the vital role of employing QST in the translation of animal genetic findings to clinical studies of human patients.

## Future Research

Collectively, the studies reviewed in this chapter highlight the potential utility of examining individual's QST responses (DNIC in particular) and suggest mechanisms whereby baseline pain sensitivity and pain processing impacts clinical pain or the development of postoperative pain conditions. Prospective longitudinal studies that follow individuals over time and evaluate individual differences in the development of pain are of great interest and clinical importance. Such studies would help establish implications and causal mechanisms of altered pain perception and development of chronic pain.

A growing body of evidence also suggests great value in genotyping for genetic variability and markers associated with pain. For example, certain genetic polymorphisms may be protective and minimize the probability of developing a chronic pain condition by either promoting or inhibiting the function of enzymes involved in the maintenance and functioning of central and peripheral pain-processing systems.[2,41] Of note, both DNIC and genetic markers measure individual differences (in inhibitory capacity and allelic frequency, respectively). For example, ethnic differences have been found in DNIC in healthy individuals[26] and in allelic frequency[40]; therefore, future studies should control for these factors.

Through use of QST and genotyping, patients that have an increased risk profile for further deterioration, exacerbation, or the development of a chronic intractable pain condition may be identified. This issue may be the most relevant and clinically

useful to assess with regard to postoperative care. Individuals found to be vulnerable based on risk profile and phenotypic or genotypic characteristics may be appropriate for additional care beyond that of standard practice. Studies examining these individual differences and successful implementation of targeted strategies to regulate the issues that put these individuals at increased risk will be the wave of the future.

## Conclusion

The factors influencing and contributing to the development of chronic pain are multiple and complex. Alterations in peripheral and CNS processing of pain-related information play a key role. Identification of premorbid biologic (eg, genetic predisposition) or behavioral (eg, dysfunctional coping strategies) risk factors for persistent pain is of extreme importance, given that such discoveries may lead to prevention efforts or targeted early interventions to reduce the incidence of chronic pain.

Highly pain-sensitive individuals seem to be at high risk of morbidity; tailored interventions may reduce their relatively elevated likelihood for developing chronic pain. Given the ease of assessing these factors, such as premorbid pain sensitivity, future clinical practice may routinely coordinate such assessments, with potentially sizable benefits to the patient.

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CHAPTER 19

# MECHANISMS OF SLEEP LOSS–PAIN INTERACTIONS

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The experience of clinical pain can cause sleep disturbances.[1] Reciprocally, strong experimental evidence has accumulated over the last 30 years supporting the notion that sleep loss itself can neuroplastically alter function of the nociceptive system (eg, in a reversible manner). Sleep loss has been shown to cause *hyperalgesia*, that is, an increased sensitivity to painful stimulation, and the development of spontaneous pain complaints, such as muscle pain, headache, stomach pain, or generalized body pain, arising in the absence of any peripheral input.[2] This association has been demonstrated in numerous studies using various experimental sleep models (eg, total and partial sleep deprivation and sleep disruption) and pain measurement approaches (eg, pain reports and quantitative sensory testing).

Clinically, the bidirectional relationship between sleep loss and pain may serve to perpetuate and amplify sleep loss and chronic pain via a vicious cycle[3]: A bad night's sleep enhances pain. Pain, in turn, disrupts sleep. Poor sleep quantity and quality further worsen pain, and so on. This complex inverse relationship between sleep and pain may be influenced by various biologic and psychologic factors.

However, despite the well-established bidirectional linkages between sleep loss and pain, there is surprisingly very little direct scientific knowledge of the basic neurochemical mechanisms that account for the reciprocal association. This knowledge is essential to formulate interventions that would unlock the sleep-pain

interaction to safely and effectively improve patients' emotional and physical well-being. The present chapter highlights likely neurochemical and immunologic factors that contribute to the effects of sleep disturbance on pain sensitivity and vice versa. Chapter 20 focuses on the clinical implications of this neurobiologic substrate.

## Potential Mechanisms of Interaction

Pain can be generated by multiple neurobiologic mechanisms,[4] involving neuronal as well as non-neuronal components of the opioid system, monoaminergic system, hypothalamus-pituitary-adrenal (HPA) system, immune system, and melatonin system, among others. Some of the components involved in the pathophysiology of pain are also affected by sleep loss and therefore may establish potential candidates in mediating the sleep loss–induced development of spontaneous pain and hyperalgesia. Potential mechanisms that have been hypothesized to mediate the effects of sleep loss on pain (Fig 19-1) are reviewed in the following sections.

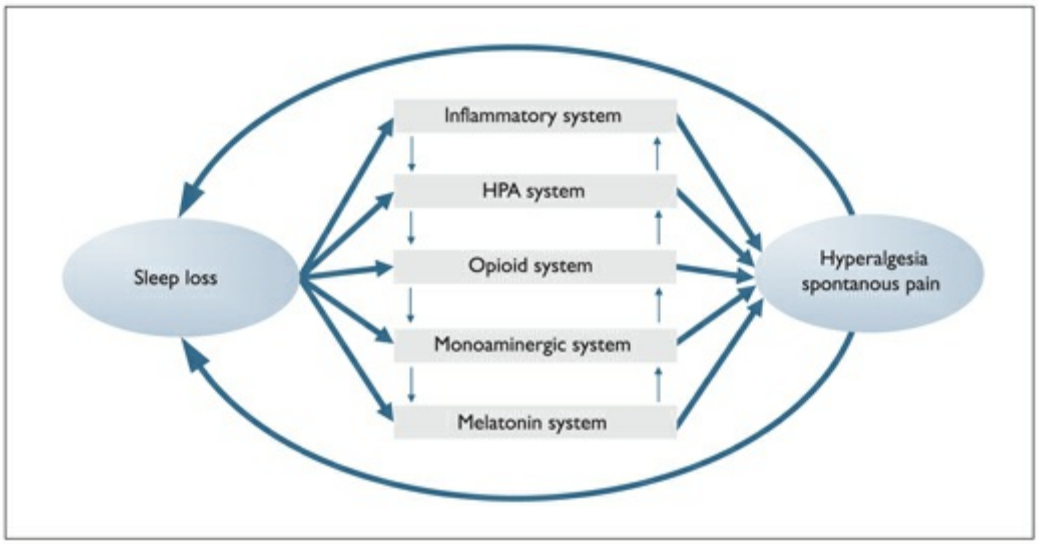


**Fig 19-1** Potential mechanisms contributing to sleep loss–induced pain enhancement.

### *Opioid system*

The opioid system is well known to modulate nociceptive processing, and painful events are associated with the release of endogenous opioid peptides in various

brain areas in animals and humans.[5] Hicks and colleagues[6] hypothesized that deprivation of rapid eye movement (REM) sleep may increase pain sensitivity in rats through alterations in the opioid system. In rats, Ukponmwan and colleagues[7] showed that the experimentally activated analgesic properties of endogenous and exogenous opioids, through stress, intracerebroventricular administration of an enkephalinase inhibitor, or the μ-opioid agonist morphine, are reversed by REM sleep deprivation. This suggests that the hyperalgesic effects of REM sleep deprivation are mediated through an opioid antinociception mechanism.[7]

In humans, the role of the opioid system in sleep-wake regulation and in mediating the hyperalgesic effects of sleep loss has not been directly addressed, but Smith and colleagues[8] have shown that sleep loss via multiple forced awakenings impairs "natural" descending pain inhibition, which is in part mediated by the endogenous opioid and monoaminergic systems. To directly evaluate the role of opioid mechanisms in sleep loss–induced hyperalgesia in humans, interventional studies using opioid agonists and antagonists are needed.

## *Monoaminergic system*

The monoaminergic (serotonin and norepinephrine) and opioidergic systems are closely related and can interact to modulate several behavioral functions, including nociception. An intact serotonergic system, along with noradrenergic neurons, appears to be necessary for μ-opioid antinociception functioning involved in endogenous pain inhibition.[9] The implication of serotonin receptors in the modulation of pain is further suggested by effectiveness of serotonin reuptake inhibitor analgesics for management of various clinical conditions, such as fibromyalgia.

The serotonergic system is also implicated in sleep-wake regulation and has long been thought to play a key role based on animal studies. Jouvet,[10] for example, induced severe insomnia by blocking serotonin synthesis. On the other hand, sleep deprivation in animals leads to impairment of the serotonergic system, including a decrease in extracellular serotonin levels in various brain areas[11] and desensitization of the serotonin 1A receptor. Given that the serotonergic system is involved in pain and sleep-wake regulation (eg, serotonin type 1 and 2 receptors), an alteration in this system may present a potential mechanistic factor mediating the hyperalgesic effects of sleep loss that deserves further investigation.

## *Hypothalamus-pituitary-adrenal system*

The HPA system mediates the response to physical and psychologic stress. The release of corticotropin-releasing hormone from the hypothalamus stimulates the secretion of adrenocorticotropin hormone from the pituitary, which stimulates the secretion of glucocorticoids from the adrenal cortex (cortisol in humans and corticosterone in rats). Cortisol, the principal stress hormone, affects various immunologic functions and has mostly anti-inflammatory effects.

Activation of the HPA system during inflammatory responses and subsequent inhibition or upregulation of proinflammatory and anti-inflammatory cytokine production appear to be key mechanisms through which stress affects disease susceptibility.[12] In patients with chronic pain conditions, such as rheumatoid arthritis, fibromyalgia, or headaches, adrenocortical hyporesponsiveness has been reported. This may cause weak immunoregulation and increase the risk of inflammation.

HPA system activity demonstrates a robust circadian rhythm, with the lowest concentrations of cortisol observed early in the night and peak values at the end of the sleep phase. Mild increases in cortisol secretion have been found in several human sleep deprivation or fragmentation experiments. When sleep is chronically disrupted, the effects on the HPA axis may accumulate and lead to adverse health consequences.[13]

Cortisol and synthetic glucocorticoids (eg, prednisolone and dexamethasone) may modulate the nociceptive system indirectly, through changes in the secretion of proinflammatory and proalgesic cytokines and prostaglandin $E_2$ biosynthesis,[14] as well as release of opioids[15] or changes in serotonergic function.[16]

## *Immune system*

Activation of the inflammatory system is a key feature in various types of painful conditions and experimental sleep loss. Inflammatory markers are elevated during sleep deprivation and various painful conditions. The role of the prostaglandin (PG) system and the proinflammatory cytokine system, which are involved in pain and sleep-wake modulation, will be reviewed.

**Inflammatory markers and pain**

PGs mediate some of the cardinal features of inflammation.[17] They belong to a class of lipid mediators called *eicosanoids* that are derived from unsaturated fatty acids, such as arachidonic acid, the major lipid component of the cell membrane. Free arachidonic acids are converted to PGs through activation of cyclooxygenase 1 (COX-1) and cyclooxygenase 2 (COX-2) catalysts by cytokines, growth factors, and other inflammatory processes at the site of the injury and in the central nervous system. There are several endogenously produced PGs in the human body ($PGD_2$, $PGE_2$, $PGF_2\alpha$, $PGI_2$, and thromboxane $A_2$).

$PGE_2$ appears to have a major role in mediating pain and pain hypersensitivity, but other PGs have been shown to have proalgesic properties. PGs generate pain hypersensitivity through sensitization of primary sensory neurons and reduce the nociceptor response threshold to a number of stimuli within the nociceptive peripheral terminals.[18] PGs have been found to be increased in various experimental models of inflammation and in clinical disorders, including increased PGs in the synovial fluid of patients with temporomandibular disorders, rheumatoid arthritis, and elevated levels in gingival tissue of patients suffering from periodontal disease.[19–21] Further, evidence of PG involvement in the development of pain in inflammatory diseases is the demonstration of the marked analgesic therapeutic effect of nonsteroidal anti-inflammatory drugs, which primarily act by preventing the synthesis of PGs through inhibition of COX-1 and/or COX-2 enzymes.

Besides PGs as the classic pain-sensitizing substances, cytokines, such as interleukin 1(IL-1), interleukin 6 (IL-6), and tumor necrosis factor α (TNF-α), have been identified as potent pain-inducing and pain-facilitating factors capable of sensitizing the primary sensory neurons, leading to hyperalgesia in an animal model.[22] IL-6, for example, is a small protein that is produced mainly by monocytes and macrophages but also by cells such as adipocytes, neurons, and glial cells. IL-6 has pleiotropic effects. It plays a critical role in the acute-phase inflammatory response. It is one of the major cytokines that can activate the HPA system, and it increases the basal lipolysis. It is upregulated in peripheral nerves of animals under conditions of experimental pain, and peripheral injection of IL-6 induces pain.[23]

In humans, Edwards et al[24] recently showed that experimentally inducing pain in patients with rheumatoid arthritis elevates serum levels of IL-6. Infection- and injury-related sickness behavior of nonspecific symptoms, such as fever, increased sleep, depressed mood, and hyperalgesia, are also attributed to proinflammatory cytokines, in particular IL-1 β, TNF-α, and IL-6.[25]

### Inflammatory markers and sleep

Sleep and the immune system are reciprocally linked. Strong evidence in animal studies has shown that challenging the immune system with infectious agents such as bacterial, viral, or fungal organisms causes disruption in sleep-wake behavior, manifested in most studies as an increase in the amount and intensity of non-REM sleep.[26] In human studies, a low-grade activation of the host response with endotoxin, which causes an increase in plasma cytokine levels, has been shown to increase the amount and intensity of non-REM sleep.[27]

The common belief that normal sleep serves to enhance the immune system to overcome infections has been tested within experimental models of sleep deprivation prior to and/or following inoculation with microorganisms, endotoxin, or vaccines. However, animal and human studies reveal mixed results.[28] In the absence of an infectious challenge, various cytokines have been shown to be involved in the regulation and/or modulation of sleep. In humans, studies suggest a potential role of IL-6 in sleep-wake modulation. A robust finding in human studies is an increase in IL-6 levels when undergoing various amounts of sleep loss.[29–31] Sleep loss–induced alterations in other cytokine systems, such as the TNF system, are more variable across human studies.

