Sleep Medicine

(Study of Sleep Diseases and Disorders)

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Chapter 1

Sleep Medicine

An example of a sleep diary layout.

Sleep medicine is a medical specialty or subspecialty devoted to the diagnosis and therapy of sleep disturbances and disorders. From the middle of the 20th century, research has provided increasing knowledge and answered many questions about sleep-wake functioning. The rapidly evolving field has become a recognized medical subspecialty in some countries. Dental sleep medicine also qualifies for board certification in some countries. Properly organized, minimum 12-month, postgraduate training programs are still being defined in the United States. In some countries, the sleep researchers and the doctors who treat patients may be the same people.

The first sleep clinics in the United States were established in the 1970s by interested doctors and technicians; the study, diagnosis and treatment of obstructive sleep apnea were their first tasks. As late as 1999, virtually any American doctor, with no specific training in sleep medicine, could open a sleep laboratory.

Disorders and disturbances of sleep are widespread and can have significant consequences for affected individuals as well as economic and other consequences for society. The US National Transportation Safety Board has, according to Dr. Charles

Czeisler, member of the Institute of Medicine and Director of the Harvard University Medical School Division of Sleep Medicine at Brigham and Women's Hospital, discovered that the leading cause of fatal-to-the-driver heavy truck crashes is fatigue-related (fatigue – 31%, alcohol and other drug use – 29%), and sleep deprivation has been a significant factor in dramatic accidents, such as the Exxon Valdez oil spill, the nuclear incidents at Chernobyl and Three Mile Island and the explosion of the space shuttle *Challenger*.

Scope and classification

Competence in sleep medicine requires an understanding of a plethora of very diverse disorders, many of which present with similar symptoms such as excessive daytime sleepiness, which, in the absence of volitional sleep deprivation, "is almost inevitably caused by an identifiable and treatable sleep disorder," such as sleep apnea, narcolepsy, idiopathic central nervous system (CNS) hypersomnia, Kleine-Levin syndrome, menstrual-related hypersomnia, idiopathic recurrent stupor, or circadian rhythm disturbances. Another common complaint is insomnia, a set of symptoms that can have many causes, physical and mental. Management in the varying situations differs greatly and cannot be undertaken without a correct diagnosis.

ICSD, *The International Classification of Sleep Disorders*, was restructured in 1990, in relation to its predecessor, to include only one code for each diagnostic entry and to classify disorders by pathophysiologic mechanism, as far as possible, rather than by primary complaint. Training in sleep medicine is multidisciplinary, and the present structure was chosen to encourage a multidisciplinary approach to diagnosis. Sleep disorders often do not fit neatly into traditional classification; differential diagnoses cross medical systems. Minor revisions and updates to the ICSD were made in 1997 and in following years. The present classification system in fact follows the groupings suggested by Nathaniel Kleitman, the "father of sleep research," in his seminal 1939 book *Sleep and Wakefulness*.

The revised ICSD, ICSD-R, placed the primary sleep disorders in the subgroups (1) dyssomnias, which include those that produce complaints of insomnia or excessive sleepiness, and (2) the parasomnias, which do not produce those primary complaints but intrude into or occur during sleep. A further subdivision of the dyssomnias preserves the integrity of circadian rhythm sleep disorders, as was mandated by about 200 doctors and researchers from all over the world who participated in the process between 1985–1990. The last two subgroups were (3) the medical or psychiatric sleep disorder section and (4) the proposed new disorders section. The authors found the heading "medical or psychiatric" less than ideal but better than the alternative "organic or non-organic," which seemed more likely to change in the future. Detailed reporting schemes aimed to provide data for further research. A second edition, called ICSD-2, was published in 2005.

MeSH, *Medical Subject Headings*, a service of the US National Library of Medicine and the National Institutes of Health, uses similar broad categories: (1) dyssomnias, including narcolepsy, apnea, and the circadian rhythm sleep disorders, (2) parasomnias, which

include, among others, bruxism (tooth-grinding), sleepwalking and bedwetting, and (3) sleep disorders caused by medical or psychiatric conditions. The system used produces "trees," approaching each diagnosis from up to several angles such that each disorder may be known by several codes.

DSM-IV-TR, the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*, using the same diagnostic codes as the *International Statistical Classification of Diseases and Related Health Problems* (ICD), divides sleep disorders into three groups: (1) primary sleep disorders, both the dyssomnias and the parasomnias, presumed to result from an endogenous disturbance in sleep-wake generating or timing mechanisms, (2) those secondary to mental disorders and (3) those related to a general medical condition or substance abuse.

Recent thinking opens for a common cause for mood and sleep disorders occurring in the same patient; a 2010 review states that, in humans, "single nucleotide polymorphisms in *Clock* and other clock genes have been associated with depression" and that the "evidence that mood disorders are associated with disrupted or at least inappropriately timed circadian rhythms suggests that treatment strategies or drugs aimed at restoring 'normal' circadian rhythmicity may be clinically useful."

History

A 16th-century physician wrote that many laborers dozed off exhausted at the start of each night; sexual intercourse with their wives typically occurring in the *watching period*, after a recuperative first sleep. Anthropologists find that isolated societies without electric light sleep in a variety of patterns; seldom do they resemble our modern habit of sleeping in one single eight-hour bout. Much has been written about dream interpretation, from biblical times to Freud, but sleep itself was historically seen as a passive state of not-awake.

The concept of sleep medicine belongs to the second half of the 20th century. Due to the rapidly increasing knowledge about sleep, including the growth of the research field chronobiology from about 1960 and the discoveries of REM sleep (1952–53) and sleep apnea (first described in the medical literature in 1965), the medical importance of sleep was recognized. The medical community began paying more attention than previously to primary sleep disorders, such as sleep apnea, as well as the role and quality of sleep in other conditions. By the 1970s in the US, and in many western nations within the two following decades, clinics and laboratories devoted to the study of sleep and the treatment of its disorders had been founded. Most sleep doctors were primarily concerned with apnea; some were experts in narcolepsy. There was as yet nothing to restrict the use of the title "sleep doctor," and a need for standards arose.

Basic medical training has paid little attention to sleep problems; according to Benca in her review *Diagnosis and Treatment of Chronic Insomnia* (2005), most doctors are "not well trained with respect to sleep and sleep disorders," and a survey in 1990–91 of 37 American medical schools showed that sleep and sleep disorders were "covered" in less

than two (2) hours of total teaching time, on average. Benca's review cites a 2002 survey by Papp et al. of more than 500 primary care physicians who self-reported their knowledge of sleep disorders as follows: Excellent – 0%; Good – 10%, Fair – 60%; and Poor – 30%. The review of more than 50 studies indicates that both doctors and patients appear reluctant to discuss sleep complaints, in part because of perceptions that treatments for insomnia are ineffective or associated with risks, and:

> “ Physicians may avoid exploring problems such as sleep difficulties in order to avoid having to deal with issues that could take up more than the normal allotted time for a patient. ”

Also, an editorial in the American College of Chest Physicians' (pulmonologists') journal *CHEST* in 1999 was quite concerned about the *Conundrums in Sleep Medicine*. The author, then chair of her organization's Sleep Section, asked "What is required to set up a sleep laboratory? Money and a building! Anyone can open a sleep laboratory, and it seems that just about everyone is." On the accreditation process for sleep laboratories, she continues: "This accreditation, however, is currently not required by most states, or more importantly, by most insurance carriers for reimbursements... There is also an American Board of Sleep Medicine (ABSM) that certifies individuals as sleep specialists. This certification presumably makes those individuals more qualified to run a sleep laboratory; however, the certification is not required to run a laboratory or to read sleep studies." Her concern at the turn of the century was:

> “ Not all patients with hypersomnia have sleep apnea, and other diagnoses may be missed if the physician is only trained to diagnose and treat sleep apnea. Also, when a physician runs a sleep laboratory, they are "assumed" to be a sleep expert and are asked to evaluate and treat all types of sleep disorders when they are not adequately trained to do so. ”

In the UK, knowledge of sleep medicine and possibilities for diagnosis and treatment seem to lag. Guardian.co.uk quotes the director of the Imperial College Healthcare Sleep Centre: "One problem is that there has been relatively little training in sleep medicine in this country – certainly there is no structured training for sleep physicians." The Imperial College Healthcare site shows attention to obstructive sleep apnea syndrome (OSA) and very few other disorders, specifically not including insomnia.

Training and certification

Worldwide

The World Federation of Sleep Research & Sleep Medicine Societies (WFSRSMS) was founded in 1987. As its name implies, members are concerned with basic and clinical research as well as medicine. Member societies in the Americas are the American

Academy of Sleep Medicine (AASM), the Sleep Research Society of the United States (SRS), the Canadian Sleep Society (CSS) and the Federation of Latin American Sleep Societies (FLASS). WFSRSMS publishes the *Journal of Sleep Research*, the *Journal of Clinical Sleep Medicine*, *SLEEP* and *Sleep and Biological Rhythms* and promotes both sleep research and physician training and education.

Africa

The Colleges of Medicine of South Africa (CMSA) provide the well-defined specialty Diploma in Sleep Medicine of the College of Neurologists of South Africa: DSM(SA), which was first promulgated by the Health Professions Council in 2007. The newly formed South African Society of Sleep Medicine (SASSM) was launched at its inaugural congress in February 2010. The society's membership is diverse; it includes general practitioners, ENT surgeons, pulmonologists, cardiologists, endocrinologists and psychiatrists.

Asia

WFSRSMS members in Asia include the Australasian Sleep Association (ASA) of New Zealand and Australia and the Asian Sleep Research Society (ASRS), an umbrella organization for the societies of several Asian nations.