In addition to the role of cytokine networks in sleep-wake modulation, the PG system has been shown to play a significant role in animal sleep.[32] While animal studies have shown an increase of central PG production in response to sleep deprivation, there is some preliminary evidence in humans suggesting an association between peripheral PG production and quantity or quality of sleep. For example, the urinary secretion of $PGE_2$ metabolite was recently measured in healthy participants undergoing a prolonged period of total sleep deprivation of up to 88 hours under controlled in-laboratory conditions. The concentration of $PGE_2$ metabolite in 24-hour urine collections was significantly greater in sleep-deprived individuals than in participants with a regular amount of 8 hours of sleep per night.[33]

## *Melatonin system*

Synthesis of melatonin, the main hormone secreted by the pineal gland, is stimulated by darkness and suppressed by light. (The threshold is around 200 to 400 lux, which is equivalent to normal fluorescent light.) In humans, maximal plasma levels occur during the night, between 3 and 4 AM. Melatonin has many actions and properties,

including anti-inflammatory, analgesic, and sleep-promoting effects. For example, melatonin is able to inhibit $PGE_2$ synthesis and reduce upregulation of proinflammatory cytokines, both markers known for their pain-sensitizing actions. Mechanisms of melatonin's analgesic properties are not entirely clear but may also involve β-endorphin, which is increased in cell cultures after melatonin administration, or potentiating γ-aminobutyric acid transmission, which is involved in endogenous pain-inhibitory actions. Patients suffering from primary insomnia have been found to have lower serum melatonin concentrations than healthy controls,[34] and potentiating the melatonin signal by exogenous melatonin administration has been shown to have a modest sleep-promoting effect.[35]

Changes in the melatonin signal appear to be of particular importance in the pathophysiology of headache disorders.[36] Headache and sleep complaints often coexist, and based on patients' reports, insufficient sleep may trigger or worsen headache that is alleviated by adequate sleep. Thus, the melatonin system may present another potential mechanistic candidate through which insufficient sleep may facilitate pain, and this may be of particular importance in those vulnerable to headaches.

## Conclusion

Sleep loss changes the activation of various systems known to influence nociceptive processing, including the opioid, monoaminergic, HPA, immune, and melatonin systems. Complex and reciprocal interactions among these systems may establish potential mechanistic pathways by which insufficient sleep facilitates hyperalgesia. An understanding of the exact mechanisms will be important for the development of interventions that mitigate the sleep-pain interaction and improve the physical well-being in those undergoing periods of insufficient sleep.

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CHAPTER 20

# CLINICAL IMPLICATIONS OF SLEEP LOSS–PAIN INTERACTIONS

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Poor sleep quality and sleep loss are common for many groups in society whose individual sleep-wake rhythm is fragmented or forced to change frequently, such as health care workers with on-call duty, military personnel, parents attending to infants and toddlers, nightshift workers, time zone travelers, patients in the intensive care unit and hospital environment, older adults, and those suffering from painful medical conditions and sleep disorders (such as insomnia, apnea, or periodic leg movements). The prevalence of adults reporting insufficient sleep is estimated to be approximately 40% in the general population; 40% obtain 7 hours or less total sleep time, and 15% report sleeping less than 6 hours per night.[1] A recent longitudinal study of 971 participants showed that obtaining less than 6 hours of sleep per night predicted next-day pain report in the general population.[2]

## Potential Influences on Sleep Loss and Pain

### *Inflammatory markers*

**Influence on sleep**

As discussed in chapter 19, poor quantity or quality of sleep may facilitate nociceptive processing through various mechanisms. In humans, one of the most robust findings in experimental sleep deprivation studies is an increase of various inflammatory markers, in particular proinflammatory cytokines, which are known for their pain-sensitizing effects.

In clinical settings, patients suffering from *primary insomnia*, that is, difficulties falling asleep and staying asleep, waking up often during the night, and waking up too early, show increased interleukin 6 (IL-6) levels[3] and a diurnal shift of IL-6 levels from nighttime peak to evening peak. These alterations in the secretory pattern have been suggested to explain daytime fatigue and poor concentration in insomnia patients.[4] Indeed, increases in plasma IL-6 levels were associated with tiredness and fatigue in healthy participants undergoing prolonged sleep restriction.[5] IL-6 has also been found to increase in disorders in which sleep disturbances are common, such as sleep apnea[6] and depression.[7] Although the IL-6 system has not been directly antagonized in human subjects, administration of a tumor necrosis factor α (TNF-α) receptor blocker, which lowers IL-6 levels, led to a decrease in sleepiness in apnea patients.[8]

Prostaglandins (PGs) have rarely been investigated in relationship to sleep quantity and quality in experimental and clinical human studies. This may be due to the fact that circulating PGs are difficult to quantify directly. Prostaglandin $D_2$ ($PGD_2$) and prostaglandin $E_2$ ($PGE_2$) are unstable components that are rapidly metabolized. However, measurement of their metabolites in plasma or urine permits a reliable estimation of activation of the PG pathway. In subjects with a heterogenous group of primary sleep disorders (primary insomnia and breathing-related disorders), $PGE_2$ released from mitogen-stimulated whole blood was shown to be significantly greater than that released by healthy controls.[9]

Alteration in the PGD system has been reported in several disorders characterized by sleep disturbance or hypersomnia, such as African sleeping sickness, sleep apnea, major depression, and narcolepsy. In narcolepsy, for example, blood levels of lipocalin-type PGD synthase, which is responsible for the biosynthesis of $PGD_2$ in the brain, is increased and associated with the degree of sleepiness.[10]

### Influence on pain

It is well recognized that both proinflammatory cytokines and PGs, and in particular IL-6 and $PGE_2$ mediators, have pronociceptive properties. Anti-inflammatory

medications given for 1 day or more prior to surgery may preemptively minimize postoperative pain by blocking the establishment of nociceptor sensitization. A recent study demonstrated that presurgical administration of cyclooxygenase (COX) inhibitors reduced both peripheral and central $PGE_2$ and IL-6 levels and decreased postoperative pain.[11]

Although inflammatory markers appear to be bona fide mechanistic mediators of the pain-enhancing effect of insufficient sleep, these data are largely correlational; causation has yet to be established. However, under controlled, in-laboratory conditions, increased IL-6 levels observed in response to sleep restriction to 4 hours per night over a 10-day period were associated with the degree of spontaneous pain experienced by the participants, including headaches, muscle, and joint pain.[5] In a more recent study of total sleep deprivation, in which participants were kept awake for 88 hours under controlled in-laboratory conditions, an increase in urinary $PGE_2$ metabolite levels was associated with the frequency and intensity of spontaneous pain experienced by participants.[12]

These findings lend support to the hypothesis that inflammatory markers, such as IL-6 and $PGE_2$, may play a role in mediating the effects of sleep loss on the development of pain. However, to establish a causal relationship, interventional studies are needed.

## *Pharmaceutical influences*

A sleep- or sleepiness-promoting role of the PG system is also supported by studies showing that inhibition of PG synthesis through administration of a cyclooxygenase 2 (COX-2) inhibitor reduces spontaneous sleep in rats.[13] In humans, some studies have suggested that acute administration of dual-COX inhibitors, such as ibuprofen or aspirin, disturbs sleep physiology in healthy adults. Aspirin given in a dose of 1,800 mg per day over 4 consecutive days appears to reduce deep slow-wave sleep and increase stage 2 sleep.[14] An increase in nocturnal awakenings has been reported after administration of aspirin (1,950 mg per day) or ibuprofen (1,200 mg per day) over a single day.[15]

The long-term effect of nonsteroidal anti-inflammatory drugs (NSAIDs) on sleep in clinical pain populations is largely unknown. At least one study, however, found that NSAIDs had minimal sleep-disrupting effects in patients with chronic widespread pain.[16] Given that NSAIDs are one of the most frequently used over-the-

counter medications in the United States, clinicians should inform their patients that acute administration may interfere with sleep physiology and thereby may counteract to some extent their pain-relieving properties.

### *Emotional influences*

Sleep loss not only enhances pain, it also modifies emotional well-being, which is an integral part of the pain experience. Being optimistic has been shown to be associated with lower levels of bodily pain[17] as well as with higher pain tolerance in patients suffering from painful medical conditions.[18] When healthy young participants are restricted to 4 hours of sleep per night across 10 days, optimism and sociability, that is, a positive outlook and psychosocial functioning, markedly decreased compared to those exhibited by control subjects permitted 8 hours of sleep per night.[19] Thus, sleep loss–induced deterioration of emotional well-being may present an additional means by which insufficient sleep contributes to the experience of pain.

## Potential Interventions

### *Pharmacotherapy*

To examine the causal mechanisms by which sleep loss augments pain, interventional studies using target-and mechanism-selective drugs are needed.[20] For example, the involvement of inflammatory markers in sleep loss–induced pain can be assessed through inhibition of inflammatory signals. Targeting inflammatory and other potential mechanisms (see chapter 19) will improve understanding of their role in mediating the sleep loss–pain connection.

Based on findings in humans, interventions may target the COX enzyme system or the proinflammatory cytokine mediator system. $PGE_2$ is produced by both COX isoforms, COX-1 and COX-2. Thus, commonly prescribed dual-COX inhibitors, such as aspirin, ibuprofen, and acetaminophen, could be a worthy model in addressing the involvement of the COX system in sleep loss–induced pain enhancement in humans. However, some data in pain-free subjects suggest that these agents induce mild sleep disruption, indicating that the decision to utilize these

agents for this purpose in patients with chronic pain is complex and requires further study. As suggested by the study on these agents in patients with widespread chronic pain,[16] however, their mild detrimental effects on sleep in pain-free individuals may be far outweighed by their beneficial effects in reducing the interference of pain in sleep processes.

With respect to proinflammatory cytokine systems, a TNF-α receptor blocker has been successfully used for the treatment of rheumatoid arthritis and has been shown to be associated with a reduction of the proalgesic cytokine IL-6,[8] which most consistently increases in response to sleep loss. Unfortunately, the side effects of headache, dizziness, and itching limit the use of current specific cytokine blockers because they may interfere with assessment of pain outcome measures in response to sleep loss.

Alternative strategies to test whether inflammatory markers mediate the sleep loss–pain connection may target *n*-3 fatty acids (also known as *omega-3 fatty acids*), intermediates in the synthesis of eicosanoids such as PGs; these fatty acids are found in vegetable seeds, marine products, and fish oil. Although there is some indication in humans that the intake of moderate to high levels of *n*-3 fatty acids over a 3-month period decreases production of proinflammatory cytokines,[21,22] further rigorous investigation is needed to support the efficacy of these dietary interventions.

Other avenues sometimes used to manage the sleep loss–pain interaction include serotonin- and norepinephrine-related medications such as nortriptyline, duloxetine, and trazodone; melatonin; γ-hydroxybutyric acid/sodium oxybate; anticonvul-sants such as pregabalin; hypnotics; and muscle relaxants (see chapters 19 and 23). However, not all of the aforementioned medications are cleared by regulatory agencies to manage sleep or pain.

## *Behavioral intervention*

Another avenue to address mechanistic factors underlying the sleep loss–pain connection is through sleep improvement strategies. Restoring sleep homeostasis, or adequate amounts and quality of sleep, is expected to decrease hyperalgesia and spontaneous pain. Monitoring changes in various physiologic and psychologic factors while subjects undergo sleep improvement strategies will help to elucidate these mechanisms. Cognitive behavioral therapy in cancer patients suffering from insomnia, for example, has been shown to alter several inflammatory markers.[23]

However, few studies have examined the therapeutic efficacy of sleep improvement interventions on pain sensitivity, and results of these have been mixed. These studies, however, were underpowered and primarily designed to determine whether these interventions improved short-term measures of sleep. More systematic investigations are needed over long-term follow-up periods (see chapter 24).

## Significance of Sleep Loss and Pain

The nociceptive and sleep-wake systems function in a complex and reciprocal interrelationship. The experience of pain can impair the quantity and quality of sleep, and in turn, sleep loss induces and/or intensifies spontaneous pain and hyperalgesia. The prevalence of sleep disturbances in various clinical pain conditions constitutes a major epidemiologic problem; approximately 22% to 60% of patients hospitalized for acute care report sleep disturbances, and approximately 20% of the general population experiences some sort of chronic pain and sleep disturbances.[24,25] The combination of pain and sleep disturbance has negative consequences for patients' overall well-being and daily functioning, and there is a compelling need to investigate the mediators that interlink pain and sleep.

Clarification of these mechanisms is crucial for development of therapeutic strategies to improve sleep and control pain. Therapeutic strategies such as novel anti-inflammatory agents have the potential to minimize the impact of sleep disruption and pain on the socioeconomic cost to society and physical function in at-risk populations: nightshift workers, frequent travelers, parents with infants and toddlers, sleep-deprived motor vehicle drivers, and students as well as the population of patients with pain in acute hospital settings and in chronic pain management clinics.[26]

Sleep patterns in the postoperative period can be severely disrupted with a suppression of both slow-wave and rapid eye movement (REM) sleep. The quantity and quality of sleep after surgery are influenced by a multitude of factors, including the extent of tissue injury, the effectiveness of the analgesics, and the activation of surgical stress response. Opiates have been shown to disrupt sleep in humans and suppress both slow-wave and REM sleep,[27] suggesting that opioids may contribute to postoperative sleep disturbances.[28] A sleep-disrupting effect also has been suggested for acute treatment with COX enzyme inhibitors such as NSAIDs, based on short-term studies in healthy volunteers. However, little is known about the effect of clinical use of COX enzyme inhibitors on sleep in subjects with pain.

## Conclusion

The biologically and psychologically interrelated triad of sleep disturbance, pain, and analgesia is complex and requires further research. A better understanding of this triad remains a challenge for the management of patients suffering from acute and chronic pain, sleep disorders, or both. The rational development of pharmacologic agents designed to relieve pain without concomitant unfavorable sleep effects and vice versa is particularly needed.

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CHAPTER 21

# ASSOCIATION OF OROFACIAL PAIN CONDITIONS AND SLEEP DISTURBANCE

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From both the theoretical and practical points of view, there may be several different ways that orofacial pain and sleep can interact. One possibility is that orofacial pain leads to sleep disturbances. A second possibility is that sleep disturbances contribute to orofacial pain. A third possibility is that orofacial pain and sleep disturbances interact in a mutually reinforcing manner. Finally, there may be no clear association between orofacial pain and sleep disturbances (Fig 21-1).

From a diagnostic and management perspective, dentists should attempt to establish the most applicable characterization of the relationship within each individual patient, to the extent which this is possible and practical. Furthermore, the nature of the sleep-pain relationship within a given patient may shift over time; therefore, reevaluation is often necessary to maintain the best ongoing care. This chapter briefly reviews the putative mechanisms of orofacial pain conditions, discusses the associations with sleep disturbances, and suggests a clinical approach to management.

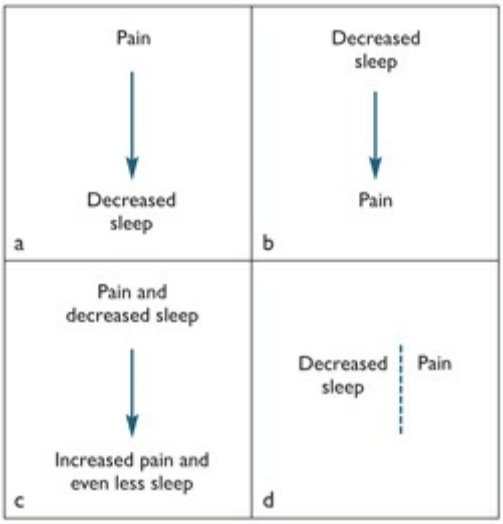


**Fig 21-1** Theoretical relationships between orofacial pain and sleep disturbances include the following possibilities: *(a)* Orofacial pain leads to sleep disturbances; *(b)* sleep disturbances contribute to orofacial pain; *(c)* orofacial pain and sleep disturbances interact in a mutually reinforcing manner; *(d)* there is no clear association between orofacial pain and sleep disturbances.

## Orofacial Pain Mechanisms

Considerable efforts have been devoted to establishing a mechanism-based classification of pain that builds on advances in the understanding of the neurobiologic mechanisms involved in different painful conditions (Fig 21-2). Currently, four non–mutually exclusive types of pain are recognized[1]: nociceptive, inflammatory, neuropathic, and functional. Clinicians also must understand that multiple pain mechanisms may coexist in chronic pain disorders, and the mechanisms at work may change over time. The key concept is that pain is a dynamic process that will require careful assessment and reevaluation.

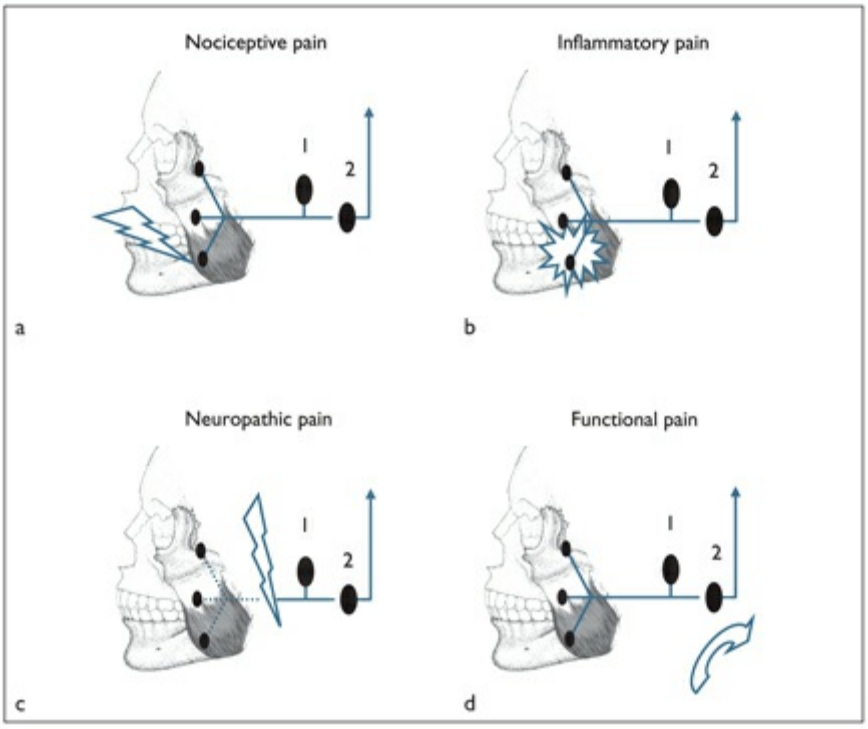


**Fig 21-2** Different types of orofacial pain. The first-order neuron (1) is located in the trigeminal ganglion, and the primary afferent nerve fiber innervates, for example, the masseter muscle. *(a)* Nociceptive pain is illustrated as the activation of peripheral endings through different ion channels and receptors *(small black ovals)*, which can be activated by high-intensity and potentially tissue damaging stimuli *(lightning flash)*. *(b)* In conditions with inflammatory pain *(burst)*, the peripheral tissue is damaged, and inflammatory cells (eg, macrophages, mast cells, and neutrophil granulocytes) are accumulated and can contribute to changes in the local environment. *(c)* Neuropathic pain *(lightning flash)* is characterized by lesions or diseases affecting the somatosensory nerve system; for example, cutting a peripheral nerve fiber will trigger an intense reaction for a short period or will persist for a long time. *(d)* In functional pain conditions, the peripheral tissues look normal, but there is an increased amplification *(arrow)* in the second-order neurons (2) at the level of the central nervous system (central sensitivity syndrome). These types of pain may overlap.

## *Nociceptive pain*

Nociceptive pain is the most commonly understood type of pain. Most physiology textbooks still primarily emphasize nociceptive pain, which is the end result of

activation of pain-sensing receptors (nociceptors).[1] Nociceptive pain is transient, and as the term implies, this type of pain is by definition acute; once the stimulus is removed or becomes less intense, the pain rapidly fades away.

The nociceptor is the basic receptor on primary afferent nerve fibers innervating all types of orofacial tissues. On the peripheral terminals, multiple transducing receptors and ion channels have been identified, including acid-sensing ion channels, a family of transient receptor potential channels, and P2X3 receptors. P2X3 receptors are unique because they detect and respond to specific high-intensity stimuli (thermal heat, cold, mechanical, and chemical stimuli) potentially associated with tissue damage.[2] Therefore, these nociceptors essentially serve as a useful warning system.

The nociceptors in the muscles, joints, tendons, ligaments, oral mucosa, tooth pulp, and periodontium can also be activated unintentionally during a variety of dental procedures (procedural types of pain). For example, pain following activation of orthodontic equipment can often exert forces sufficient to activate nociceptors in the periodontal ligament.

## *Inflammatory pain*

Tissue damage, such as that resulting from trauma or surgical procedures, is most often associated with pain that can be viewed as part of the classic cardinal signs of inflammation (calor, dolor, rubor, turgor, and functio laesa).[1] Oral mucositis following irradiation therapy of the orofacial region, myositis caused by infection, pulpitis, and synovitis in the temporomandibular joint are examples that share some of the cardinal inflammatory characteristics.

At the molecular level, significant progress has been made in terms of understanding the neurobiologic changes in the nociceptive system in these conditions. One important aspect is that the nociceptor can initiate spontaneous activity without a peripheral stimulus, leading to spontaneous pain. Another key characteristic is sensitization, when the threshold for activation of the nociceptor is reduced and the responses are longer and stronger.[2] Additionally, previously silent nociceptors can be awakened and further contribute to pain. There is also evidence that functional shifts occur in the number and activity of receptors and ion channels on the nociceptor; for example, receptors for neurotrophic factors, bradykinin, and prostaglandins are activated, increasing membrane excitability. Second-order neurons in the trigeminal sensory nucleus complex react to the increased trafficking

of action potentials from the nociceptor, and the neurons in the central nervous system are sensitized.[1] A multitude of biologic responses takes place, involving phosphorylation of N-methyl-D-aspartate receptors and activation of neurokinin and neurotrophic receptors. The understanding of the intracellular pathways linked to inflammatory pain is fairly advanced; it is known that these pathways include alterations in gene expression of neurotransmitters and neuromodulators.

Although the phenomenon of peripheral and central sensitization can develop within minutes, usually these processes are completely reversible in conditions with inflammatory types of pain. There are more chronic types of inflammatory conditions, such as gingivitis and periodontitis, which rarely are associated with pain. In contrast, rheumatoid arthritis, which may also affect the temporomandibular joint, can often be associated with long-lasting and debilitating pain.

## *Neuropathic pain*

Neuropathic pain, pain arising from nervous system injury, can occur if the peripheral nerve fibers are damaged, for example, during surgery (eg, third molar surgery, orthognathic surgery on the maxilla and mandible, or placement of implants) or by disease (eg, trigeminal neuralgia, postherpetic neuralgia, diabetic neuropathy, and even pulpitis).[1] Neuropathic pain may also develop following injury to the central somatosensory system, for example, stroke, multiple sclerosis, or spinal cord injuries.

The consequences of these lesions are spontaneous pain and hypersensitivity to painful stimuli (hyperalgesia) as well as nonpainful stimuli; for example, simple touch stimuli can be perceived as unpleasant and painful (allodynia). Thus, the primary afferent nerve fiber can initiate spontaneous discharges as a result of ectopic neural activity near the peripheral nerve lesion. Phenotypic changes and alterations in the expression and distribution of ion channels can occur, which contribute to an increase in membrane excitability. Therefore, it is easily understood how sensitized nerve fibers play an important role in neuropathic pain. The central nervous system also plays a significant role in these conditions. For example, one response at the second-order neuron is the loss of normal inhibitory mechanisms mediated by the neurotransmitter γ-aminobutyric acid and glycine. There is also evidence that signs of apoptosis appear in the dorsal horn neurons 1 week after nerve injury.

Unfortunately, in some patients, the neurobiologic mechanisms underlying

neuropathic pain appear to be irreversible and often resistant to current pharmacologic therapies. Different genotype subgrouping may explain such discrepancies between different subjects' response to injury and pain.[3]

### *Functional pain*

The concept of functional pain (also called *central sensitivity syndromes*) is emerging. No visible pathologic condition can be identified in the peripheral tissues, but it is believed that, for as yet unclear reasons, perhaps nonadaptive interactions between genotype and environment, there is an abnormal amplification and processing of peripheral stimuli in the central parts of the somatosensory system.[1] Temporomandibular disorder (TMD) pain, persistent idiopathic orofacial pain, burning mouth syndrome, fibromyalgia, irritable bowel syndrome, and tension-type headaches may fall into this category.[4]

In contrast to the inflammatory and neuropathic types of pain, in which local changes induce hypersensitivity to painful stimuli, functional types of pain result in more widespread and generalized hypersensitivity. Impaired psychosocial function, mood, and quality of life are also characteristic features of functional types of pain.

## Orofacial Pain–Sleep Disturbance Associations

Several types of pain mechanisms may and often do coexist in the same patient. At present, it is not known if the interaction with sleep is dependent on the specific type of orofacial pain. The following sections describe experimental and clinical pain studies examining the links between pain and sleep disorders.

### *Experimental studies*

Two different approaches have been used to examine the relationship between orofacial pain and sleep disturbances. The first one assesses pain sensitivity after the normal sleep pattern in healthy volunteers is disrupted with more or less selective deprivation of the different sleep stages. The other strategy studies the effects of inducing experimental pain in healthy subjects during sleep by recording changes in sleep parameters (see chapters 19 and 20).

Moldofsky et al[5] demonstrated, in six healthy young subjects, that auditory stimuli presented at the onset of stage 4 (deep non–rapid eye movement [non-REM]) sleep was able to decrease slow-wave sleep and increase sensitivity to deep painful stimuli and occurrence of musculoskeletal symptoms. Several studies have subsequently examined the effects of slow-wave sleep or rapid eye movement (REM) deprivation on various types of pain sensitivity (thermal or mechanical) and development of spontaneous pain symptoms.[6–8] One concern about these studies is that the duration of sleep deprivation is fairly short (typically 3 nights, for practical and ethical reasons), limiting the extrapolation to clinical conditions. Nevertheless, most studies have been able to demonstrate moderate increases in pain sensitivity in response to sleep deprivation; in particular, sleep continuity disturbances seem important for perturbation of endogenous pain-inhibitory systems and reports of spontaneous pain.[9]

The other approach involving experimental noxious stimulation during sleep has demonstrated relatively subtle effects on sleep patterns, with brief (6- to 12-second) noxious painful thermal stimuli inducing more awakenings and arousals within non-REM stage 2 and REM sleep than within slow-wave sleep.[10] Injections of hypertonic saline (minutes) may better mimic clinical deep pain conditions and have been shown to cause equipotent responses across sleep stages without significant impact on sleep quality ratings.[11] Relatively moderate-to-high suprathreshold stimulus intensities are required to alter sleep, suggesting that in normal individuals sleep attenuates nociceptive processing. Longer painful stimulation (minutes) during sleep seems more capable of disrupting the sleep pattern and quality than brief stimuli (seconds).[10–12]

Overall, both experimental approaches—sleep deprivation studies and the application of noxious stimuli during sleep—have provided some support to the scenarios that pain deteriorates sleep and poor sleep aggravates pain, but the clinical relevance of transient pain and a few nights' sleep deprivation needs further study. Some longitudinal data also support the view that the sleep-pain relationship is best described as reciprocally interacting.[13]

## *Clinical studies*

There is some further indication that pain per se can lead to sleep disturbances for both patients with acute pain and those with persistent pain. The majority of patients (90%) report that they have poorer sleep after the onset of new pain problems.[14]

Similarly, many orofacial pain patients (77%) report reduced sleep quantity after onset of pain.[15] About two-thirds of patients with persistent pain may report poor sleep quality (see Lavigne et al[16] for review).

The following sections review the association between various clinical orofacial pain conditions and sleep disturbances.

## *Temporomandibular disorders and sleep bruxism*

A significant proportion of patients with TMD pain (60%) report sleep disturbances, as do many patients with bruxism (37%).[17] However, sleep bruxism (SB) may not be associated with frank disturbances of sleep continuity or sleep architecture, and many SB patients do not report insomnia. SB has been consistently linked, however, to more subtle sleep microstructure disturbances, including arousals and autonomic activation.[18]

Bruxers with pain usually report that they experience the highest levels of pain in the morning, whereas myofascial TMD patients more often report higher levels of pain in the evening. In fact, when objective electromyographic (EMG) measurements are made, SB is not associated with higher levels of TMD pain[2,19] (Fig 21-3). This is further supported by the observation that the number of patients with a low frequency of SB events (estimated using EMG and audio-video recordings) who reported pain the next morning was higher than the number of patients with a higher frequency of jaw muscle activity during sleep who reported pain.