Europe

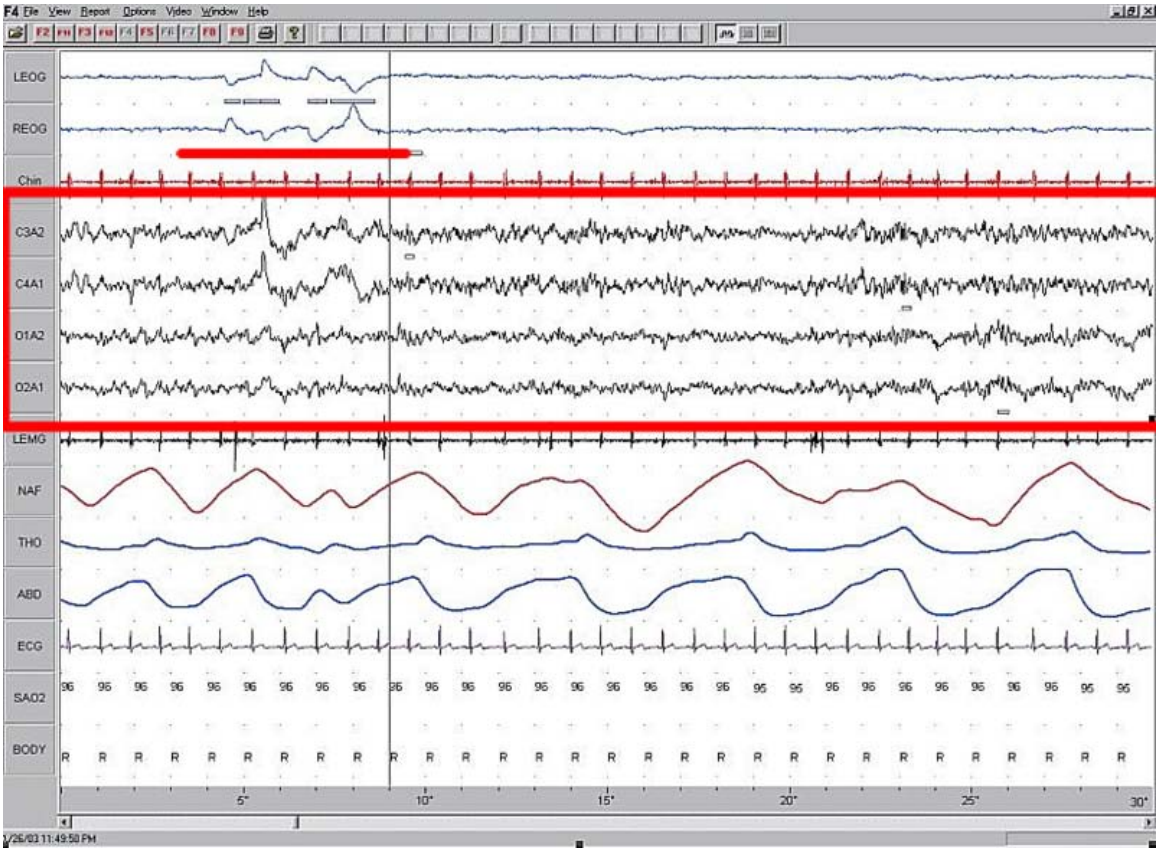
The European Sleep Research Society (ESRS) is a member of the WFSRSMS. The Assembly of National Sleep Societies (ANSS), which includes both medical and scientific organizations from 26 countries as of 2007, is a formal body of the ESRS. The ESRS has published *European Accreditation Guidelines for SMCs* (Sleep Medicine Centres), the first of several proposed guidelines to coordinate and promote sleep science and medicine in Europe.

United States

The American Academy of Sleep Medicine (AASM), founded in 1978, administered the certification process and sleep medicine examination for doctors until 1990. Its independent daughter entity the American Board of Sleep Medicine (ABSM) was incorporated in 1991 and took over the aforementioned responsibilities. As of 2007, the ABSM ceased administering its examination, as it conceded that an examination process recognized by the American Board of Medical Specialties (ABMS) was advantageous to the field. Candidates who passed the ABSM exam in 1978–2006 retain lifetime certification as Diplomates of that organization.

The American Board of Psychiatry and Neurology (ABPN), and the corresponding boards of Internal Medicine, of Pediatrics, and of Otolaryngology (ear, nose and throat, ENT) now administer collectively the Sleep Medicine Certification exam for their members. Each board supervises the required 12 months of formal training for its

candidates, while the exam is administered to all of them at the same time in the same place. For the first five years, 2007–2011, during "grandfathering," there is a "practice pathway" for ABSM certified specialists. Additional, coordinated requirements are to be added after 2011. The ABPN provides information about the pathways, requirements and the exam on its website.



Detail from a polysomnogram, one of the tools used by specialists in sleep medicine

Sleep medicine is now a recognized subspecialty within internal medicine, family medicine, pediatrics, otolaryngology, psychiatry and neurology in the US. Certification in Sleep Medicine by the several "Member Boards" of the ABMS shows that the specialist:

> “ has demonstrated expertise in the diagnosis and management of clinical conditions that occur during sleep, that disturb sleep, or that are affected by disturbances in the wake–sleep cycle. This specialist is skilled in the analysis and interpretation of comprehensive polysomnography, and well-versed in emerging research and management of a sleep laboratory. ”

Pulmonologists, already subspecialists within internal medicine, may be accepted to sit for the board and be certified in Sleep Medicine after just a six-month fellowship,

building on their knowledge of sleep-related breathing problems, rather than the usual twelve-month fellowship required of other specialists.

Sleep dentistry (bruxism, snoring and sleep apnea), while not recognized as one of the nine dental specialties, qualifies for board-certification by the American Board of Dental Sleep Medicine (ABDSM). The resulting Diplomate status is recognized by the AASM, and these dentists are organized in the Academy of Dental Sleep Medicine (USA). The qualified dentists collaborate with sleep doctors at accredited sleep centers and can provide several types of oral appliances or upper airway surgery to treat or manage sleep-related breathing disorders as well as tooth-grinding and clenching.

Laboratories for sleep-related breathing disorders are accredited by the AASM, and are required to follow the *Code of Medical Ethics* of the American Medical Association. The new and very detailed *Standards for Accreditation* are available online. Sleep disorder centers, or clinics, are accredited by the same body, whether hospital-based, university-based or "freestanding"; they are required to provide testing and treatment for *all* sleep disorders and to have on staff a sleep specialist who has been certified by the American Board of Sleep Medicine and otherwise meet similar standards.

Diagnostic methods

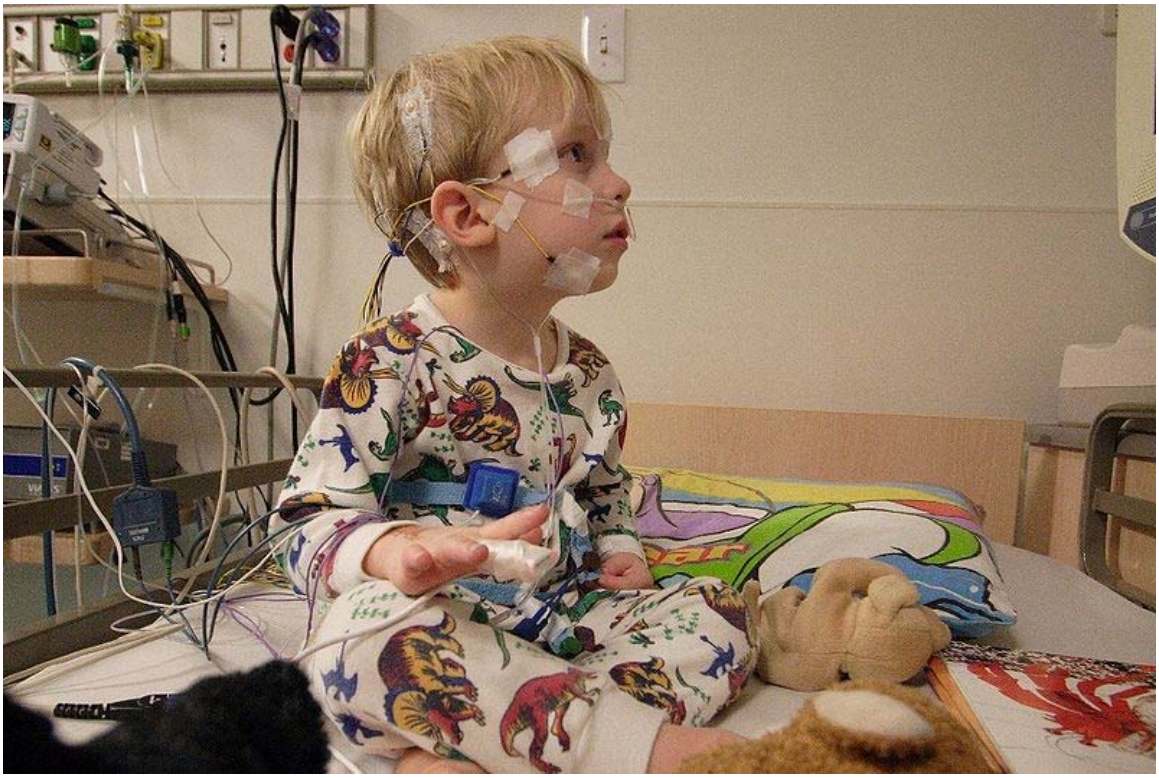
The taking of a thorough medical history while keeping in mind alternative diagnoses and the possibility of more than one ailment in the same patient is the first step. Symptoms for very different sleep disorders may be similar and it must be determined whether any psychiatric problems are primary or secondary.

The patient history includes previous attempts at treatment and coping and a careful medication review. Differentiation of transient from chronic disorders and primary from secondary ones influences the direction of evaluation and treatment plans.

The Epworth Sleepiness Scale (ESS), designed to give an indication of sleepiness and correlated with sleep apnea, or other questionnaires designed to measure excessive daytime sleepiness, are diagnostic tools that can be used repeatedly to measure results of treatment.