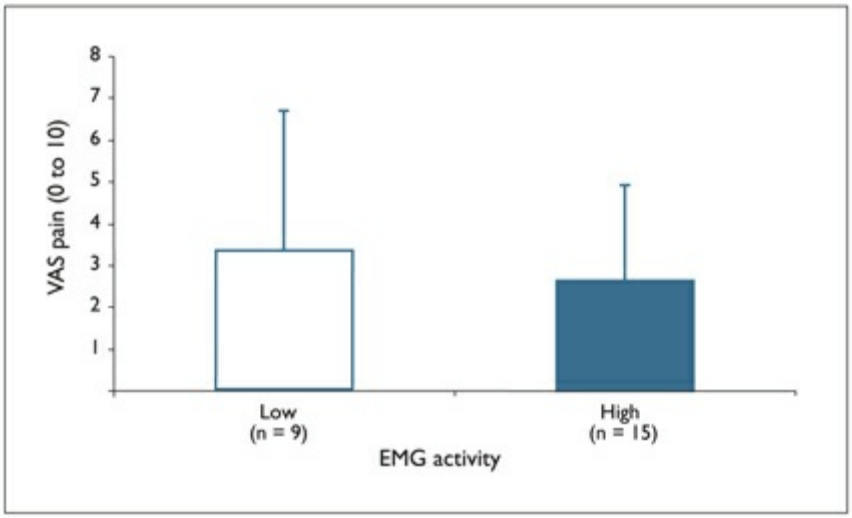


**Fig 21-3** EMG activity and orofacial pain. A total of 24 subjects were examined

with ambulatory recordings of EMG activity in the anterior temporalis muscle. The number of EMG episodes per hour of sleep were determined, and the group was divided into subgroups with low (fewer than 6 episodes per hour; n = 9) or high (more than 6 episodes per hour; n = 15) frequency of muscle activity. There was no statistically significant difference in perceived intensity of jaw muscle pain between the two groups (unpaired *t*-test: *P* = .53). (VAS) visual analog scale.

The relationship between TMDs and SB is complex and requires naturalistic studies, using state-of the-art polysomnographic methods, to clarify the nature of the relationship. Similarly, diagnostic polysomnographic studies of TMDs are needed because the majority of the literature on sleep disturbances in TMDs is reliant on self-reported data. A recent polysomnographic study in 53 TMD patients, however, found that 68% of these patients met diagnostic criteria for a sleep disorder, including 36% who met the criteria for insomnia and 28% who met the criteria for obstructive sleep apnea.

A study done in a large cohort of patients with SB also revealed that sleep-disordered breathing is critical to investigate.[20] In the presence of comorbid conditions such as posttraumatic stress disorders, sleep disturbances (eg, insomnia and sleep-disordered breathing) in patients with TMDs may be even more prominent.[21] These data indicate that clinicians treating TMD patients should consider referring patients for formal sleep studies if the pain complaints are associated with poor quality of sleep, snoring, or other breathing events such as cessation of breathing, and, more importantly, wake-time sleepiness (eg, falling asleep while driving).

## *Burning mouth syndrome and persistent idiopathic orofacial pain*

Patients with burning mouth syndrome often report (70%) that sleep relieves the pain.[22] Sleep disturbances and awakenings, however, are reported more frequently by patients with burning mouth syndrome than by matched control subjects but are apparently not directly related to the oral burning pain.[23] Persistent idiopathic orofacial pain also appears to have a limited influence on sleep.[24]

## *Toothache*

Anecdotally, toothache is one of the orofacial pain conditions that can interfere significantly with sleep. Patients with acute pulpitis or apical periodontitis often report awakenings and lack of sleep due to pain. Epidemiologic studies have, indeed, substantiated the influence of toothaches on sleep.[25] Periodontal pain after adjustment of orthodontic arch-wires is reported to have little influence on sleep.

## *Trigeminal neuralgia*

Although the literature is scarce, at least one study found that patients with trigeminal neuralgia rarely complain about sleep disturbance related to the pain.[22] However, higher pain severity scores have been associated with greater interferences with sleep in patients with trigeminal neuralgia.[26]

## *Headaches*

Patients with migraine have changes in the quality of sleep a few days before the onset of a migraine attack but have fairly normal sleep patterns outside the attacks.[27] Cluster headaches, which involve attacks of severe unilateral orbital, supraorbital, or temporal pain lasting 15 to 180 minutes, notably associated with unilateral conjunctival injection, lacrimation, nasal congestion, rhinorrhea, forehead and facial sweating, miosis, ptosis, and eyelid edema, frequently occur during sleep. Hypnic headaches, which are rare, recurrent types of headache usually beginning after 50 years of age, also involve attacks during sleep and are characterized by bilateral mild-to-moderate pain that lasts for up to 180 minutes.

Tension-type headache and chronic daily headache are also frequently associated with sleep disturbances and poor sleep quality, but to a lesser extent than in myofascial TMD pain patients.[28] Although the relation between SB and pain remains unclear,[2] it seems warranted to assess a possible linkage between tension-type headache and SB and sleep-disordered breathing.

There are currently too few systematic and prospective studies that have used accurate and reliable tools to assess sleep and establish the relationship of headaches to different types of orofacial pain complaints. However, it appears that many orofacial pain conditions and headaches potentially can interact with sleep. In particular, intense and paroxysmal pain can lead to awakenings during sleep and poor sleep quality.[27]

## Conclusion

It is important to establish the correct orofacial pain diagnosis and institute appropriate pain management because these are likely to have a beneficial effect on sleep, although they may not be sufficient to completely restore normal sleep. The clinician should also consider and target sleep disorders (eg, insomnia, sleep-disordered breathing, and periodic limb movement) in the treatment plan and refer patients for professional evaluation, if necessary. As described in detail in chapters 16 and 17, sleep management therapies, in terms of information and counseling (sleep hygiene and cognitive-behavioral approaches) as well as pharmacology, should be offered to patients with orofacial pain.[2] There is general agreement that outcome measures of orofacial pain also must include measures of sleep quality.

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CHAPTER 22

# IMPACT OF COMMON TEMPOROMANDIBULAR DISORDER COMORBIDITIES ON SLEEP QUALITY AND OROFACIAL PAIN

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Chronic pain and sleep disturbances are significant global health concerns. Each of these common problems has been independently linked to decreased quality of life, increased psychiatric and medical morbidity, and disability. An estimated 50% to 88% of chronic pain patients exhibit sleep disturbance,[1] and when these conditions co-occur, their deleterious effects may be compounded, if not magnified.

Temporomandibular disorders (TMD) are pain disorders that have been associated with significant sleep disturbance. TMDs, characterized by episodic, masticatory muscle and/or joint pain, are the most common chronic orofacial pain conditions. The estimated prevalence of TMDs in the general population is approximately 12%. While the pathophysiology of TMDs is poorly understood, the syndrome is often classified by the presence and degree of assumed masticatory muscle pathology, articular disc dysfunction, temporomandibular joint (TMJ) arthritis, and/or TMJ pain (arthritides). As in most chronic pain syndromes, poor sleep is a ubiquitous complaint among patients with TMDs; recent data suggest that up to 77% of orofacial pain patients report reduced quality and quantity of sleep.[2]

Prevalence studies have found that subjects who describe sleep difficulties are twice as likely to report frequent jaw pain symptoms.[3] Although poor sleep is often predicted by greater pain severity, accumulating evidence indicates that a vicious cycle may be established, wherein untreated sleep problems may also reciprocally

feedback and exacerbate pain (see chapter 21). Pain disrupts sleep, and disturbed sleep in turn aggravates pain. Thus, the direct assessment and treatment of insomnia are increasingly recognized as important areas requiring focused clinical attention in many chronic pain conditions.

The causes of sleep disturbances in patients with TMDs are often complex and may involve multiple psychologic and medical contributions that are independent of the TMD-related pain. Numerous studies have reported that sleep disturbance in individuals with TMDs is linked with increased psychologic distress, particularly anxiety and affective disorders.[2,4] TMD patients also suffer from a number of pain-related medical comorbidities that need to be considered in treatment planning. The purpose of this chapter will be to summarize what is known about sleep problems associated with TMD and to discuss common medical and psychologic comorbidities that may contribute to sleep disturbance and pain augmentation in patients with this condition.

## Sleep and TMDs

Adequate sleep is increasingly recognized as essential for the maintenance of both mental and physical health and well-being. Although individuals vary widely in their sleep needs, most adults typically sleep between 6 and 9 hours on average (see chapter 1). Sleep is divided into two main categories: non–rapid eye movement (non-REM) and rapid eye movement (REM) sleep. Non-REM sleep is further subdivided into three stages: Non-REM stages 1 and 2 are often described as *light sleep*, while slow-wave sleep is commonly referred to as *deep sleep*.[5] Evidence suggests that slow-wave sleep is particularly critical for both somatic and mental restoration. REM sleep is sometimes referred to as *paradoxical sleep* or *active sleep*, particularly in animals. Although the functions of both non-REM and REM sleep are still poorly understood, evidence has implicated REM sleep in various memory processes and neuroplasticity.

During sleep, people typically progress from non-REM stages 1 and 2 to slow-wave sleep before transitioning into REM sleep (see chapter 1); this cycle, which lasts approximately 90 minutes, repeats three to six times per night and is referred to as the *ultradian cycle*. Sleep is generally more fragmented in patients with chronic pain than in healthy individuals. Fragmented sleep is characterized by frequent arousals (15 seconds or less) and awakenings (more than 15 seconds), increased

shifting between sleep stages, and more frequent body movements during sleep.

In healthy controls, experimental painful stimuli have been shown to trigger sleep-related arousals (3 to 15 seconds). An arousal is characterized by a transient increase in brain (cortical) activity and/or autonomic, cardiorespiratory activity. Experimentally induced pain-related arousals are also often accompanied by increased muscle tone, shifts in sleep stages, and frank awakenings, depending on the intensity and duration of the noxious stimuli.[6] Thus, it is not surprising that sleep disturbance is frequently observed in patients with chronic pain; fragmentation of sleep may interfere with sleep recovery or restorative processes. Sleep fragmentation may be independent of or concomitant with the chronic pain and may reduce sleep duration as measured objectively in a sleep laboratory, in-home by ambulatory polysomnography, or with actigraphy.

Although objective sleep fragmentation is often observed in patients diagnosed with insomnia, the term *insomnia*, by definition, refers to a subjective complaint of poor sleep quality that impacts daytime functioning. Insomnia may or may not be associated with reduced total sleep time (partial sleep deprivation) within the 24-hour circadian cycle.

Only a handful of investigations have systematically sought to evaluate the sleep quality of TMD patients. These studies have consistently found that the majority of TMD patients report poor sleep quality and that subjective ratings of poor sleep are associated with increased severity of clinical pain and psychologic distress.[2,7] The presence of sleep disturbances was investigated in 128 orofacial pain patients, of whom 55% had a muscular facial pain disorder, 20% had a TMJ disc derangement or degenerative TMJ disorder, and 9% had fibromyalgia.[2] Measured from the date of onset of their pain event, up to 77% of these patients experienced a reduction in total sleep time, reporting a mean sleep duration of 5.9 hours per night. This value is below the boundary of 6 hours that is reported to be critical for mood alteration and health risks (see chapters 1, 19, 20, and 21).

Also in this study, cross-sectional examination of the data found that poor sleep quality was more closely related to psychosocial distress (ie, depression and/or anxiety) than it was to pain. However, longitudinally, baseline pain and depression were found to predict subsequent sleep disturbance, but sleep was not found to predict pain.[2] Caution is indicated in evaluating the results of the aforementioned study because many of these types of studies are limited by an inadequate assessment of subjective sleep complaints, and most are limited by a lack of objective assessment (eg, the measurement of sleep in a sleep laboratory or at home by ambulatory polysomnography or with actigraphy).

Recent work evaluated the rates of sleep disorders in 53 TMD patients (43 women and 10 men; mean age of 33.6 ± 12.4 years) by combining structured diagnostic interviews with in-laboratory polysomnography.[8] It was found that 75% of the sample met self-report criteria for sleep bruxism (SB) but only 17% met polysomnographic criteria for active SB (see chapter 14). Furthermore, 43% percent of the TMD patients were diagnosed with two or more sleep disorders. Insomnia disorders (36%) and sleep apnea (28.4%) were the most prevalent sleep disorders, aside from self-reported SB. These data indicate that clinicians treating patients with TMDs should have a low threshold for referring patients reporting significant sleep complaints (eg, sleepiness, a sleep partner's report of choking sounds, cessation of breathing during sleep, all suggestive of obstructive sleep apnea-hypopnea) for evaluation by a specialist.

A recent study comparing chronic daily headache, myofascial pain, and TMJ intracapsular pain patients found significantly more overall self-reported sleep dysfunction (according to the Pittsburgh Sleep Quality Index) in the myofascial pain patients than in the other two groups.[9] Furthermore, a significant proportion of patients with TMDs reported engaging in daytime bruxism and SB.

However, the relationship between bruxism and TMDs is complex and the literature conflicting. Bruxism has been speculated as a possible factor contributing to the development and maintenance of TMDs, either via muscle tension or by causing muscular microtrauma, leading to postexercise muscle soreness. However, considerable controversy exists as to whether it is a cause of TMDs or a comorbid condition.[10] For example, in a 1-night polysomnographic study comparing SB patients with myofascial pain to bruxism patients without myofascial pain, no significant differences were found between the two groups in measures of bruxism and sleep.[11] However, in a sample of Japanese adolescents, severe SB (more than 125 events per night) was associated with TMJ clicking.[12]

Indeed, recent work using objective polysomnographic measurement of sleep and SB has failed to establish the long-assumed relationship that SB is the primary driver of next-day pain in TMD patients.[13] Interestingly, in a study investigating the association between SB and increased risk for pain among subjects with a history of tooth grinding reported by a sleep partner, those who displayed very low levels of jaw muscle activity during sleep (a lower index of rhythmic masticatory muscle activity on electromyographic and audio-video recordings), in comparison to subjects with a higher frequency of tooth grinding, were more at risk of reporting next-day pain in the morning. Thus, the belief that increased muscle activity results

in more pain is no longer tenable.[14]

At this time, the role of SB in TMD pain must be considered unclear and requires more systematic study using valid outcome measures of oromotor activity. Future studies must control for nonspecific activity (such as swallowing, coughing, and sleep talking) observed during sleep (see chapters 12, 15, and 21). It should also be noted that, although SB is linked to sleep-related arousals and increased sympathetic tone during sleep, many sleep bruxers do not complain of frank sleep continuity disturbance or poor sleep quality.[11,13] This raises the possibility that SB may reflect a biologic vulnerability to pain and sleep disturbances rather than directly cause symptoms.

## Medical Conditions Concomitant With TMDs

It is important to have a comprehensive understanding of the associated medical conditions that have similar clinical presentations to that of TMDs in order to form an accurate diagnosis and an effective treatment plan. Various medical conditions share symptoms with TMDs, including fibromyalgia (increasingly termed *chronic widespread pain*), chronic fatigue syndrome, irritable bowel syndrome, multiple chemical sensitivity syndrome, hyperpro-lactinemia, mitral valve prolapse syndrome (also known as *dysautonomia*), hypothyroidism, and migraine or tension-type headache.