A sleep diary, also called sleep log or sleep journal, kept by a patient at home for at least two weeks, while subjective, may help determine the extent and nature of sleep disturbance and the level of alertness in the normal environment. A parallel journal kept by a parent or bed partner, if any, can also be helpful. Sleep logs also can be used for self-monitoring and in connection with behavioral and other treatment. The image at the top of this page, with nighttime in the middle and the weekend in the middle, shows a layout that can aid in noticing trends

An actigraph unit is a motion-sensing device worn on the wrist, generally for one week. It gives a gross picture of sleep-wake cycles and is often used to verify the sleep diary. It is cost-efficient when full polysomnography is not required.



Pediatric polysomnography

Polysomnography is performed in a sleep laboratory while the patient sleeps, preferably at his or her usual sleeping time. The polysomnogram (PSG) objectively records sleep stages and respiratory events. It shows multiple channels of electroencephalogram (EEG), electrooculogram (EOG), electrocardiogram (ECG), nasal and oral airflow, abdominal, chest and leg movements and blood oxygen levels. A single part of a polysomnogram is sometimes measured at home with portable equipment, for example oximetry, which records blood oxygen levels throughout the night. Polysomnography is not routinely used in the evaluation of patients with insomnia or circadian rhythm disorders, except as needed to rule out other disorders. It will usually be a definitive test for sleep apnea.

A Multiple Sleep Latency Test (MSLT) is often performed during the entire day after polysomnography while the electrodes and other equipment are still in place. The patient is given nap opportunities every second hour; the test measures the number of minutes it takes from the start of a daytime nap period to the first signs of sleep. It is a measure of daytime sleepiness; it also shows whether REM sleep is achieved in a short nap, a typical indication of narcolepsy.

Imaging studies may be performed if a patient is to be evaluated for neurodegenerative disease or to determine the obstruction in obstructive sleep apnea.

Treatments

When sleep complaints are secondary to pain, other medical or psychiatric diagnoses, or substance abuse, it may be necessary to treat both the underlying cause and the sleep problems.

When the underlying cause of sleep problems is not immediately obvious, behavioral treatments are usually the first suggested. These range from patient education about sleep hygiene to cognitive behavioral therapy (CBT). Studies of both younger and older adults have compared CBT to medication and found that CBT should be considered a first-line and cost-effective intervention for chronic insomnia, not least because gains may be maintained at long-term follow-up. Sleep physicians and psychologists, at least in the US, are not in agreement about who should perform CBT nor whether sleep centers should be required to have psychologists on staff. Behavioral therapies include progressive relaxation, stimulus control (to reassociate the bed with sleepiness), limiting time-in-bed to increase sleep efficiency and debunking misconceptions about sleep.

Walgreens brand melatonin.

Pharmacology is necessary for some conditions. Medication may be useful for acute insomnia and for some of the parasomnias. It is almost always needed, along with scheduled short naps and close follow-up, in the treatment of narcolepsy and idiopathic hypersomnia.

Chronic circadian rhythm disorders, the most common of which is delayed sleep phase disorder, may be managed by specifically timed bright light therapy, timed oral administration of the hormone melatonin, and/or chronotherapy. Stimulants may also be prescribed. When these therapies are unsuccessful, counseling may be indicated to help a person adapt to and live with the condition. People with these disorders who have chosen a lifestyle in conformity with their sleeping schedules have no need of treatment, though

they may need the diagnosis in order to avoid having to meet for appointments or meetings during their sleep time.

A CPAP machine.

Continuous positive airway pressure (CPAP) machines and oral appliances are used nightly at home to manage sleep-related breathing disorders such as apnea. Occasionally, upper airway surgery is indicated. In mild cases in obese people, weight reduction may be sufficient. The treatments prevent airway collapse, which interrupts breathing during sleep.

Chapter 2

Sleep Disorder

Sleep disorder	
ICD-10	F51., G47.
ICD-9	307.4, 327, 780.5
DiseasesDB	26877
eMedicine	med/609
MeSH	D012893

A **sleep disorder** (somnipathy) is a medical disorder of the sleep patterns of a person or animal. Some sleep disorders are serious enough to interfere with normal physical, mental and emotional functioning. A test commonly ordered for some sleep disorders is the polysomnography.

Disruptions in sleep can be caused by a variety of issues, from teeth grinding (bruxism) to night terrors. When a person suffers from difficulty in sleeping with no obvious cause, it is referred to as insomnia. In addition, sleep disorders may also cause sufferers to sleep excessively, a condition known as hypersomnia. Management of sleep disturbances that are secondary to mental, medical, or substance abuse disorders should focus on the underlying conditions.

Common disorders

The most common sleep disorders include:

- Primary insomnia: Chronic difficulty in falling asleep and/or maintaining sleep when no other cause is found for these symptoms.

- Bruxism: Involuntarily grinding or clenching of the teeth while sleeping.
- Delayed sleep phase syndrome (DSPS): inability to awaken and fall asleep at socially acceptable times but no problem with sleep maintenance, a disorder of circadian rhythms. (Other such disorders are advanced sleep phase syndrome (ASPS), non-24-hour sleep-wake syndrome (Non-24), and irregular sleep wake rhythm, all much less common than DSPS, as well as the transient jet lag and shift work sleep disorder.)
- Hypopnea syndrome: Abnormally shallow breathing or slow respiratory rate while sleeping.
- Narcolepsy: Excessive daytime sleepiness (EDS) often culminating in falling asleep spontaneously but unwillingly at inappropriate times.
- Cataplexy: a sudden weakness in the motor muscles that can result in collapse to the floor.
- Night terror: *Pavor nocturnus*, sleep terror disorder: abrupt awakening from sleep with behavior consistent with terror.
- Parasomnias: Disruptive sleep-related events involving inappropriate actions during sleep; sleep walking and night-terrors are examples.
- Periodic limb movement disorder (PLMD): Sudden involuntary movement of arms and/or legs during sleep, for example kicking the legs. Also known as nocturnal myoclonus..
- Rapid eye movement behavior disorder (RBD): Acting out violent or dramatic dreams while in REM sleep.
- Restless legs syndrome (RLS): An irresistible urge to move legs. RLS sufferers often also have PLMD.
- Situational circadian rhythm sleep disorders: shift work sleep disorder (SWSD) and jet lag.
- Sleep Apnea, and mostly Obstructive sleep apnea: Obstruction of the airway during sleep, causing lack of sufficient deep sleep; often accompanied by snoring. Other forms of sleep apnea are less common.
- Sleep paralysis: is characterized by temporary paralysis of the body shortly before or after sleep. Sleep paralysis may be accompanied by visual, auditory or tactile hallucinations. Not a disorder unless severe. Often seen as part of Narcolepsy.
- Sleepwalking or *somnambulism*: Engaging in activities that are normally associated with wakefulness (such as eating or dressing), which may include walking, without the conscious knowledge of the subject.
- Nocturia: A frequent need to get up and go to the bathroom to urinate at night. It differs from Enuresis, or bed-wetting, in which the person does not arouse from sleep, but the bladder nevertheless empties.
- Somniphobia: a dread of sleep.

Types

- Dyssomnias - A broad category of sleep disorders characterized by either hypersomnolence or insomnia. The three major subcategories include intrinsic (i.e., arising from within the body), extrinsic (secondary to environmental

conditions or various pathologic conditions), and disturbances of circadian rhythm. MeSH
    - Insomnia
    - Narcolepsy
    - Sleep Disordered Breathing (SDB), including (non exhaustive):
        - Several types of Sleep apnea
        - Snoring
        - Upper airway resistance syndrome
    - Restless leg syndrome
    - Periodic limb movement disorder
    - Hypersomnia
        - Recurrent hypersomnia - including Kleine-Levin syndrome
        - Posttraumatic hypersomnia
        - "Healthy" hypersomnia
    - Circadian rhythm sleep disorders
        - Delayed sleep phase syndrome
        - Advanced sleep phase syndrome
        - Non-24-hour sleep-wake syndrome
- Parasomnias - A category of sleep disorders that involve abnormal and unnatural movements, behaviors, emotions, perceptions, and dreams in connection with sleep.
    - REM sleep behaviour disorder
    - Sleep terror
    - Sleepwalking (or somnambulism)
    - Bruxism (Tooth-grinding)
    - Bedwetting or sleep enuresis.
    - Sleep talking (or somniloquy)
    - Sleep sex (or sexsomnia)
    - Exploding head syndrome - Waking up in the night hearing loud noises.
- Medical or Psychiatric Conditions that may produce sleep disorders
    - Psychosis (such as Schizophrenia)
    - Mood disorders
        - Depression
        - Anxiety
    - Panic
    - Alcoholism
- Sleeping sickness - a parasitic disease which can be transmitted by the Tsetse fly.

General principles of treatment

Treatments for sleep disorders generally can be grouped into four categories:

- behavioral/ psychotherapeutic treatments
- rehabilitation/management
- medications
- other somatic treatments

None of these general approaches is sufficient for all patients with sleep disorders. Rather, the choice of a specific treatment depends on the patient's diagnosis, medical and psychiatric history, and preferences, as well as the expertise of the treating clinician. Often, behavioral/psychotherapeutic and pharmacological approaches are not incompatible and can effectively be combined to maximize therapeutic benefits. Management of sleep disturbances that are secondary to mental, medical, or substance abuse disorders should focus on the underlying conditions.

Medications and somatic treatments may provide the most rapid symptomatic relief from some sleep disturbances. Some disorders, such as narcolepsy, are best treated pharmacologically. Others, such as chronic and primary insomnia, may be more amenable to behavioral interventions, with more durable results.

Chronic sleep disorders in childhood, which affect some 70% of children with developmental or psychological disorders, are under-reported and under-treated. Sleep-phase disruption is also common among adolescents, whose school schedules are often incompatible with their natural circadian rhythm. Effective treatment begins with careful diagnosis using sleep diaries and perhaps sleep studies. Modifications in sleep hygiene may resolve the problem, but medical treatment is often warranted.

Special equipment may be required for treatment of several disorders such as obstructive apnea, the circadian rhythm disorders and bruxism. In these cases, when severe, an acceptance of living with the disorder, however well managed, is often necessary.