Certain TMDs, particularly myogenic TMDs, are often considered to be an idiopathic pain disorder, along with fibromyalgia, irritable bowel syndrome, chronic headaches, interstitial cystitis, chronic pelvic pain, chronic tinnitus, and vulvar vestibulitis.[15] In addition to pain, idiopathic pain disorders typically involve disturbances of sleep, motor function, and neuroendocrine function, symptoms of fatigue, and mild cognitive dysfunction. Although idiopathic pain disorders have poorly understood etiologies, they have all been linked with a state of pain amplification (hyperalgesia) and psychologic distress.[16,17] Pain amplification and psychologic distress are therefore believed to represent two principal pathways by which individuals may develop an idiopathic pain disorder.[15]

In addition to overlapping signs and symptoms, idiopathic pain disorders have remarkably high comorbidity rates. Among a sample of patients with TMDs, patients also reported symptoms consistent with chronic fatigue syndrome, fibromyalgia, irritable bowel syndrome, tension-type headache, multiple chemical sensitivity

syndrome, and chronic pelvic pain.[18] More specifically, 20% of the TMD sample met Research Diagnostic Criteria (RDC) for chronic fatigue syndrome, 13% met RDC for fibromyalgia, 64% met RDC for irritable bowel syndrome, and 8% met RDC for tension-type headache.[18] Estimates suggest that from 20% to 70% of patients meeting criteria for fibromyalgia also meet diagnostic criteria for chronic fatigue syndrome, and conversely, 35% to 70% of patients with chronic fatigue syndrome also meet criteria for fibromyalgia.[19] Similarly, a recent study found that 18% of patients with TMDs also had fibromyalgia, while 75% of those with fibromyalgia satisfied RDC for a myofascial TMD.[20] Another study reported that 53% of fibromyalgia subjects experienced facial pain, of whom 71% met diagnostic criteria for TMDs.[21]

Fibromyalgia is characterized by widespread body pain, which may or may not include TMDs and orofacial pain. It has been reported that from 70% to 90% of fibromyalgia patients experience some form of sleep difficulty.[22] In this widespread pain disorder, poor sleep quality has been found to predict further pain, fatigue, and impaired social functioning.[22]

Compared to the literature regarding TMDs, there is a relatively extensive body of literature describing sleep abnormalities in fibromyalgia patients. The sleep architecture of fibromyalgia patients has been associated with an increase in non-REM stage 1 sleep and a decrease in the duration of slow-wave sleep.[23,24] However, the opposite was also recently observed in a sleep laboratory study.[25] Chronic widespread pain patients exhibited normal duration of sleep stages 3 and 4, although their sleep duration was approximately 60 minutes less and they lost between one and two ultradian non-REM-to-REM sleep cycles compared to healthy controls. One of the first abnormalities observed in the sleep architecture of fibromyalgia subjects, compared to healthy controls, was a high frequency of electroencephalographic fast alpha-wave intrusions during non-REM sleep, which has been associated with greater pain and more tender points.[26,27] However, such observations were later reported to not be particular to or pathognomonic of fibromyalgia.[13,28]

Some recent research also suggests that occult sleep-disordered breathing (increased upper airway resistance or apnea-hypopnea) and periodic limb movements may be present in some patients with fibromyalgia.[25,29] Evaluation of TMD patients for comorbid sleep-disordered breathing is therefore recommended, especially if patients exhibit other risk factors such as loud snoring, excessive daytime sleepiness, obesity, retrognathia, large tonsils, a deep palate, or a large

tongue. Because of the possible overlapping etiologies of TMDs and fibromyalgia, clinicians treating TMD patients should evaluate the possibility that their patient may have comorbid fibromyalgia or a sleep disorder (eg, insomnia, breathing-related sleep disorder, or periodic limb or jaw movement) that may require additional intervention efforts beyond treatment of TMD-related pain. Chapter 3 provides more information on the classification of sleep disorders.

TMDs are also prevalent in headache patients, with up to 56% of headache patients meet diagnostic criteria for a TMD.[30] Sleep deprivation and disruption are known triggers for headaches, and some headache disorders, such as cluster headache, appear to be particularly tied to sleep and chronobiologic factors.[31] In this disorder, headache events often occur in clusters during particular seasons and may be triggered during sleep.

## Psychologic Symptoms and TMDs

Depression, anxiety, and fatigue have complex interactions with pain and sleep. In patients with TMDs, psychologic factors and stress are important with respect to the onset, maintenance, and exacerbation of chronic orofacial pain. In cross-sectional studies of orofacial pain patients, reduced sleep duration has been associated with depression and pain.[2] Decreased ratings of sleep quality have also been associated with negative affects.[2] Insomnia (trouble initiating or maintaining sleep with daytime consequences) is a hallmark feature of most psychiatric disorders, particularly anxiety and depression. Although sleep disturbances are not pathognomonic of a psychiatric disorder, TMD patients reporting chronic sleep disturbance should be evaluated by a mental health professional or behavioral sleep medicine specialist for possible psychiatric contributions to their sleep problem.

Positive interrelationships linking depression and anxiety with general somatic complaints and TMD-related pain have been reported.[32] It was found, however, that individuals with a single pain condition (eg, TMDs) did not have a greater incidence of major depression than did individuals without a pain condition; however, those with multiple pain conditions were at greater risk for depression.[33] In another study, more than 25% of the facial pain clinic patients in the study sample were found to suffer from major depression, while another 25% met criteria for minor depression.[34] Similar results were obtained in another study of TMD patients in which approximately 20% of the sample received clinically meaningful scores on a

measure of depression.[35] Consequently, direct assessment screening for and treatment of depression should constitute an important component of the evaluation and treatment of TMD patients.

Few studies have examined whether psychologic symptoms of depression and anxiety are true risk factors for the development of TMDs. In a study examining the comorbidity of depression with TMDs, it was found that 41% of the study sample (patients with TMDs) had a lifetime history of major depressive disorder, suggesting that depression may be a risk factor for the development of TMDs or occur as a result of it.[36] A more rigorous study examined whether psychologic characteristics predict the risk for the development of new-onset TMDs in healthy subjects.[37] The results indicated that depression, perceived stress, and negative mood predicted twofold to threefold increases in new-onset TMDs. These psychologic factors were independent of risk factors associated with genetic polymorphisms encoding for catechol-*O*-methyltransferase.

In addition to symptoms of depression and anxiety, patients with TMDs frequently report more significant levels of stress in daily life than do healthy controls.[38] Chronic pain itself may be conceptualized as a form of stress. Generally, environmental stressors are thought to contribute to the onset and worsening of TMDs, but definitive work in this regard has yet to be conducted.

Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, a major system involved in the stress response, has been documented in depression,[39] fibromyalgia,[40] and TMDs.[41] One study of patients with TMDs found increased cortisol (a major stress hormone) reactivity to a laboratory-induced psychologic stressor,[41] and another found significantly elevated daytime plasma cortisol levels.[42] Stress-related pain disorders are frequently accompanied by disturbances in the limbic system and in the HPA axis. Despite the strong link among chronic pain, stress-related disorders, and limbic abnormalities, the underlying mechanisms clarifying the effects of chronic pain on the HPA axis are not clearly understood.

## Conclusion

This literature review reveals that there are various etiologic pathways linking TMDs to other disorders, both psychologic and physiologic, which can increase the risk for clinical pain. It also underscores the need for a multidimensional approach to the treatment and prevention of TMDs, with an emphasis on assessment and

treatment of psychologic distress and sleep disturbance as well as common medical comorbidities. Clinicians should more thoroughly screen for sleep disturbances in patients with orofacial pain and realize that treatment of the sleep disturbance will require a focus separate from treatment of the pain.

In addition to chronic insomnia, some evidence suggests that sleep-disordered breathing may be an underrecognized problem impacting a substantial subset of TMD patients. TMDs are also highly comorbid with other idiopathic pain disorders, particularly fibromyalgia (chronic widespread pain) and headache disorder. Psychologic stress is also common, and many TMD patients have high rates of depression and anxiety, which may require independent assessment and treatment.

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CHAPTER 23

# PHARMACOLOGIC MANAGEMENT OF SLEEP-PAIN INTERACTIONS

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The aim of this chapter is to overview how pain and sleep interact and provide some insight into the pharmacologic management of this interaction. The high prevalence of sleep disturbances in patients with chronic pain is due in part to pain-sleep bidirectional phenomena, in which pain disturbs sleep and poor sleep reduces the pain threshold and aggravates pain. Although it is assumed that effective treatment of ongoing pain with analgesic drugs will also improve sleep, the interaction between certain analgesic drugs and sleep may exacerbate rather than alleviate sleep disturbances in patients with chronic pain.

## Interactions Between Sleep and Pain

Chronic pain is associated with patients' complaints of poor quality sleep, and research has demonstrated increased sleep arousal and decreased deep sleep (slow-wave sleep of sleep stages 3 and 4; see chapter 1) in these patients. Although experimentally induced acute pain in healthy subjects is not necessarily comparable to the chronic pain conditions, painful stimuli administered to healthy volunteers during sleep lead to increased arousal (brief and repetitive rise in brain, heart, and muscle activity).[1] Both clinical and experimental data support the notion of a bidirectional influence in the pain-sleep relationship.[2]

The effect of decreases in sleep duration or in the length of a given sleep stage is lowered pain thresholds.[3] Although the relative contribution of particular types of

sleep loss to hyperalgesic states is not entirely clear, evidence suggests that rapid eye movement (REM) sleep deprivation, slow-wave sleep loss, several nights of curtailed sleep, general sleep fragmentation, and short-term total sleep deprivation (over 36 hours or more) all enhance pain sensitivity and alter mood, a variable that may interact with pain threshold assessments.[4–7]

A loss of normal opioidergic and monoaminergic descending inhibitory mechanisms has been suggested to underlie the effects of REM sleep deprivation,[6,8] and others have found evidence that sleep loss may alter cytokines known to sensitize nociceptors and enhance clinical pain.[7] In healthy individuals, the pain threshold appeared to increase with shorter latency to REM sleep onset, and a higher percentage of time spent in REM sleep has been associated with hyperalgesia to suprathreshold painful stimuli.[8] These REM-related features, which have been linked to monoaminergic and cholinergic dysfunction, have also been associated with risk for depression, suggesting possible overlapping neural substrates between depression and some idiopathic pain disorders.[6]

## Pharmacology of Sleep

The neurochemical changes associated with changes from wakefulness to sleep remain incompletely understood (see chapter 2). Of particular relevance to the management of sleep disturbance in chronic pain patients is the proposal that wakefulness is maintained, in part, by a combination of cholinergic, noradrenergic, dopaminergic, and histaminergic tone in key areas of the brain.[9] A decrease in the tone of one or more of these neurotransmitters, for example, as a side effect of certain analgesic drugs, can lead to a decrease in arousal, cause an increase in drowsiness, and promote the transition from wakefulness to light sleep and ultimately to deep sleep.

The exact trigger for the natural decrease in the tone of all these neurotransmitters, which coincides with the onset of sleep, is not known. Serotonergic neurons of the raphe nucleus play a permissive role in this process by increasing their firing during the transition to deep sleep, although whether this event is a trigger or is merely part of a cascade of events leading to the onset of sleep requires further investigation.[9] Nevertheless, an active process, which involves an increase in γ-aminobutyric acid–ergic (GABAergic) tone, results in the onset and maintenance of sleep.

The sleep cycle is characterized by long periods of deep sleep intersected by

short periods of REM sleep, which progressively increase in length as sleep progresses (see Fig 1-3). The transition to REM sleep is associated with a profound decrease in aminergic tone as well as an increase in cholinergic tone.[9] Thus, wakefulness and REM sleep states are both thought to be maintained by enhanced cholinergic tone in the central nervous system. However, during REM sleep, noradrenergic tone and serotonergic tone are minimized through an increase in GABAergic tone, which leads to a significant decrease in central nervous system levels of these neurotransmitters during the REM sleep state.[10]

## Effects of Analgesics on Sleep

### *Nonsteroidal anti-inflammatory drugs*

Nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, diclofenac, and indomethacin, are extensively used for the treatment of acute and chronic orofacial pain. NSAIDs inhibit cyclooxygenase, and as a result, they suppress the synthesis of prostaglandin $D_2$ and $E_2$, which promote sleep and wakefulness, respectively.[11] Nevertheless, except when administered at doses well above those required for analgesia, NSAIDs do not appear to have deleterious effects on sleep architecture in chronic pain patients or healthy pain-free individuals.[2,12]

### *Opiates*

Opiates such as codeine, morphine, and fentanyl are among the most commonly employed analgesics for both acute and chronic orofacial pain of moderate-to-severe intensity. The analgesic effects of these drugs are mediated primarily through activation of a group of classic opioid receptor subtypes, designated μ, δ, and κ. Activation of the μ and, to a lesser extent, κ receptor subtypes is thought to be responsible for the sedating properties of this drug class.[13]

The most prominent effect of morphine and other opiate analgesics on healthy individuals is a significant suppression of REM sleep, which may continue for the entire period of administration.[14] Acute administration of tramadol—a weak μ-opioid receptor agonist with monoamine reuptake inhibitor properties that has been investigated for postsurgical dental pain—decreased slow-wave sleep and markedly

reduced REM sleep duration in young, healthy nonaddicted volunteers.[15,16] The use of opiates such as morphine or fentanyl to treat acute surgical pain has been associated with decreased sleep and in particular decreased REM sleep, although it is difficult to know whether these effects are mediated by the acute pain or the opiate.[17] Burn patients who received chronic morphine administration had highly fragmented sleep with a strong association between pain intensity and decreased sleep duration.[18] Another related concern is an apparent dose-dependent relationship between chronic opiate use for pain and the development of new or aggravation of existing sleep apnea.[19]

## *Antidepressants*

Antidepressants, and in particular tricyclic antidepressants, are employed to treat neuropathic pain and are sometimes used as analgesics for the treatment of temporomandibular disorders.[20] These drugs act as monoamine reuptake inhibitors to block reuptake of serotonin (5-HT) and norepinephrine. Although they can increase overall sleep, they may also suppress REM sleep for the duration of their administration.[21] Newer antidepressant compounds such as nefazodone, which has a modest ability to inhibit the reuptake of 5-HT and norepinephrine but also possesses antagonist properties at 5-$HT_2$ receptors, have no significant effect on sleep time.[22] The role of newer antidepressant drugs (eg, duloxetine) as well as older agents such as trazodone, which has been used to increase slow-wave sleep in nonorganic insomnia related to somatoform pain disorder,[23] in the treatment of orofacial pain has not been established.

## *Antiepileptics*

Antiepileptics, such as carbamazepine, are commonly used for the treatment of trigeminal neuralgia.[20] Carbamazepine slows the rate of recovery of voltage-activated sodium channels in a voltage- and use-dependent manner and can cause significant drowsiness but has little overall effect on sleep architecture.[24] Gabapentin and pregabalin are newer antiepileptic agents used for neuropathic pain that exert their analgesic effects, at least in part, by binding to the α2δ subunit of L-type voltage-dependent calcium channels. These drugs also appear to increase deep sleep without affecting REM sleep, but the enhancement of sleep is modest in healthy

adults.[25] With the exception of carbamazepine, these agents have not been used extensively to treat orofacial pain.

### *Antispasmodics and muscle relaxants*

Antispasmodics and muscle relaxants, such as cyclobenzaprine, methocarbamol, dantrolene, and baclofen, are used to treat skeletal muscle spasticity, but their effects on sleep have not been extensively studied. Clonazepam, a benzodiazepine that acts at central $GABA_A$ receptors, can significantly decrease masseter muscle activity as well as objective and subjective sleep quality.[26] Baclofen, a centrally acting $GABA_B$ receptor agonist that is used to treat painful spasms in spinal injury patients, has been shown to significantly increase REM sleep but has little effect on deep sleep.[27] It is not known whether pain patients would achieve similar benefits from baclofen or other antispasmodics.

### *Other agents*

Pramipexole is a dopamine $D_3$ receptor agonist with some activity at the $\alpha_2$-adrenergic receptor that is being employed to treat certain chronic musculoskeletal pain syndromes.[28] It is not known whether pramipexole alters sleep in patients with chronic pain; however, use of pramipexole to treat patients with Parkinson disease has been associated with increased risk of addictive gambling.[29]

## Management of Analgesic Drug–Sleep Interactions in Pain Patients

### *Sleep hygiene education and behavioral treatment approaches*

Before or in addition to pharmacologic interventions, an evaluation of presleep activities and environment contributors to sleep disturbance should be conducted (Fig 23-1). Adjustment of local and environmental factors (eg, preparation of an

undisturbed room with desirable humidity and temperature, comfortable mattress and pillows for support, and elimination of sleep-interfering stimulants and use of alcohol before bed) and referral for formal cognitive-behavioral therapy for insomnia should be considered[30] (see chapter 24).

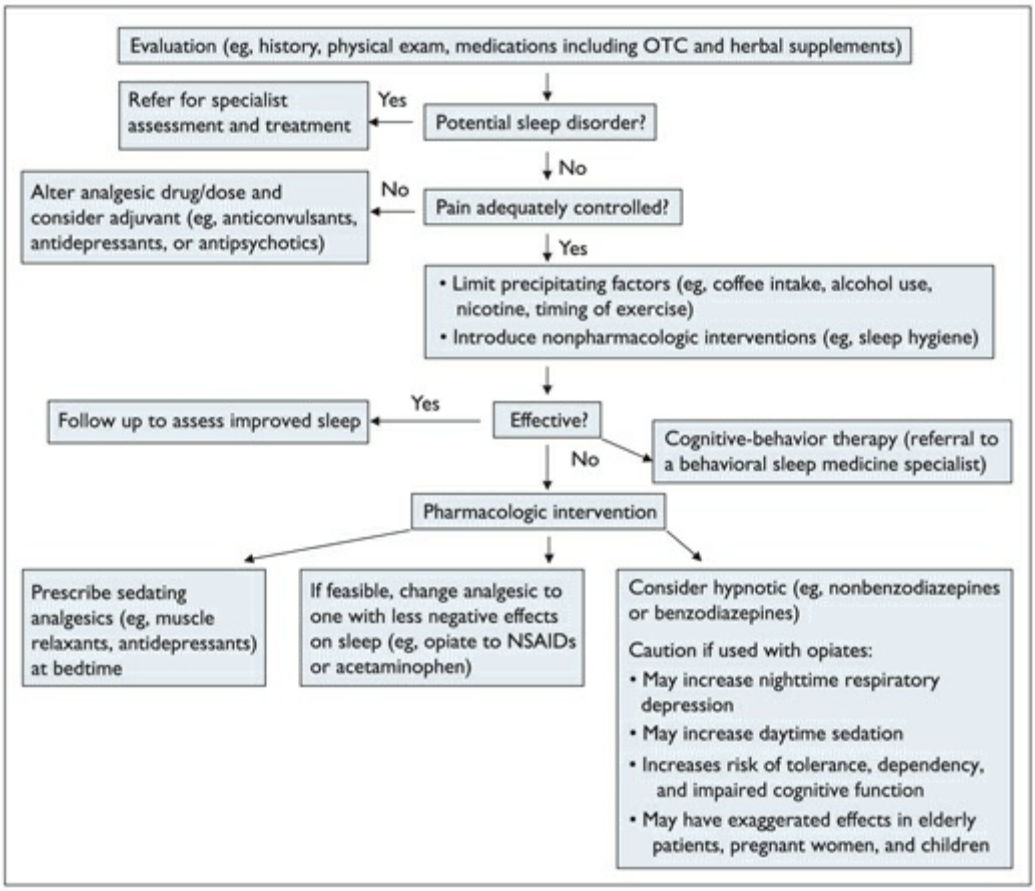


**Fig 23-1** Management of sleep disturbances in patients with chronic orofacial pain. (OTC) over the counter.

## *Over-the-counter medications*

It is important to ask patients about nonprescription drug measures they are using to improve their sleep because many patients may also try over-the-counter sleep aids or herbal medicines (Table 23-1). Many herbal products have the potential to increase the sedating properties of analgesic and hypnotic medications, and their use should be discouraged or at the very least carefully monitored to help minimize adverse effects.

**Table 23-1 Common over-the-counter and herbal sleep aids***

| Sleep aids | Other uses | Mechanism(s) | Potential interactions |
|---|---|---|---|
| Diphenhydramine | Antihistamine, antiemetic, and antitussive | Antihistamine and anticholinergic | Concurrent use with other central depressants (eg, benzodiazepines and ethanol) should be avoided. |
| Chamomile *(Matricaria recutita, Chamaemelum nobeli)* | Anxiety | Benzodiazepine receptor agonist? | Concurrent use with other central depressants (eg, benzodiazepines and ethanol) should be avoided. |
| Ibuprofen and diphenhydramine (eg, Advil PM, Wyeth Consumer Healthcare) | Sleeplessness associated with mild pain | NSAID plus antihistamine and anticholinergic | Same interactions as for diphenhydramine plus may induce or exacerbate existing ulcers, renal dysfunction, or hypertension. |
| St John's wort *(Hypericum perforatum)* | Depression | Monoamine oxidase inhibitor? Monoamine reuptake inhibitor? Facilitates GABAergic transmission? | Interacts with antidepressants and cytochrome P450. |
| Valerian *(Valeriana officinalis)* | Muscle pain | Facilitates GABAergic transmission | Concurrent use with other central depressants should be avoided. |

*Data from Spinella.[31]

## *Analgesics*

In individuals suffering from orofacial pain who have a history of sleep disturbance, acetaminophen is a good choice because its use does not affect sleep architecture and may even increase the amount of sleep.[2] As discussed above, NSAIDs also normally have minimal effects on sleep. It may be possible to further minimize any effects of NSAIDs on sleep by using topical NSAID-containing creams and ointments. Although opiates such as morphine may be required for adequate analgesia in cases of moderate-to-severe acute and chronic orofacial pain, most

opiates significantly alter sleep architecture and may further exacerbate symptoms of poor sleep in patients with sleep disturbances, eg, sleep-disordered breathing (described in chapter 4).[14]

## *Concomitant hypnotic agents*

Before employing any hypnotic drug as a sleep aid, the clinician must rule out primary sleep disorders, particularly sleep-disordered breathing, because many hypnotic agents may exacerbate such conditions.[30] Analgesic drugs with known sedating effects, for example, tricyclic antidepressants, skeletal muscle relaxants, and antiepileptics, may be administered in the early evening to improve sleep and minimize daytime drowsiness. Nonbenzodiazepine hypnotic agents, such as zolpidem, zopiclone, and eszopiclone (Table 23-2), or longer-acting benzodiazepines, such as oxazepam and tamazepam, have been shown to improve sleep and reduce awakenings and may be considered as adjunctive therapy.[30] Some data suggest that these newer agents may have less potential to exacerbate sleep apnea (relative to myo-relaxing benzodiazepines, such as zolpidem[32]).

**Table 23-2** **Properties of newer benzodiazepine BzR and MT receptor agonists**

| Agent | Mechanism | Dose (mg) | Half life (h) | Comments |
|---|---|---|---|---|
| Zolpidem | $GABA_A\alpha_1$ BzR agonist | 5.00–20.00 | 1.4–4.5 | More useful in sleep-onset insomnia than for improving sleep maintenance. Risk of dependence and rebound. Abuse potential. |
| Zolpidem ER | $GABA_A\alpha_1$ BzR agonist | 6.25–12.50 | 1.6–5.5 | Improves sleep onset and sleep maintenance in elderly patients with primary insomnia. |
| Zaleplon | $GABA_A\alpha_1$ BzR agonist | 5.00–20.00 | 0.5–1.0 | Useful for sleep-onset insomnia but not for sleep-maintenance insomnia. No |

| | | | | |
|---|---|---|---|---|
| | | | | tolerance or hangover effect. |
| Zopiclone | $GABA_A\omega_1$ BzR agonist | 3.75–7.50 | 5.0 | Treatment of transient, short-term, and chronic insomnia in adults, including difficulties with falling asleep and nocturnal awakening. Approved for elderly patients and for chronic use. |
| Eszopiclone | $GABA_A$ BzR agonist | 1.00–3.00 | 5.0–7.0 | Useful in sleep-onset insomnia and improving sleep maintenance. |
| Ramelteon | MT1 and MT2 receptor agonist | 8.00 | 1.5 | Shortened sleep-onset latency and increased sleep duration in patients with transient and chronic insomnia. Use with caution in patients with depression. Do not use with fluvoxamine. |

(BZR) benzodiazepine receptor; (MT) melatonin.

Careful monitoring must be undertaken if hypnotics are used with opiates because the combination can significantly inhibit respiratory drive. Short-term therapy with hypnotics may be of benefit in selected patients with chronic pain to improve subjective sleep complaints but should not be expected to alter pain symptoms. It is important to initiate hypnotic therapy at the lowest therapeutic dose and to slowly increase the dose to maximize sleep while minimizing adverse effects. [33]

Clinical trials investigating longer-term use of benzodiazepine receptor agonists and their potential to improve pain are currently being conducted, but no data are yet available.

# Conclusion

The management of sleep disturbances in patients with chronic orofacial pain is challenging and requires careful evaluation, appropriate diagnosis, and knowledge of both pharmacologic and nonpharmacologic interventions.

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CHAPTER 24

# NONPHARMACOLOGIC MANAGEMENT OF INSOMNIA AND PAIN

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Among the many orofacial pain patients seen by dentists each day, it has been estimated that 70% to 80% of these patients complain of insufficient sleep duration and frequent awakenings. About 55% to 60% of them report difficulty falling asleep and having restless sleep following the onset of pain.[1,2] Effective management of sleep disturbances in these patients is absolutely crucial because prolonged sleep disruption and deprivation can exacerbate pain,[3,4] contribute to poorer psychosocial functioning, and worsen treatment outcomes.[5,6]

Despite recent advances in the development of sleep-promoting analgesics (eg, gabapentin and pregabalin) and a newer generation of hypnotics (eg, benzodiazepine receptor agonists such as eszopiclone, indiplon, and zolpidem), insomnia co-occurring with chronic pain remains difficult to treat (see chapter 23). Although hypnotics are typically recommended for a period of less than 1 month, their long-term use is commonplace.

Sole reliance on drugs for the management of chronic insomnia is not without risks and is not desired by many. Furthermore, the safety and effectiveness of frequent (ie, nightly), extended (ie, more than 6 months) use of sleep medication have yet to be satisfactorily established in high-quality randomized controlled trials (RCTs). Both benzodiazepines and nonbenzodiazepine hypnotics are known to have residual effects that can compromise alertness, psychomotor coordination, and cognitive performance the following day. Whether the apprehension is accurate or not, many patients are skeptical about taking sleep medications because of their concerns about possible tolerance of and dependence on the drugs.[7] Cutting down on

medication is often a particularly high priority for pain patients.[7,8]

Confronted with these challenges, the field has assiduously developed and refined nonpharmacologic interventions for chronic insomnia. As a result of this effort, cognitive-behavioral therapy for insomnia (CBT-I) has gradually matured as a viable treatment alternative over the last two decades to the point of being considered a first-line intervention for primary insomnia.[9] (*Primary insomnia* refers to sleep difficulty that does not occur exclusively during the course of another sleep disorder, medical condition, or psychiatric condition and that is not due to the direct physiologic effects of a substance or drug.) More recently, CBT-I has also been applied to treat insomnia occurring in the context of chronic pain with some success. The aims of this chapter, therefore, are to keep the reader abreast of these recent developments and to highlight some practical issues to be considered by dentists when treating orofacial pain patients with comorbid insomnia.

# Nonpharmacologic Treatments for Primary Insomnia

## *Principal treatment components*

Contemporary nonpharmacologic treatments for insomnia comprise a selection of time-limited and structured cognitive-behavioral strategies designed to target the psychologic factors involved in the maintenance of chronic insomnia. Several studies of chronic pain patients have demonstrated that factors such as conditioned presleep arousal, inactivity, poor sleep hygiene, psychologic distress, and rumination (ie, circular thinking) related to pain may play as much, if not more, of a role in maintaining insomnia than the pain itself.[10] CBT-I is a multimodal treatment that typically contains:

- A psychoeducational component that serves to teach the patients about sleep and the factors affecting sleep (eg, homeostatic regulation, circadian rhythm, age, and social and work schedules)
- A behavioral component that works towards minimizing unwanted arousal at bedtime and altering the patient's sleep habits to increase sleep propensity and regularity
- A cognitive component that seeks to address people's worries and beliefs about

sleep, particularly those anxiety-provoking thoughts ("I'm losing control over my sleep") and safety-seeking behaviors (eg, drinking excessive coffee and extending time in bed) that are not conducive to good sleep

## *Delivery format*

A standard course of CBT-I is typically delivered by trained psychologists or behavioral sleep medicine (BSM) specialists across 8 to 12 weekly sessions. However, depending on the nature of the sleep problems, the intensity and emphasis of the treatment can be adjusted to meet individual needs. The therapy can be conducted in an individual or a small-group format.