Some sleep disorders have been found to compromise glucose metabolism.

Sleep medicine

Due to rapidly increasing knowledge about sleep in the 20th century, including the discovery of REM sleep and sleep apnea, the medical importance of sleep was recognized. The medical community began paying more attention than previously to primary sleep disorders, such as sleep apnea, as well as the role and quality of sleep in other conditions. By the 1970s in the USA, clinics and laboratories devoted to the study of sleep and sleep disorders had been founded, and a need for standards arose.

Sleep Medicine is now a recognized subspecialty within internal medicine, family medicine, pediatrics, otolaryngology, psychiatry and neurology in the United States. Certification in Sleep Medicine shows that the specialist:

"has demonstrated expertise in the diagnosis and management of clinical conditions that occur during sleep, that disturb sleep, or that are affected by disturbances in the wake-sleep cycle. This specialist is skilled in the analysis and interpretation of comprehensive polysomnography, and well-versed in emerging research and management of a sleep laboratory."

Competence in sleep medicine requires an understanding of a myriad of very diverse disorders, many of which present with similar symptoms such as excessive daytime sleepiness, which, in the absence of volitional sleep deprivation, "is almost inevitably caused by an identifiable and treatable sleep disorder", such as sleep apnea, narcolepsy, idiopathic central nervous system (CNS) hypersomnia, Kleine-Levin syndrome, menstrual-related hypersomnia, idiopathic recurrent stupor, or circadian rhythm disturbances. Another common complaint is insomnia, a set of symptoms which can have a great many different causes, physical and mental. Management in the varying situations differs greatly and cannot be undertaken without a correct diagnosis.

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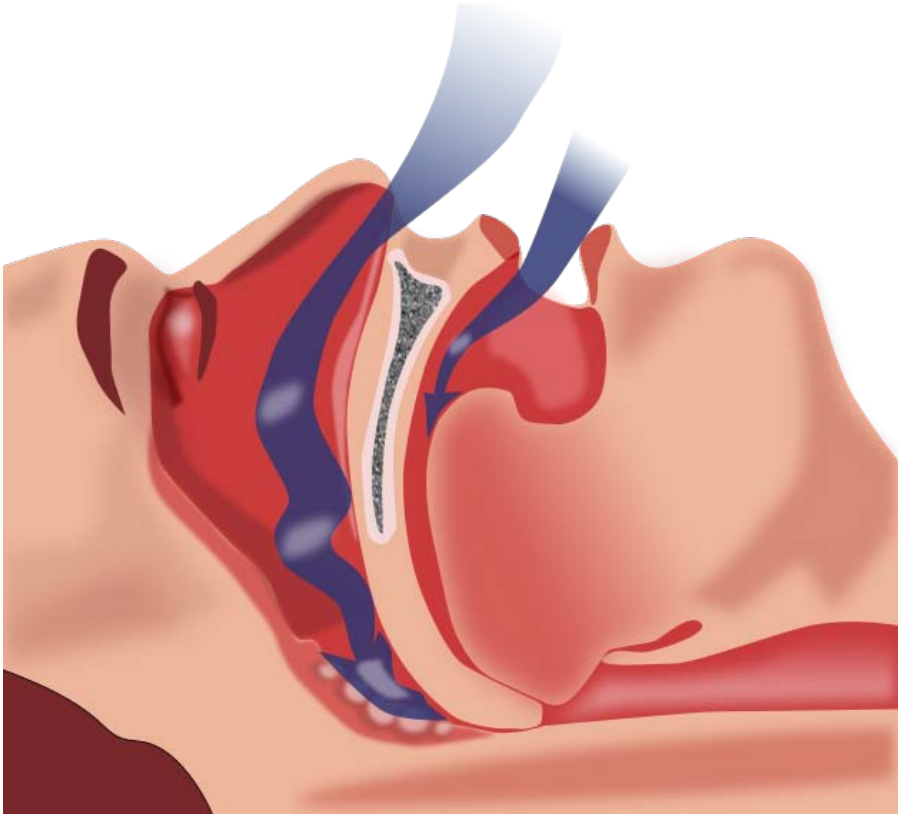
In the UK, knowledge of sleep medicine and possibilities for diagnosis and treatment seem to lag. Guardian.co.uk quotes the director of the Imperial College Healthcare Sleep Centre: "One problem is that there has been relatively little training in sleep medicine in this country – certainly there is no structured training for sleep physicians." The Imperial College Healthcare site shows attention to obstructive sleep apnea syndrome (OSA) and very few other sleep disorders.

Chapter 3

Sleep Apnea

Sleep apnea



Obstructive sleep apnea

ICD-10	G47.3
ICD-9	327.23, 780.57
eMedicine	ped/2114
MeSH	D012891

Sleep apnea (or **sleep apnoea** in British English) is a sleep disorder characterized by abnormal pauses in breathing or instances of abnormally low breathing, during sleep. Each pause in breathing, called an apnea, can last from a few seconds to minutes, and may occur 5 to 30 times or more an hour. Similarly, each abnormally low breathing event is called a hypopnea. Sleep apnea is diagnosed with an overnight sleep test called a polysomnogram, or "sleep study".

There are three forms of sleep apnea: central (CSA), obstructive (OSA), and complex or mixed sleep apnea (i.e., a combination of central and obstructive) constituting 0.4%, 84% and 15% of cases respectively. In CSA, breathing is interrupted by a lack of respiratory effort; in OSA, breathing is interrupted by a physical block to airflow despite respiratory effort, and snoring is common.

Regardless of type, an individual with sleep apnea is rarely aware of having difficulty breathing, even upon awakening. Sleep apnea is recognized as a problem by others witnessing the individual during episodes or is suspected because of its effects on the body (*sequelae*). Symptoms may be present for years (or even decades) without identification, during which time the sufferer may become conditioned to the daytime sleepiness and fatigue associated with significant levels of sleep disturbance.

Diagnosis

The diagnosis of Sleep Apnea is based on the conjoint evaluation of clinical symptoms (e.g. excessive daytime sleepiness and fatigue) and of the results of a formal sleep study (polysomnography, or reduced channels home based test). The latter aims at establishing an "objective" diagnosis indicator linked to the quantity of apneic events per hour of sleep (Apnea Hypnea Index(AHI), or Respiratory Disturbance Index (RDI)), associated to a formal threshold, above which a patient is considered as suffering from Sleep Apnea, and the severity of his sleep apnea can be then quantified. Nevertheless, due to the number and variability in the actual symptoms and nature of apneic events (hypopnea vs apnea, central vs. obstructive...), the variability of patients physiology, the intrinsic imperfections of the experimental setups and methods, this field is opened to debate. Within this context, the definition of an apneic event depends of several factors (e.g. patient's age) and account for this variability through a multi-criteria decision rule described in several, sometimes conflicting, guidelines. One example of a commonly adopted definition of an apnea (for an adult) includes a minimum 10 second interval between breaths, with either a neurological arousal (a 3-second or greater shift in EEG

frequency, measured at C3, C4, O1, or O2) or a blood oxygen desaturation of 3–4% or greater, or both arousal and desaturation.

Classification

Obstructive sleep apnea

Obstructive sleep apnea (OSA) is the most common category of sleep-disordered breathing. The muscle tone of the body ordinarily relaxes during sleep, and at the level of the throat the human airway is composed of collapsible walls of soft tissue which can obstruct breathing during sleep. Mild occasional sleep apnea, such as many people experience during an upper respiratory infection, may not be important, but chronic severe obstructive sleep apnea requires treatment to prevent low blood oxygen (hypoxemia), sleep deprivation, and other complication.

Individuals with low muscle tone and soft tissue around the airway (e.g., because of obesity) and structural features that give rise to a narrowed airway are at high risk for obstructive sleep apnea. The elderly are more likely to have OSA than young people. Men are more likely to suffer sleep apnea than women and children are, though it is not uncommon in the latter two population groups.

The risk of OSA rises with increasing body weight, active smoking and age. In addition, patients with diabetes or "borderline" diabetes have up to three times the risk of having OSA.

Common symptoms include loud snoring, restless sleep, and sleepiness during the daytime. Diagnostic tests include home oximetry or polysomnography in a sleep clinic.

Some treatments involve lifestyle changes, such as avoiding alcohol or muscle relaxants, losing weight, and quitting smoking. Many people benefit from sleeping at a 30-degree elevation of the upper body or higher, as if in a recliner. Doing so helps prevent the gravitational collapse of the airway. Lateral positions (sleeping on a side), as opposed to supine positions (sleeping on the back), are also recommended as a treatment for sleep apnea, largely because the gravitational component is smaller in the lateral position. Some people benefit from various kinds of oral appliances to keep the airway open during sleep. Continuous positive airway pressure (CPAP) is the treatment of choice . There are also surgical procedures to remove and tighten tissue and widen the airway.

As already mentioned, snoring is a common finding in people with this syndrome. Snoring is the turbulent sound of air moving through the back of the mouth, nose, and throat. Although not everyone who snores is experiencing difficulty breathing, snoring in combination with other conditions such as overweight and obesity has been found to be highly predictive of OSA risk. The loudness of the snoring is not indicative of the severity of obstruction, however. If the upper airways are tremendously obstructed, there may not be enough air movement to make much sound. Even the loudest snoring does not

mean that an individual has sleep apnea syndrome. The sign that is most suggestive of sleep apneas occurs when snoring *stops*.

Other indicators include (but are not limited to): hypersomnolence, obesity BMI >30, large neck circumference (16 in (410 mm) in women, 17 in (430 mm) in men), enlarged tonsils and large tongue volume, micrognathia, morning headaches, irritability/mood-swings/depression, learning and/or memory difficulties, and sexual dysfunction.

The term "sleep-disordered breathing" is commonly used in the U.S. to describe the full range of breathing problems during sleep in which not enough air reaches the lungs (hypopnea and apnea). Sleep-disordered breathing is associated with an increased risk of cardiovascular disease, stroke, high blood pressure, arrhythmias, diabetes, and sleep deprived driving accidents. When high blood pressure is caused by OSA, it is distinctive in that, unlike most cases of high blood pressure (so-called essential hypertension), the readings do *not* drop significantly when the individual is sleeping. Stroke is associated with obstructive sleep apnea.

In the June 27, 2008, edition of the journal *Neuroscience Letters*, researchers revealed that people with OSA show tissue loss in brain regions that help store memory, thus linking OSA with memory loss. Using magnetic resonance imaging (MRI), the scientists discovered that sleep apnea patients' mammillary bodies were nearly 20 percent smaller, particularly on the left side. One of the key investigators hypothesized that repeated drops in oxygen lead to the brain injury.

Central sleep apnea

In pure central sleep apnea or Cheyne-Stokes respiration, the brain's respiratory control centers are imbalanced during sleep. Blood levels of carbon dioxide, and the neurological feedback mechanism that monitors them, do not react quickly enough to maintain an even respiratory rate, with the entire system cycling between apnea and hyperpnea, even during wakefulness. The sleeper stops breathing and then starts again. There is no effort made to breathe during the pause in breathing: there are no chest movements and no struggling. After the episode of apnea, breathing may be faster (hyperpnea) for a period of time, a compensatory mechanism to blow off retained waste gases and absorb more oxygen.

While sleeping, a normal individual is "at rest" as far as cardiovascular workload is concerned. Breathing is regular in a healthy person during sleep, and oxygen levels and carbon dioxide levels in the bloodstream stay fairly constant. The respiratory drive is so strong that even conscious efforts to hold one's breath do not overcome it. Any sudden drop in oxygen or excess of carbon dioxide (even if tiny) strongly stimulates the brain's respiratory centers to breathe.

In central sleep apnea, the basic neurological controls for breathing rate malfunction and fail to give the signal to inhale, causing the individual to miss one or more cycles of breathing. If the pause in breathing is long enough, the percentage of oxygen in the

circulation will drop to a lower than normal level (hypoxaemia) and the concentration of carbon dioxide will build to a higher than normal level (hypercapnia). In turn, these conditions of hypoxia and hypercapnia will trigger *additional* effects on the body. Brain cells need constant oxygen to live, and if the level of blood oxygen goes low enough for long enough, the consequences of brain damage and even death will occur. Fortunately, central sleep apnea is more often a chronic condition that causes much milder effects than sudden death. The exact effects of the condition will depend on how severe the apnea is and on the individual characteristics of the person having the apnea. Several examples are discussed below, and more about the nature of the condition is presented in the section on Clinical Details.

In any person, hypoxia and hypercapnia have certain common effects on the body. The heart rate will increase, unless there are such severe co-existing problems with the heart muscle itself or the autonomic nervous system that makes this compensatory increase impossible. The more translucent areas of the body will show a bluish or dusky cast from cyanosis, which is the change in hue that occurs owing to lack of oxygen in the blood ("turning blue"). Overdoses of drugs that are respiratory depressants (such as heroin, and other opiates) kill by damping the activity of the brain's respiratory control centers. In central sleep apnea, the effects of sleep *alone* can remove the brain's mandate for the body to breathe.

- Normal Respiratory Drive: After exhalation, the blood level of oxygen decreases and that of carbon dioxide increases. Exchange of gases with a lungful of fresh air is necessary to replenish oxygen and rid the bloodstream of built-up carbon dioxide. Oxygen and carbon dioxide receptors in the blood stream (called chemoreceptors) send nerve impulses to the brain, which then signals reflex opening of the larynx (so that the opening between the vocal cords enlarges) and movements of the rib cage muscles and diaphragm. These muscles expand the thorax (chest cavity) so that a partial vacuum is made within the lungs and air rushes in to fill it.
- Physiologic effects of central apnea: During central apneas, the central respiratory drive is absent, and the brain does *not* respond to changing blood levels of the respiratory gases. No breath is taken despite the normal signals to inhale. The immediate effects of central sleep apnea on the body depend on how long the failure to breathe endures. At worst, central sleep apnea may cause sudden death. Short of death, drops in blood oxygen may trigger seizures, even in the absence of epilepsy. In people *with* epilepsy, the hypoxia caused by apnea may trigger seizures that had previously been well controlled by medications. In other words, a seizure disorder may become unstable in the presence of sleep apnea. In adults with coronary artery disease, a severe drop in blood oxygen level can cause angina, arrhythmias, or heart attacks (myocardial infarction). Longstanding recurrent episodes of apnea, over months and years, may cause an increase in carbon dioxide levels that can change the pH of the blood enough to cause a metabolic acidosis.

Mixed apnea and complex sleep apnea

Some people with sleep apnea have a combination of both types. When obstructive sleep apnea syndrome is severe and longstanding, episodes of central apnea sometimes develop. The exact mechanism of the loss of central respiratory drive during sleep in OSA is unknown but is most commonly related to acid-base and CO_2 feedback malfunctions stemming from heart failure. There is a constellation of diseases and symptoms relating to body mass, cardiovascular, respiratory, and occasionally, neurological dysfunction that have a synergistic effect in sleep-disordered breathing. In some cases, a side effect from the lack of sleep is a mild case of Excessive Daytime Sleepiness (EDS) where the subject has had minimal sleep and this extreme fatigue over time takes its toll on the subject. The presence of central sleep apnea without an obstructive component is a common result of chronic opiate use (or abuse) owing to the characteristic respiratory depression caused by large doses of narcotics.

Complex sleep apnea has recently been described by researchers as a novel presentation of sleep apnea. Patients with complex sleep apnea exhibit OSA, but upon application of positive airway pressure the patient exhibits persistent central sleep apnea. This central apnea is most commonly noted while on CPAP therapy after the obstructive component has been eliminated. This has long been seen in sleep laboratories and has historically been managed either by CPAP or BiLevel therapy. Adaptive servo-ventilation (ASV) modes of therapy have been introduced to attempt to manage this complex sleep apnea. Studies have demonstrated marginally superior performance of the adaptive servo ventilators in treating Cheyne-Stokes breathing; however, no longitudinal studies have yet been published, nor have any results been generated that suggest any differential outcomes versus standard CPAP therapy. At the AARC 2006 in Las Vegas, NV, researchers reported successful treatment of hundreds of patients on ASV therapy; however, these results have not been reported in peer-reviewed publications as of July 2007.

An important finding by Dernaika et al. suggests that transient central apnea produced during CPAP titration (the so-called "complex sleep apnea") is "…transient and self-limited." The central apneas may in fact be secondary to sleep fragmentation during the titration process. As of July 2007, there has been no alternate convincing evidence produced that these central sleep apnea events associated with CPAP therapy for obstructive sleep apnea are of any significant pathophysiologic importance.

Research is ongoing, however, at the Harvard Medical School, including adding dead space to positive airway pressure for treatment of complex sleep-disordered breathing.

Treatment

For mild cases of sleep apnea, a treatment which is a lifestyle change is sleeping on one's side, which can prevent the tongue and palate from falling backwards in the throat and blocking the airway. Another is avoiding alcohol and sleeping pills, which can relax throat muscles, contributing to the collapse of the airway at night.

For moderate to severe sleep apnea, the most common treatment is the use of a continuous positive airway pressure (CPAP) device, which 'splints' the patient's airway open during sleep by means of a flow of pressurized air into the throat. The patient typically wears a plastic facial mask, which is connected by a flexible tube to a small bedside CPAP machine. The CPAP machine generates the required air pressure to keep the patient's airways open during sleep. Advanced models may warm or humidify the air and monitor the patient's breathing to ensure proper treatment. Although CPAP therapy is extremely effective in reducing apneas and less expensive than other treatments, some patients find it extremely uncomfortable. Many patients refuse to continue the therapy or fail to use their CPAP machines on a nightly basis.

In addition to CPAP, dentists specializing in sleep disorders can prescribe Oral Appliance Therapy (OAT). The oral appliance is a custom-made mouthpiece that shifts the lower jaw forward, opening up the airway. OAT is usually successful in patients with mild to moderate obstructive sleep apnea. OAT is a relatively new treatment option for sleep apnea in the United States, but it is much more common in Canada and Europe.

Several levels of obstruction may be addressed in physical treatment, including the nasal passage, throat (pharynx), base of tongue, and facial skeleton. Surgical treatment for obstructive sleep apnea needs to be individualized in order to address all anatomical areas of obstruction. Often, correction of the nasal passages needs to be performed in addition to correction of the oropharynx passage. Septoplasty and turbinate surgery may improve the nasal airway. Tonsillectomy and uvulopalatopharyngoplasty (UPPP or UP3) are available to address pharyngeal obstruction. Base-of-tongue advancement by means of advancing the genial tubercle of the mandible may help with the lower pharynx. A myriad of other techniques are available, including hyoid bone myotomy and suspension and various radiofrequency technologies.