## *Individual treatment strategies*

The content and objectives of the eight most evaluated CBT-I strategies are outlined in Table 24-1, including: *(1)* stimulus control therapy, (2) relaxation training, *(3)* sleep restriction, *(4)* paradoxical intention, *(5)* biofeedback, *(6)* cognitive therapy, *(7)* sleep hygiene education, and *(8)* imagery training. As individual treatment strategies, the evidence base is the strongest in support of stimulus control therapy, relaxation, and sleep restriction as effective individual treatments for chronic insomnia.[12] When evaluated as a treatment package in which the individual strategies are used in combination, three independent meta-analyses[14–16] and two comprehensive reviews conducted by the Standard of Practice Committee of the American Academy of Sleep Medicine (AASM)[12,17] have consistently found this approach of treatment to be effective, producing reliable and durable changes in the sleep patterns of patients with chronic insomnia.

**Table 24-1** **Individual treatment components of CBT-I***

| Therapy | Content | Objectives | AASM level of recommendation† | Overlap with pain management‡ | Potential contraindications and compliance issues |
|---|---|---|---|---|---|
| | Instructing the patient to: (1) go to bed only when sleepy; | | | | |

| | | | | | |
|---|---|---|---|---|---|
| Stimulus control therapy | (2) use the bedroom only for sleep and sex; (3) get out of bed if not asleep within 15 to 20 minutes; (4) maintain a regular sleep-wake schedule; and (5) avoid naps | To train the patient to reassociate the bed and bedroom with rapid sleep onset | Standard | No | Frequent getting out of bed may prove to be a challenge to frail patients or patients with restricted mobility |
| Relaxation training | Techniques to reduce somatic or cognitive tension around bedtime | To deactivate the arousal system and facilitate sleep onset | Standard | Yes | Paradoxical agitation |
| Sleep restriction | Cutting the amount of time in bed down to the actual amount of time asleep | To increase sleep pressure and consolidate sleep by introducing a mild form of conditions and increase daytime sleep deprivation | Guideline | No | Initial sleep loss may aggravate comorbid medical and psychiatric conditions and increase daytime sleepiness |
| Paradoxical intention | Instructing the patient to remain awake and avoid any effort or intention to fall asleep | To reduce sleep effort and performance anxiety that inhibits sleep onset | Guideline | No | |
| Biofeedback | Providing visual or auditory feedback to patients to help increase their control over some biologic | To reduce somatic arousal and improve self-efficacy | Guideline | Yes | |

| | | | | | |
|---|---|---|---|---|---|
| | responses | | | | |
| Cognitive therapy | Identifying and challenging patients' unhelpful cognitions about sleep and replacing them with more helpful substitutes through the flexible use of a range of discussion techniques | To alter unhelpful beliefs and attitudes about sleep and to reduce patients' emotional distress associated with sleep | No recommendation level | Yes, but focused on pain-related thoughts | |
| Sleep hygiene education | Teaching patients the potential impact of certain environmental, dietary, and behavioral factors on sleep | To increase awareness of environmental factors and health practices that may either promote or interfere with sleep | No recommendation level | No | Instructions to exercise should be given at a level that is appropriate to the patient's physical capability |
| Imagery training | Use of visualization techniques to focus patients' attention on pleasant or neutral images | To reduce presleep cognitive arousal or shift the focus of attention away from distressing, sleep-interfering thoughts | No recommendation level | Yes, but focused on pain-related imageries; for relaxation or distraction | |

* Adapted from Tang[11] with permission.

†Level of recommendation in the American Academy of Sleep Medicine (AASM) Report by Morgenthaler et al.[12] *Standard* is defined as a "generally accepted patient care strategy which reflects a high degree of clinical certainty." *Guideline* is defined as a "patient care strategy which reflects a moderate degree of clinical certainty."

‡Based on the description of treatment for chronic pain proposed by Turk.[13]

### *Efficacy and effectiveness*

The average effect sizes achieved by a standard course of multicomponent CBT-I range from 0.87 to 1.05 for sleep-onset latency, 0.53 to 0.83 for number of awakenings after sleep onset, 0.65 to 1.03 for wake time after sleep onset, 0.42 to 0.49 for total sleep time, and 0.94 to 1.44 for sleep quality. These effect sizes are moderate to large by statistical standards, although compared to cognitive-behavioral therapies for other psychologic disorders, CBT-I has the potential to further optimize its treatment efficacy.[19]

When measured directly against pharmacologic therapy for insomnia, psychologic therapy has been found to be just as efficacious as hypnotics during the acute treatment phase.[16] As for the durability of the treatment gain, it is now known that improvements associated with CBT-I are generally well maintained for 3 months to as long as 2 years after treatment.[20] Finally, CBT-I has also been demonstrated to be effective in the real world of clinical practice where insomnia diagnoses are not as clear-cut and resources do not support the provision of high-intensity (eg, one-to-one) interventions by sleep specialists.[21,22]

## Application of CBT-I to Insomnia Concomitant With Chronic Pain

To date, there are no available data on clinical trials of CBT-I for patients with orofacial pain. A handful of high-quality RCTs have evaluated the application of CBT-I to heterogenous samples of chronic pain, fibromyalgia, and cancer patients (Table 24-2), and results support its use in the treatment of orofacial pain. Furthermore, CBT-I has been found to be effective in patients with chronic insomnia occurring in the context of psychiatric disorders such as major depression.[10] Beyond the differences in etiology among various pain disorders, the conditions are comparable to chronic orofacial pain in the sense that they all are characterized by persistent pain and share a high prevalence of insomnia complaints.[28–30] Reviewing the outcomes of these studies should allow an evidence-based estimate of the utility of CBT-I in orofacial pain.

**Table** **Summary of five RCTs evaluating the utility of CBT-I for chronic pain, fibromyalgia, and c**

| | | | | Treatment outco | | |
|---|---|---|---|---|---|---|
| **Study** | **Sample size and characteristics** | **CBT-I package/components** | **Treatment format** | **Objective sleep** | **Subjective sleep** | **Pai rela** |
| Currie et al[23] | *n = 60*<br>Chronic nonmalignant pain patients<br>Mean age = 45 y<br>Female = 45% | CBT-I package (versus waitlist) | 7 weekly sessions (group) | N/A | At posttreatment, participants in the CBT condition showed significantly greater improvements in SOL, SE,WASO, and SQ (PSQI), compared to the waitlist. Improvements were maintained at 3-month follow-up. | "Ar the Pai Sev sco pro only sign mai for CB pati not sign low rati con con the size redu was moc |
| Jungquist et al[24]* | *n = 28*<br>Chronic nonmalignant pain patients<br>Mean age = 49 y<br>Female = 79% | CBT-I package (versus nonactive control) | 8 weekly sessions | N/A | "Significant group differences were found posttreatment for [SOL, WASO, and SE; at 3-month, forTST and SE; at 6-month, forWASO,TST, and SE]." | "Pr ana sug sign diff on p outc how moc effe on p rela outc wer obs |
| | | | | Paired | Paired comparison showed that the | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Edinger et al[25] | *n = 47*<br>Fibromyalgia patients<br>Mean age = 49 y<br>Female = 96% | CBT-I without sleep hygiene education<br>(versus sleep hygiene and TAU) | 6 weekly sessions (individual) | comparison showed that the CBT-I average posttreatment and (6-month) follow-up actigraphic SOL were actigraphic SOL were that of the usual care group. | CBT-I average posttreatment and (6-month) posttreatment and (6-month) the average TWT, SOL, and ISQ scores were lower than those of the TAU.The sleep hygiene group average ISQ score was lower than that of theTAU group. | "Pa<br>rec<br>the<br>hyg<br>ther<br>had<br>BP<br>MP<br>sco<br>did<br>[TA<br>pati |
| Fiorentino et al[26]* | *n = 47*<br>Breast cancer survivors<br>Mean age = 61 y<br>Female = 100% | CBT-I package<br>(versus TAU) | 6 weekly sessions (individual) | "The pooled analyses of pre- and post-CBT-I treatment for all 14 participants revealed significant improvement in [WASO, number of wakes, and sleep percent]." | "Pooled analyses of pre- and post-CBT-I… revealed significant improvements in [sleep quality ments in [sleep quality of wakes] ….Benefits were maintained at 6-week follow-up." | N/A |
| Savard et al[27] | *n = 57*<br>Breast cancer survivors<br>Mean age = 54 y<br>Female = 100% | CBT-I package and fatigue management<br>(versus waitlist control) | 8 weekly sessions (group) | "PSG data were not significantly more improved in treated patients compared with control patients….No significant group-time interaction | "Treated patients showed a significantly greater improvement of their sleep at post-treatment… compared with control patients." This applied to all sleep variables except TST. Maintenance of | N/A |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | was observed. | gains were observed at 3-, 6-, and 12-month follow-ups. | |

*Published abstract.
(N/A) not available; (SOL) sleep-onset latency (in minutes); (SE) sleep efficiency (in percentage); (WASO) wa
onset (in minutes); (SQ) sleep quality; (PSQI) Pittsburgh Sleep Quality Index; (MPI) Multidimensional Pain Inve
Depression Inventory; (TST) total sleep time (in hours); (TAU) treatment as usual; (TWT) total wake time (in r
Insomnia Symptom Questionnaire; (BPI) Brief Pain Inventory; (MPQ) McGill Pain Questionnaire; (POMS) Pro
(PSG) polysomnography; (HAD) Hospital Anxiety and Depression Inventory; (QLQ-C30+3)The European Org
and Treatment of Cancer Quality of Life Questionnaire.

In the first RCT that specifically examined the efficacy of CBT-I in chronic pain, Currie and associates[23] provided a 7-week group CBT-I program to 60 patients with chronic pain. The intervention comprised sleep education, sleep restriction, stimulus control, relaxation training, sleep hygiene, and cognitive therapy. At the end of treatment, the group that received CBT-I demonstrated significantly shorter sleep-onset latency, shorter wake time after sleep onset, higher sleep efficiency (total sleep time ÷ total time in bed × 100%), and better self-reported sleep quality than did waitlisted control patients. These results were maintained at the 3-month follow-up. However, the consolidation in sleep was not followed by significant improvements in pain and mood. This clinical trial, however, was not statistically powered to detect changes in pain, although an estimation of the effect size of CBT on pain demonstrated a promising moderately sized effect. Comparable findings were obtained in a recent trial conducted by Jungquist and colleagues[24] in patients with chronic low-back pain, in which participants in an 8-week CBT-I program experienced clinically significant gains in sleep, but not reductions in pain, compared to the control subjects.

In a sample of patients with fibromyalgia, Edinger and coworkers[25] led a three-arm RCT testing the efficacy of a CBT-I package of sleep education, stimulus control, and sleep restriction against sleep hygiene instructions only (sleep hygiene group) and usual care. Immediately following treatment and at 6-month follow-up, the group that received CBT-I showed significantly greater improvements than those provided usual care, not only in the primary sleep diary measures but also in an objective, actigraphic estimate of sleep-onset latency. CBT-I was also associated with an improvement in mood. Consistent with findings from Currie et al,[23] CBT-I did not bring about a greater reduction in pain ratings than usual care. However, a

subgroup analysis demonstrated that patients randomized to the sleep hygiene group who self-adopted some of the CBT-I components experienced improvements in the pain measures relative to those in the usual care group. The authors attributed this unexpected relief in pain to the inclusion of "instructions to exercise…an intervention with proved efficacy for [fibromyalgia] management."

Equally positive treatment response was obtained for breast cancer survivors treated with CBT-I, with or without added components of fatigue management.[26,27] In particular, it is encouraging to note that in this patient group posttreatment improvements in sleep reports were associated with a significant reduction in anxiety and depression and an overall increase in quality of life.[27]

Taken together, despite the modest size of the pain-related insomnia literature, findings from existing RCTs attest to the feasibility of applying CBT-I to different subgroups of patients with chronic pain. In keeping with the outcomes achieved in patients with primary insomnia, the use of CBT-I in patients with pain-related insomnia is associated with a significant improvement in sleep continuity that can be maintained for 6 to 12 months. The effect of CBT-I on pain- and mood-related outcomes, however, is less conclusive, indicating the necessity to develop hybrid treatments that would cater to the needs of patients who suffer from both pain and insomnia.

## Identification and Management of Insomnia in the Dental Setting

Although most dentists do not receive training in behavioral interventions, dentists treating orofacial pain patients have an opportunity to detect and manage underlying sleep disorders such as sleep-disordered breathing, periodic limb movements, sleep bruxism, and chronic insomnia. Because the literature suggests high rates of primary sleep disorders, such as sleep-disordered breathing, in patients with TMDs (Smith MT, unpublished data, 2008) and fibromyalgia,[31] dentists should have a low threshold for referring patients for polysomnographic study, particularly if they report excessive daytime sleepiness, loud persistent snoring, or awakening gasping for breath.

Once the presence of sleep apnea or other underlying sleep disorders has been ruled out, insomnia may be an important intervention target in the orofacial pain patient's treatment plan. In general, insomnia is considered clinically significant if it

persists for a month or longer and the patient has trouble initiating or maintaining sleep 3 nights a week or more. Sometimes the problem presents primarily as nonrestorative sleep. For short-term acute insomnia, pharmacotherapy should be considered (see chapter 23).

Dentists practicing in a variety of settings may be able to significantly help many patients with insomnia by using basic sleep hygiene education tactics. Although studies of sleep hygiene as monotherapy for chronic insomnia indicate that sleep hygiene education is often an insufficient management approach, discussion of sleep hygiene principles may be an important first step to increase patients' awareness that insomnia is a serious problem that impacts their pain disorder and one that requires aggressive intervention; focusing treatment exclusively on pain management is unlikely to resolve a chronic insomnia problem.

Box 24-1 highlights basic principles of sleep hygiene, tailored to the orofacial pain patient. Typically, the most effective approach to sleep hygiene education involves a collaborative review of each principle with the aim of identifying one or two factors as a reasonable initial target. The approach is systematic, requires follow-up visits, and encourages changes that the patient has a relatively high chance of implementing and that can be progressively expanded.

In the event that sleep hygiene education proves ineffective, the dentist should strongly consider referring the patient to a BSM expert to formally evaluate the insomnia and determine appropriate interventions. Because most patients and physicians outside the sleep field are unaware of the short-and long-term efficacy of CBT-I, the dentist can play an extremely important role in educating the patient about this treatment option, which significantly increases the likelihood that the patient will follow up with a specialty appointment.