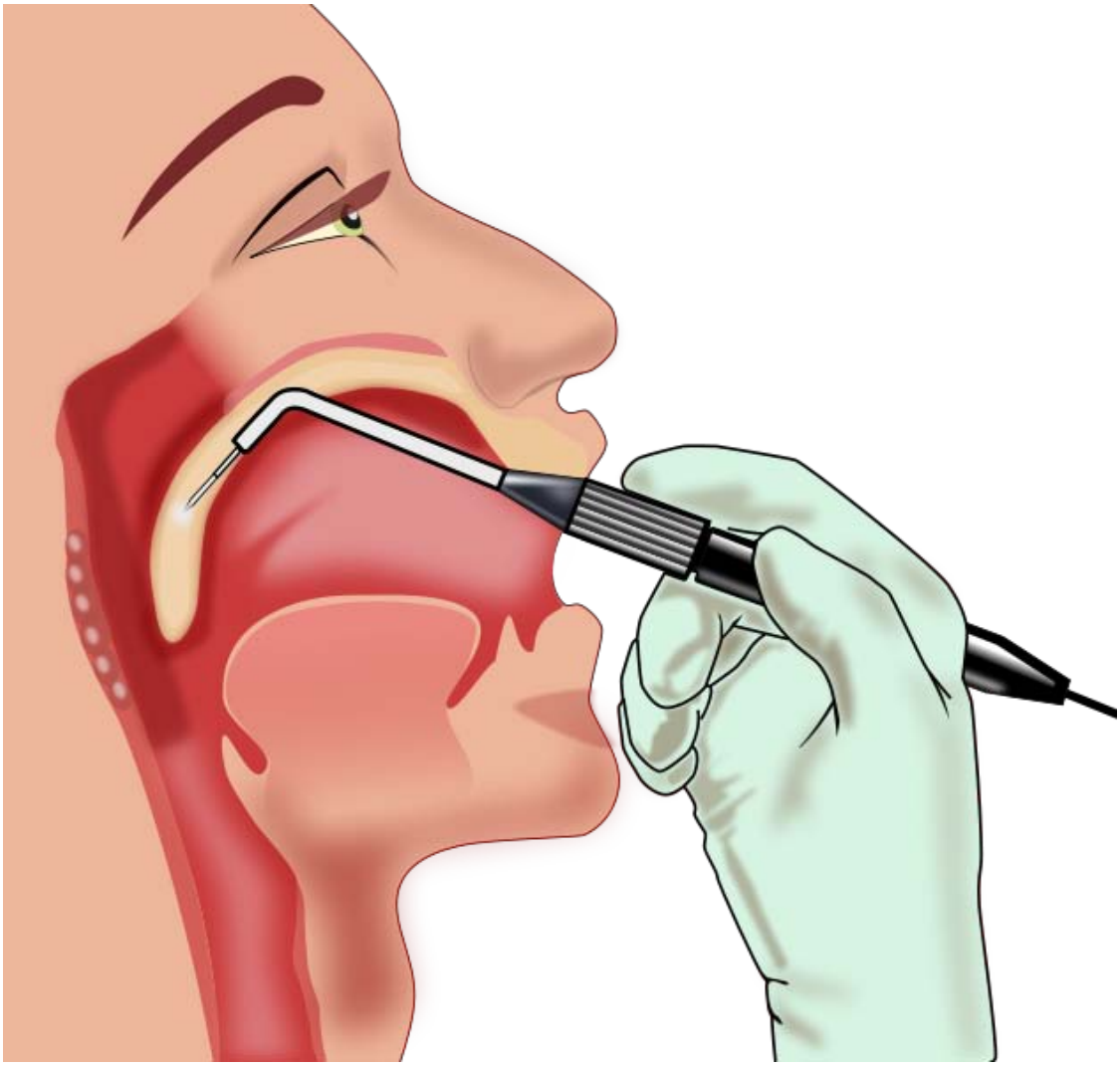


Illustration of surgery on the mouth and throat

Other surgery options may attempt to shrink or stiffen excess tissue in the mouth or throat, procedures done at either a doctor's office or a hospital. Small shots or other treatments, sometimes in a series, are used for shrinkage, while the insertion of a small piece of stiff plastic is used in the case of surgery whose goal is to stiffen tissues.

Possibly owing to changes in pulmonary oxygen stores, sleeping on one's side (as opposed to on one's back) has been found to be helpful for central sleep apnea with Cheyne-Stokes respiration (CSA-CSR).

Medications like Acetazolamide lower blood pH and encourage respiration. Low doses of oxygen are also used as a treatment for hypoxia but are discouraged due to side effects.

Surgery

CPAP is the most consistently safe and effective treatment for obstructive sleep apnea but it is not a cure, and people are less likely to use it in the long term. The Stanford Center for Excellence in Sleep Disorders Medicine achieved a 95% cure rate of sleep apnea patients by surgery. Maxillomandibular advancement (MMA) is considered the most effective surgery for sleep apnea patients, because it increases the posterior airway space (PAS). The main benefit of the operation is that the oxygen saturation in the arterial blood increases. In a study published in 2008, 93.3.% of surgery patients achieved an adequate quality of life based on the Functional Outcomes of Sleep Questionnaire (FOSQ). Surgery led to a significant increase in general productivity, social outcome, activity level, vigilance, intimacy and sex, and the total score postoperatively was P = .0002. Overall risks of MMA surgery are low: The Stanford University Sleep Disorders Center found 4 failures in a series of 177 patients, or about one out of 44 patients.

Several inpatient and outpatient procedures use sedation. Many drugs and agents used during surgery to relieve pain and to depress consciousness remain in the body at low amounts for hours or even days afterwards. In an individual with either central, obstructive or mixed sleep apnea, these low doses may be enough to cause life-threatening irregularities in breathing or collapses in a patient's airways. Use of analgesics and sedatives in these patients postoperatively should therefore be minimized or avoided.

Surgery on the mouth and throat, as well as dental surgery and procedures, can result in postoperative swelling of the lining of the mouth and other areas that affect the airway. Even when the surgical procedure is designed to improve the airway, such as tonsillectomy and adenoidectomy or tongue reduction, swelling may negate some of the effects in the immediate postoperative period. Once the swelling resolves and the palate becomes tightened by postoperative scarring, however, the full benefit of the surgery may be noticed.

Sleep apnea patients undergoing any medical treatment must make sure his or her doctor and/or anesthetist are informed about their condition. Alternate and emergency procedures may be necessary to maintain the airway of sleep apnea patients. If an individual suspects he or she may have sleep apnea, communication with their doctor about possible preprocedure screening may be in order.

Alternative treatments

A 2005 study in the British Medical Journal found that learning and practicing the didgeridoo helped reduce snoring and sleep apnea as well as daytime sleepiness. This appears to work by strengthening muscles in the upper airway, thus reducing their tendency to collapse during sleep.

A 2009 study published in the American Journal of Respiratory and Clinical Care Medicine found that "oropharyngeal exercises derived from speech therapy may be an effective treatment option for patients with moderate" obstructive sleep apnea .

Epidemiology

The Wisconsin Sleep Cohort Study estimated in 1993 that roughly one in every 15 Americans were affected by at least moderate sleep apnea. It also estimated that in middle-age as many as nine percent of women and 24 percent of men were affected, undiagnosed and untreated.

The costs of untreated sleep apnea reach further than just health issues. It is estimated that in the U.S. the average untreated sleep apnea patient's annual health care costs $1,336 more than an individual without sleep apnea. This may cause $3.4 billion/year in additional medical costs. Whether medical cost savings occur with treatment of sleep apnea remains to be determined.

History

The clinical picture of this condition has long been recognized as a character trait, without an understanding of the disease process. The term "Pickwickian syndrome" that is sometimes used for the syndrome was coined by the famous early 20th century physician, William Osler, who must have been a reader of Charles Dickens. The description of Joe, "the fat boy" in Dickens's novel *The Pickwick Papers*, is an accurate clinical picture of an adult with obstructive sleep apnea syndrome.

The early reports of obstructive sleep apnea in the medical literature described individuals who were very severely affected, often presenting with severe hypoxemia, hypercapnia and congestive heart failure.

The management of obstructive sleep apnea was revolutionized with the introduction of continuous positive airway pressure (CPAP), first described in 1981 by Colin Sullivan and associates in Sydney, Australia. The first models were bulky and noisy, but the design was rapidly improved and by the late 1980s CPAP was widely adopted. The availability of an effective treatment stimulated an aggressive search for affected individuals and led to the establishment of hundreds of specialized clinics dedicated to the diagnosis and treatment of sleep disorders. Though many types of sleep problems are recognized, the vast majority of patients attending these centers have sleep-disordered breathing.

Chapter 4

Hypopnea

Hypopnea (sometimes spelled **hypopnœa**) is a medical term for a disorder which involves episodes of overly shallow breathing or an abnormally low respiratory rate. This differs from apnea in that there remains some flow of air. Hypopnea events may happen while asleep or while awake.

During sleep, hypopnea is classed as a sleep disorder. With moderate to severe hypopnea, sleep is disturbed such that patients may get a full night's sleep but still not feel rested because they did not get the right kind of sleep. The disruption in breathing causes a drop in blood oxygen level, which may in turn disrupt the stages of sleep.

Daytime hypopnea events are mostly limited to those with severely compromised respiratory muscles, as occurs in certain neuromuscular diseases. Similarly, daytime hypopnea can also cause a drop in blood oxygen level.

Etymology

Hypopnea comes from the Greek roots *hypo-* (meaning *low*, *under*, *beneath*, *down*, *below normal*) and *pnoe* (meaning *breathing*). Literally it means underbreathing.

General information

In the context of diagnosis and treatment of sleep disorders, a hypopnea event is not considered to be clinically significant unless there is a 30% (or greater) reduction in flow lasting for 10 seconds or longer and an associated 4% (or greater) desaturation in the person's O_2 levels, or if it results in arousal or fragmentation of sleep.

The direct consequence of hypopnea (as well as apnea) is that the CO_2 in the blood increases and the oxygen level in the patient’s blood decrease is proportionate to the severity of the airway obstruction. This disruptive pattern of breathing generates disruptive sleep patterns, the consequences of which being that those individuals may exhibit increased fatiguability, lethargy, decreased ability to concentrate, increased

irritability, and morning headaches. Basically, those individuals are extremely tired due to their inability to get a good night's sleep.

Hypopneas can be either central (i.e., as part of a waxing and waning in breathing effort) or obstructive in origin. During an obstructive hypopnea, in comparison to an obstructive apnea, the airway is only partially closed. However, this closure is still enough to cause a physiological effect (i.e., an oxygen desaturation and/or an increase in breathing effort terminating in arousal).