**Box 24-1 Basic principles of sleep hygiene***

**Maintain regular sleep-wake patterns and a consistent presleep routine (wind down)**

- Arise at the same time each day (7 days a week), regardless of sleep quantity or quality the night before.
- Avoid extended naps to compensate for poor nighttime sleep (limit naps to 30 minutes).
- Eat regular meals and avoid heavy, spicy foods for 2 hours prior to bed.

- Establish a relaxing bedtime ritual (discontinue stress-provoking activities well before bedtime).
- When unable to sleep, do not spend more than 15 to 20 minutes lying awake in bed. Get up and relax in a separate room. Return to bed only when sleepy. Repeat this routine as often as necessary. This avoids establishing your room as a cue for alertness and distress.

**Control environmental factors**

- Ensure adequate light exposure in the morning and into the late evening.
- Take a 30-minute hot bath, 60 to 90 minutes before bedtime (not closer to bedtime).
- Set a wake-up alarm and keep the clock face turned away. Do not focus on how much time is spent awake in the middle of the night.
- Keep the sleeping environment dark, quiet, comfortable, and slightly on the cool side.
- Use a white noise machine to screen out background noise and decrease arousal threshold.

**Exercise**

- Take regular exercise each day.
- Avoid vigorous exercise right before bed.

**Limit stimulating substances and know drug effects**

- Avoid smoking or nicotine several hours before bedtime, and never smoke in the middle of the night.
- Limit the use of alcohol at night because it fragments sleep as it is metabolized.
- Reduce caffeine use, and discontinue all caffeine 8 hours before bedtime (coffee, tea, soft drinks, chocolate, etc).
- Avoid over-the-counter sleep medication. Consult a sleep specialist about medication.
- Review the timing of all medications with your doctor because they may negatively impact sleep and might be substituted or scheduled differently.
- Ensure adequate pain medication at night if needed.

*Adapted from Smith and Haythornthwaite[32] with permission.

## *Who provides CBT-I ?*

Competent delivery of CBT-I requires a clinician who has a firm understanding of both sleep medicine and the science and practice of cognitive-behavioral treatments. Although CBT-I has traditionally been developed and provided by clinical psychologists, dentists are well positioned to acquire additional training in BSM, developing expert knowledge in the management of insomnia specifically linked to orofacial pain. Given the increasing demand for nonpharmacologic therapy for insomnia and the scarcity of credentialed BSM specialists, streamlining of the referral and treatment process is likely to enhance the quality of patient care. From a management point of view, the incorporation of CBT-I to diversify treatment options is likely to pay dividends because it clearly addresses a clinical need that is presently unmet. In cases where additional symptoms suggest that the insomnia may reflect broader difficulty with depression or anxiety, it is recommended that patients be referred to a BSM specialist with mental health qualifications.

Currently, in the United States, BSM training programs are accredited by the AASM. Certification in BSM by the AASM is open to any doctoral level licensed clinical practitioner who obtains the appropriate training and passes the board examination. This program may represent an underrecognized and yet important niche practice opportunity for dentists, particularly those already managing patients with sleep apnea via dental appliances. At the moment, completion of a formal BSM fellowship is not required, and training can be obtained with supervision of cases from an existing certified BSM specialist. The AASM has plans both to further develop a master's level certification program and to expand the doctoral level certification process. Further information about these programs is available on the AASM website.[33]

For practitioners simply needing to refer patients to a BSM specialist in the United States or Canada, AASM-accredited centers are required to maintain a relationship with a BSM specialist if they do not have one on staff. The location of accredited sleep centers in the United States and Canada can be found on the AASM website.[34]

## *What are the treatment effects of CBT-I, and how can they be optimized?*

CBT-I is designed to reverse the psychologic factors that contribute to the perpetuation of insomnia, and as such it has proven to be both effective and durable. While both hypnotic medications and CBT-I have demonstrated efficacy in restoring normal sleep, neither treatment has been consistently shown to significantly reduce pain or improve mood in pain patients.[23,35]

Several explanations are likely. First, few studies have been specifically designed to determine whether improving the sleep of patients with chronic pain also alleviates pain or improves mood and daytime functioning. More research powered to answer these questions is needed. Second, of the few small studies that have measured outcomes other than sleep, most have a follow-up period of 6 months or less. Significant sleep-related improvement in pain and mood may require time to emerge, and sleep-related treatment gains associated with CBT-I often increase over the long run and are maintained at follow-ups as long as 2 years. Third, sleep disturbance is one of many factors that maintain distress and pain. CBT-I, although it has some overlap with CBT for pain management (eg, relaxation; see Table 24-1), does not address a variety of fundamental psychophysiologic processes linked to the persistence of pain (eg, catastrophizing, hypervigilance, mood disturbance, safety-seeking behaviors, muscle tension, and inactivity). It therefore seems unrealistic to expect robust short-term improvement in pain following CBT-I unless other pain-related factors are simultaneously addressed. Future research is required to ascertain if hybrid treatment for insomnia with additional pain interventions can achieve dual therapeutic functions, treating both sleep and pain.

The clinician should also consider adapting the delivery format of CBT-I to maximize the compatibility of the intervention to the dental setting. In the primary insomnia literature, there is some evidence suggesting that four individual, biweekly sessions represent the optimal dosing for CBT-I, compared to 1, 2, or 8 weekly sessions.[36] There is also some evidence suggesting that small-group CBT-I conducted in sleep clinics or general medical practices is just as effective as individual therapy.[22,37] If CBT-I is to be offered to patients simultaneously with sleep medication, a sequence beginning with a combined treatment followed by CBT-I alone may produce the best outcome.[38,39]

## *Who is a suitable candidate for CBT-I?*

In spite of some potential contraindications (see Table 24-1), the prescription of CBT-I in the pain population rarely results in reports of adverse effects.[23,40] The

absence of adverse effects, however, does not imply that every patient with an insomnia complaint is indicated for CBT-I, which has been developed to treat moderate to severe chronic insomnia. The success of treatment requires some level of commitment on the patient's part. Those patients showing symptoms of other sleep disorders, such as sleep apnea, periodic limb movement disorder, or narcolepsy, should be referred to a sleep clinic for evaluation by a specialist (see chapter 3). Similarly, CBT-I is not indicated for people with acute insomnia (of less than 1 month) who may derive greater benefit from hypnotic medications. For these patients, the fast action of the drugs may provide more timely relief and thus may prevent the perpetuating factors of insomnia from germinating in the first place.

Given that CBT-I is a collaborative form of treatment, individuals who do not share the cognitive-behavioral model of insomnia and those who do not adhere to the sleep restriction regimen are less likely to draw the same amount of benefit than those who do. Therefore, when the intervention strategy is selected, the patient's treatment preference and willingness and ability to engage in treatment should be taken into account as well. The reader is referred to Smith and Perlis[41] for a patient-screening heuristic and a more detailed discussion on this topic.

## Conclusion

As a treatment approach, CBT-I has garnered considerable empirical support as an efficacious treatment for primary insomnia. When applied to pain-related insomnia, CBT-I has been found to be equally successful in restoring normal sleep. Dentists, as frontline professionals dealing with a large number of patients suffering from both pain and sleep disturbance, are encouraged to promote sleep hygiene education, refer patients to BSM specialists (especially when underlying psychopathology is suspected), and consider taking on further BSM training to incorporate CBT-I principles into their clinical practice. This should contribute to the process of customization of CBT-I in the treatment of dental patients with insomnia, improving the overall quality of patient care.

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# CONCLUSION

## SCIENTIFIC AND CLINICAL FRONTIERS

As the general public better recognizes the interactions among sleep-disordered breathing (SDB), sleep bruxism (SB), sleep and orofacial pain, craniofacial form, and overall health, dentists are expected to become proficient in a broader range of health issues. In direct collaboration with physicians, dentists often identify patients who are likely to have a sleep disorder. Based on their experience with the fabrication and use of oral appliances and their skills in evaluation of jaw position, oral mucosa, craniofacial morphology, tooth movement, and jaw muscle pain, dentists are ideally suited to provide several forms of therapy in this field.

## Sleep-Disordered Breathing

Correct diagnosis of the different types of sleep-related breathing disorders is essential to identifying the best therapeutic option. Assessment for any type of sleep disorder (see chapter 3) requires a thorough clinical evaluation of the patient to determine the likelihood of the condition as well as overnight testing to demonstrate the presence of SDB before treatment is initiated. Obstructive sleep apnea (OSA) has been associated with serious long-term adverse health consequences such as hypertension, metabolic dysfunction, cardiovascular disease, neurocognitive deficits, and motor vehicle accidents (see chapter 6). Polysomnography remains the most common test for a definitive diagnosis (see chapter 7).

Portable sleep studies may be useful for confirming disease in patients with evidence of OSA, but their limitations are well documented. The value of portable monitoring as a titration aid and to assess treatment responses deserves further verification. Both static and dynamic imaging techniques have been used to examine the structure and function of the upper airway during wakefulness and sleep. The lateral pharyngeal walls, in addition to the tongue and soft palate, affect upper

airway size. Although the cause-and-effect relationship between craniofacial morphology and OSA remains to be proven, growth factors and anomalies in oropharyngeal development that predispose to upper airway obstruction may contribute to the disorder. Advanced imaging modalities such as computed tomography and magnetic resonance imaging can assist in the assessment of such patients, but the actual site of airway obstruction during sleep is extremely difficult to capture (see chapter 8). However, none of these tools has been proven to completely replace the information provided by polygraphic recordings during sleep.

Therapeutic options and treatment outcomes in the field of SDB continue to improve with time (see chapters 9 and 10). Randomized controlled clinical trials have indicated that oral appliances may be used as first-line therapy for the treatment of mild to moderate OSA. Patients who cannot tolerate nasal continuous positive airway pressure (CPAP) or who prefer oral appliance therapy may use an oral appliance, provided that a sleep study has confirmed an adequate therapeutic response to the treatment. Side effects are usually mild and transient but may influence the length of acclimatization required to complete the treatment. Occlusal changes are common, especially over the long term, and warrant careful monitoring.

Future studies are needed to compare the effectiveness of different types of oral appliances and different design and advancement features. The precise indications, complication rates, and reasons for treatment failure must be identified for each oral appliance. Only when the actual mechanisms of action are fully understood can more effective appliances be developed. Prospective validation studies are required to evaluate predictors of treatment outcome, and more research is needed to determine optimal titration protocols to increase the effectiveness of oral appliances and to decrease titration times. A compliance monitor that will allow an objective determination of the efficacy and safety of oral appliances is required.

CPAP remains the mainstay for effective treatment of significant OSA, but further research is required to define effective solutions to improve compliance. In specific patients, oral appliances may not be as effective as CPAP. In particular, oral appliances are less effective in patients with significant hypoxemia or morbid obesity. They are most effective in younger, thinner patients with mild-to-moderate OSA. However, oral appliances are not the preferred initial treatment for patients with severe or highly symptomatic OSA, in part because of the time it may take to titrate the appliance.

There is growing evidence of the beneficial role of alternative therapies (eg, positional training using sensors, t-shirts with balls or tubes, or specific pillow

types), and further research is required to define the subsets of patients for whom each of these therapies is most effective. In addition, combination (CPAP and oral appliance) and adjunctive therapies have not yet been adequately tested.

## Sleep Bruxism

The etiology of SB is not well understood but is believed to include both behavioral and physiologic factors (see chapters 12 and 15). Evidence-based studies are necessary to determine whether currently identified risk factors prevent or mitigate SB. To date, there are no rapid and reliable clinical diagnostic tests that combine diagnostic validity and cost effectiveness (see chapter 14). The exact pathophysiology of SB is not known, but current evidence suggests that jaw movement and tooth grinding appear secondary to repetitive brief arousals during sleep. There may also be a genetic component to SB, as there is to SDB.

Clinicians must be aware that a proportion of SDB patients may actually exhibit worsening symptoms when a traditional occlusal splint is used (see chapter 17). Before deciding the most appropriate management strategy for SB in adults, the clinician should carefully consider the actual or expected damage caused by SB, the anticipated side effects of therapy, and contraindications. Pediatric SB is poorly managed currently because of the lack of knowledge and evidence about its risk factors, pathophysiology, and consequences (see chapters 16 and 17).

## Sleep-Pain Interactions

Patients with orofacial pain often complain of insufficient sleep duration and frequent awakenings. Conversely, SDB may be present in a substantial number of patients with temporomandibular disorders. Temporomandibular disorders are commonly found in patients with other idiopathic pain disorders, particularly fibromyalgia and headache disorders. The complex factors that lead to the development of chronic pain are multiple and poorly understood (see chapters 18 to 21). The opioid, monoaminergic, immune, and melatonin systems are all affected by a loss of sleep. A better understanding of the triad of sleep disturbance, pain, and analgesia remains a challenge for the management of patients suffering from acute and chronic pain, sleep disorders, or both.

The management of orofacial pain and sleep disturbances is complex and requires careful evaluation, appropriate diagnosis, and knowledge of pharmacologic and nonpharmacologic interventions, including behavioral and physical therapies (see chapters 22 to 24). The development of pharmacologic agents designed to relieve pain without side effects unfavorable to sleep is particularly needed (eg, opioid use may be harmful in some OSA patients). Sleep management therapies, including information and counseling as well as pharmacologic options, should be offered to patients with orofacial pain. Conversely, outcome measures of orofacial pain should also include measures of sleep quality.

Cognitive-behavioral therapy is a viable treatment alternative as a first-line intervention for primary insomnia. Dentists, as frontline professionals dealing with a large number of patients suffering from both pain and sleep disturbances, are encouraged to promote sleep hygiene education, refer patients to behavioral sleep medicine specialists, and consider taking on further behavioral sleep medicine training (see chapter 24).

## Summary

The field of dental sleep medicine is relatively new and has made major research and clinical advances in the past decade. However, much of the currently available evidence comes from observational cohort or experimental (mechanistic) studies, which have many deficiencies, including small sample size, selection bias, and a lack of control subjects. These issues can and will be better addressed in the future by longitudinal and randomized controlled trials of adequate sample size that are controlled for the influence of known risk factors.

As a larger number of dentists are adequately trained in the field of dental sleep medicine and as the general public and the medical profession demand more from dentistry, professional services for patients with sleep disorders will continue to expand and improve. Dentists who become involved in sleep medicine are often surprised at how grateful SDB patients are after only a few nights' uninterrupted sleep and the subsequent restoration of adequate sleep. The ability to substantially improve the quality of a patient's life can be a very rewarding experience for health care providers working in this interdisciplinary field.

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