A hypopnea index (HI) can be calculated by dividing the number of hypopnea events during the sleep period by the number of hours of sleep. The apnea-hypopnea index (AHI) is an index of severity that combines apneas and hypopneas. Combining them both gives an overall severity of sleep apnea including sleep disruptions and desaturations (a low level of oxygen in the blood). The apnea-hypopnea index, like the apnea index and hypopnea index, is calculated by dividing the number of apneas and hypopneas by the number of hours of sleep. Another index that is used to measure sleep apnea is the respiratory disturbance index (RDI). The respiratory disturbance index is similar to the apnea-hypopnea index; however, it also includes respiratory events that do not technically meet the definitions of apneas or hypopneas, but do disrupt sleep.

Causes

Among the causes of hypopnea are:

- anatomical defects such as nasal septum deformation or congenital narrowness of nasal meati and the gullet;
- acute tonsillitis and/or adenoiditis;
- obesity or being overweight;
- neuromuscular disease or any condition that entails weakened respiratory muscles;
- use of sedatives (sleeping pills, etc.);
- alcohol abuse;
- smoking;
- aging;
- others;

most of which are also typical causes of airway obstruction, snoring and sleep apnea.

Symptoms

The most common hypopnea symptom is excessive sleepiness, which results from constant sleep interruption. People with hypopnea often have loud, heavy snoring that is interrupted with choking sounds or loud snorts followed by periods of silence, because not enough air can flow into the lungs through the mouth and nose. The periods of silence

can last 20 seconds or longer and can happen many times each hour, resulting in poor sleep and reduced levels of oxygen in the blood.

Other symptoms of hypopnea may include depression, forgetfulness, mood or behavior changes, trouble concentrating, loss of energy, nervousness, and morning headaches. Not all people with hypopnea experience all of these symptoms and not everyone who has these symptoms has hypopnea.

Consequences

Hypopnea is a disorder that may result in excessive daytime sleepiness and compromised quality of life, including traffic accidents, diminished productivity in the work place and emotional problems.

Cardiovascular consequences of hypopnea may include myocardial infarction, stroke, psychiatric problems, impotence, cognitive dysfunction, hypertension, coronary heart disease, and memory loss.

Treatment

The most common treatment for hypopnea is continuous positive airway pressure (CPAP). CPAP is a treatment in which the patient wears a mask over the nose and/or mouth. An air blower forces air through the upper airway. The air pressure is adjusted so that it is just enough to maintain the oxygen saturation levels in the blood. For people with neuromuscular disorders, the most common treatment is the use of BIPAP or other non-invasive ventilation.

Mild hypopnea can often be treated by losing weight or by avoiding sleeping on one's back. Also quitting smoking, and avoiding alcohol, sedatives and hypnotics (soporifics) before sleep can be quite effective.

Surgery is generally a last resort in hypopnea treatment, but is a site-specific option for the upper airway. Depending on the cause of obstruction, surgery may focus on the soft palate, the uvula, tonsils, adenoids or the tongue. There are also more complex surgeries that are performed with the adjustment of other bone structures - the mouth, nose and facial bones.

Chapter 5

Parasomnia

Parasomnia	
ICD-10	F51.3-F51.4
ICD-9	307.47, 327.4, 780.59
eMedicine	med/3131
MeSH	D020447

Parasomnias are a category of sleep disorders that involve abnormal and unnatural movements, behaviors, emotions, perceptions, and dreams that occur while falling asleep, sleeping, between sleep stages, or during arousal from sleep. Most parasomnias are dissociated sleep states which are partial arousals during the transitions between wakefulness and NREM sleep, or wakefulness and REM sleep.

NREM parasomnias

NREM parasomnias are arousal disorders that occur during stage 3 (or 4 by the R&K standardization) of NREM sleep—also known as slow wave sleep (SWS). They are caused by a physiological activation in which the patient's brain exits from SWS and is caught in between a sleeping and waking state. In particular, these disorders involve activation of the autonomic nervous system, motor system, or cognitive processes during sleep or sleep-wake transitions.

Some NREM parasomnias are common during childhood but decrease in frequency with increasing age (sleep-walking, night-terrors, and confusional arousal). They can be

triggered in certain individuals by alcohol, sleep deprivation, physical activity, emotional stress, depression, medications, or a fevered illness. These disorders of arousal can range from confusional arousals, somnambulism, to night terrors. Other specific disorders include sleepeating, sleep sex, teeth grinding, rhythmic movement disorder, restless legs syndrome, and somniloquy.

Confusional arousals

With a prevalence of 4%, confusional arousals are not observed very often in adults; however, they are common in children. Confusional arousals are occasional thrashings or inconsolable crying among children—they are characterized by movements in bed.

Sleepwalking (somnambulism)

Sleepwalking has a prevalence of 1-17% in childhood, with the most frequent occurrences around the age of eleven-twelve. About 4% of adults experience somnambulism.

Sleep terrors (night terrors)

Sleep terrors is the most disruptive arousal disorder since it may involve loud screams and panic; in extreme cases, it may result in bodily harm or property damage by running about or hitting walls. Unfortunately, all attempts to console the individual are futile and may prolong or intensify the victim's confused state. Usually the victim experiences amnesia after the event but it may not be complete amnesia. Up to 3% of adults suffer from sleep terrors, and exhibited behavior of this parasomnia can range from mild to extremely violent. They typically occur in stages 3 and 4 sleep.

Bruxism (teeth grinding)

Bruxism is a common sleep disorder where the sufferer grinds their teeth during sleep. This can cause sleep disruption for the sufferer and bed partner, wear and fracture of teeth, and jaw pain.

Restless legs syndrome & Periodic Limb Movements

Both of these conditions (RLS and PLM) are classified as dyssomnias according to the DSM-IV. They are considered parasomnias.

REM parasomnias

REM sleep behavior disorder

REM Sleep Behavior Disorder is the most common REM sleep parasomnia in which muscle atonia is absent. This allows the individual to act out their dreams and may result

in repeated injury-- bruises, lacerations and fractures-- to themselves or others. Patients may take self-protection measures by tethering themselves to bed, using pillow barricades or sleeping in an empty room on a mattress. Demographically, 90% of RBD patients are males, and most are older than 50 years of age.

Typical clinical features of REM sleep behaviour disorder are:

- Male gender predeliction
- Mean age of onset 50–65 years (range 20–80 years)
- Vocalisation, screaming, swearing that may be associated with dreams
- Motor activity, simple or complex, that may result in injury to patient or bed-partner
- Occurrence usually in latter half of sleep period (REM sleep)
- May be associated with neurodegenerative disease

Acute RBD, occurs mostly as a result of a side-effect in prescribed medication- usually antidepressants.

Chronic RBD is idiopathic or associated with neurological disorders. There is a growing association of chronic RBD with neurodegenerative disorders – Parkinson's disease, multiple system atrophy (MSA) or dementia-- as an early indicator of these conditions by as much as 10 years.

Patients with narcolepsy also are more likely to develop RBD.

Catathrenia

Catathrenia, a rapid eye movement sleep parasomnia consisting of breath holding and expiratory groaning during sleep, is distinct from both somniloquy and obstructive sleep apnea. The sound is produced during exhalation as opposed to snoring which occurs during inhalation. It is usually not noticed by the person producing the sound but can be extremely disturbing to sleep partners, although once aware of it, sufferers tend to be woken up by their own groaning as well. Bed partners generally report hearing the person take a deep breath, hold it, then slowly exhale; often with a high-pitched squeak or groaning sound.

Chapter 6

Rapid Eye Movement Behavior Disorder and Sleepwalking

Rapid eye movement behavior disorder

Rapid eye movement sleep behavior disorder

MeSH D020447

Rapid eye movement sleep behavior disorder (**RBD**) is a sleep disorder (more specifically a parasomnia) that involves abnormal behavior during the sleep phase with rapid eye movement (REM sleep). It was first described in 1986.

The major and arguably only abnormal feature of RBD is loss of muscle atonia (paralysis) during otherwise intact REM sleep. This is the stage of sleep in which most vivid dreaming occurs. The loss of motor inhibition leads to a wide spectrum of behavioral release during sleep. This extends from simple limb twitches to more complex integrated movement, in which sufferers appear to be unconsciously acting out their dreams. These behaviors can be violent in nature and in some cases will result in injury to either the patient or their bed partner.

Symptoms

RBD is characterized by the dreamer acting out his or her dreams. Usually negative ones which involve kicking, screaming, punching, grabbing, and even jumping out of bed. When awakened, one can usually recall the dream they were having which will match the actions they were performing, but they will not be aware that they were moving. Episodes occur more towards the morning hours because that is when REM sleep is more frequent.

People with RBD experience episodes at least once a week, sometimes more and each episode can result in injuries to oneself or one's bed partner.

Causes

Rapid eye movement behavior disorder occurs when there is a loss of normal voluntary muscle atonia during REM sleep resulting in motor behavior in response to dream content. It can be caused by adverse reactions to certain drugs or else during drug withdrawal; however it is most often associated with the elderly and in those with neurodegenerative disorders such as Parkinson disease, and other neurodegenerative diseases for example multiple system atrophy and Lewy Body Dementia.

Treatment

RBD is treatable. Various medications are prescribed for RBD based on varying symptoms. Low doses of clonazepam is most effective with a 90% success rate, how this drug works to restore REM atonia is unclear, however it is thought to suppress muscle activity, rather than directly restoring atonia. Melatonin is also effective and can also be prescribed as a more natural alternative. For those with Parkinson's and RBD, Levodopa is a popular choice. Pramipexole is another drug which can be an effective treatment option.

In addition to medication it is also wise to secure the sleeper's environment in preparation for episodes. Remove potentially dangerous objects from the bedroom and either place a cushion around the bed or move the mattress to the floor for added protect against injuries.

Epidemiology

The most comprehensive assessment so far has estimated RBD prevalence to be around 0.5% in individuals aged 15 to 100. It is far more common in males: most studies report that only around a tenth of sufferers are female. This may partially be due to a referral bias, as violent activity carried out by men is more likely to result in harm and injury and is more likely to be reported than injury to male bed partners by women, or it may reflect a true difference in prevalence as a result of genetic or androgenic factors. The mean age of onset is estimated to be around 60 years.

Various conditions are very similar to RBD in that sufferers exhibit excessive sleep movement and potentially violent behavior. Such disorders include sleepwalking and sleep terrors, which are associated with other stages of sleep, nocturnal seizures and obstructive sleep apnea which can induce arousals from REM sleep associated with complex behaviors. Because of the similarities between the conditions, polysomnography plays an important role in confirming RBD diagnosis.

It is now apparent that RBD appears in association with a variety of different conditions. Narcolepsy has been reported as a related disorder. Both RBD and narcolepsy involve dissociation of sleep states probably arising from a disruption of sleep control mechanisms. RBD has also been reported following cerebrovascular accident and neurinoma (tumour), indicating that damage to the brain stem area may precipitate RBD. RBD is usually chronic, however may be acute and sudden in onset if associated with drug treatment or withdrawal (particularly with alcohol withdrawal) 60% of RBD is idiopathic. This includes RBD that is found in association with conditions such as Parkinson's disease and dementia with Lewy bodies, where it is often seen to precede the onset of neurodegenerative disease. RBD has been associated with autism. Monoamine oxidase inhibitors, tricyclic antidepressants, serotonergic synaptic reuptake inhibitors, and noradrenergic antagonists can induce or aggravate RBD symptoms and should be avoided in patients with RBD.

In non-humans

RBD has been diagnosed in non-humans, specifically, dogs.

Sleepwalking

Sleepwalking	
ICD-10	F51.3

Sleepwalking as seen by a Somalian artist

Sleepwalking, also known as **somnambulism**, is a sleep disorder belonging to the parasomnia family. Sleepwalkers arise from the slow wave sleep stage in a state of low consciousness and perform activities that are usually performed during a state of full consciousness. These activities can be as benign as sitting up in bed, walking to the bathroom, and cleaning, or as hazardous as cooking, driving, extremely violent gestures, grabbing at hallucinated objects, or even homicide.

Although generally sleepwalking cases consist of simple, repeated behaviours, there are occasionally reports of people performing complex behaviours while asleep, although their legitimacy is often disputed. In 2004, sleep medicine experts in Australia claimed to have successfully treated a woman who claimed to have sex with strangers in her sleep. In December 2008, reports were published of a woman who sent semi-coherent emails while sleepwalking, including one inviting a friend around for dinner and drinks. Sleepwalkers often have little or no memory of the incident, as they are not truly conscious. Although their eyes are open, their expression is dim and glazed over. Sleepwalking may last as little as 30 seconds or as long as 30 minutes.

Nomenclature, classification, and codification

According to a study by Dr. Christina A. Gurnett, of the Washington University School of Medicine's Department of Neurology, sleepwalking was inherited as an autosomal dominant disorder with reduced penetrance in this family. Genome-wide multipoint parametric linkage analysis for sleepwalking revealed a maximum logarithm of the odds score of 3.44 at chromosome 20q12-q13.12 between 55.6 and 61.4 cM.

Explanation

Sleep stages

Sleep is categorized into stages of a cycle between REM sleep and NREM sleep. NREM sleep is further divided into four stages: stage 1 (a light sleep period), stage 2 (a consolidated sleep period), and stage 3 and 4 (slow wave sleep periods). This is followed by stage 3, stage 2, stage 1, and a REM period. In normal adults, a cycle will last about 1.5 hours. According to Lavie, Malhotra, and Pillar, "The length and content of sleep cycles change throughout the night as well as with age." Sleepwalking generally occurs during the first third of the night (between 11 p.m. and 1 a.m.) during the slow wave NREM sleep stage. High delta activity within the brain usually accompanies slow wave NREM sleep, and when 20–50% of all activity is delta activity, stage 3 is scored. When delta activity reaches 50% or higher, stage 4 is scored. Usually, if sleepwalking occurs at all, it will only occur once in a night.

Automatism

Researchers sometimes disagree about the classification of sleepwalking as an automatism. According to the popular source of MedicineNet, an automatism is "an unconscious movement that may resemble simple repetitive tics or may be a complex sequence of natural-looking movements." The individual often won't remember what he was doing or how he was doing it. These repetitive actions may include chewing, lip-smacking, pulling at clothing, or wandering around looking confused. Epileptic automatisms are also associated "with the absence attacks of petit mal epilepsy." In the case of the law, an individual can be accused of non-insane automatism or insane automatism. The first is used as a defense for temporary insanity or involuntary conduct,

resulting in acquittal. The latter results in a "special verdict of not guilty by reason of insanity." This verdict of insanity can result in a court order to attend a mental institution. Some actions that take place during sleepwalking could be classified as automatisms.

Causes

Several experts theorize that the development of sleepwalking in childhood is due to a delay in maturation. There are also high-voltage delta waves in somnambulists up to 17 years of age. This presence might suggest an immaturity in the central nervous system, also a possible cause of sleepwalking. Sleepwalking is clustered in families, and the percentage of childhood sleepwalking increases to 45% if one parent was affected, and 60% if both parents were affected. However, there is no recorded preference to male or female individuals. Thus, heritable factors appear to predispose an individual to develop sleepwalking, but expression of the trait may be also influenced by environmental factors. Other precipitating factors to sleepwalking are those factors which increase the slow wave sleep stage. These most commonly include sleep deprivation, fever, and excessive tiredness. The use of some neuroleptics or hypnotics can also cause sleepwalking to occur.

Treatment

There are some drugs that can be prescribed for sleepwalkers such as a low dose benzodiazepine, tricyclic antidepressants, and clonazepam. However, for most sleepwalkers, many experts advise putting away dangerous items and locking doors and windows before sleep to reduce risks of harmful activity. Good sleep hygiene and avoiding sleep deprivation is also recommended.

There are conflicting viewpoints on whether it is harmful to wake a sleepwalker. Some experts say that sleepwalkers should be gently guided back to bed without waking them. Others counter that idea and state that waking a sleepwalker may result in their disorientation, but it is not harmful.

Epidemiology

According to the National Sleep Foundation, sleepwalking is prevalent in 1–15% of the general populace. Sleepwalking is most prevalent in children, and usually disappears by adolescence. Sleepwalking in adults is less common, but when it does occur, the events occur three times more often per year and last for more years than in children. Sleepwalking in old age is rare and usually indicates another disorder. Old age disorders may include delirium, drug toxicity or a seizure disorder.

Children

Sleepwalking events are common in childhood and decrease with age. According to Lavie, Malhotra and Pillar, the peak age is 4–8 years, when prevalence is 20% frequency

of events. It is also known that "between 25–33% of somnambulists have nocturnal enuresis" (bed-wetting). Like sleepwalking, enuresis is more common in children and fades away as the child ages. Some children who sleepwalk are also affected by night terrors. However, night terrors are much more common in adult sleepwalkers, up to 50% more common. Some parents worry about the psychological implications of sleepwalking on their child, but Larissa Hirsch, MD, editor of the website KidsHealth, says, "Sleepwalking is not usually a sign that something is emotionally or psychologically wrong with a child. And it doesn't cause any emotional harm."

In the study "sleepwalking and sleep terrors in prepubera children" they found that if a child had another sleepdisorder such as restless leg syndrome (RLS) or sleep-disorder breathing (SDB) that they had a greater chance of sleepwalking. The study found children with chronic parasomnias may often also present SDB or, to a lesser extent, RLS. Furthermore, the disappearance of the parasomnias after the treatment of the SDB or RLS periodic limb movement syndrome suggests that the latter may trigger the former. The high frequency of SDB in family members of children with parasomnia provided additional evidence that SDB may manifest as parasomnias in children. Children with parasomnias are not systematically monitored during sleep, although past studies have suggested that patients with sleep terrors or sleepwalking have an elevated level of brief EEG arousals. When children receive polysomnographies, discrete patterns (e.g., nasal flow limitation, abnormal respiratory effort, bursts of high or slow EEG frequencies) should be sought; apneas are rarely found in children. Children's respiration during sleep should be monitored with nasal cannula/pressure transducer system and/or esophageal manometry, which are more sensitive than the thermistors or thermocouples currently used in many laboratories. The clear, prompt improvement of severe parasomnia in children who are treated for SDB, as defined here, provides important evidence that subtle SDB can have substantial health-related significance. Also noteworthy is the report of familial presence of parasomnia. Studies of twin cohorts and families with sleep terror and sleepwalking suggest genetic involvement of parasomnias. RLS and SDB have been shown to have familial recurrence. RLS has been shown to have genetic involvement.

Adults

The persistence or onset of sleepwalking in adulthood is far less common than in children. It is a misconception that adult sleepwalking always indicates a psychological disorder. Sleepwalking can, however, be a symptom of people with psychological disorders. In one study, adult test subjects were given the Minnesota Multiphasic Personality Inventory, a psychiatric test. According to the study, patients showed "outwardly directed behavior patterns...suggest[ing] that these adults had difficulty handling aggression. They did not support an interpretation of sleepwalking as 'hysterical dissociation'."

Psychological disorders and drug use

In some cases, sleepwalking in adults may be a symptom of a psychological disorder or of drug use. One study done by A.H. Crisp et al. of St. George's Hospital Medical School

in London supports the possibility of dissociation in adult sleepwalkers because the test subjects scored unusually high on the hysteria portion of the Crown-Crisp experiential index. According to J.E. Orme, an expert in psychology, "A higher incidence [of sleepwalking events] has been reported in patients with schizophrenia, hysteria and anxiety neuroses." Also, patients with migraine headaches or Tourette Syndrome are 4–6 times more likely to sleepwalk. Some medications that may increase sleepwalking include: Chlorpromazine (Thorazine), perphenazine (Trilafon), lithium, benzodiazepine (Triazolam), amitriptylin (Elavel, Endep), Zolpidem (Ambien) and beta blockers.

History

Sleepwalking has attracted a sense of mystery, but it had not been seriously investigated and diagnosed until the last century. Sleepwalking was initially thought to be a dreamer acting out a dream. For example, in one study published by the Society for Science & the Public in 1954, this was the conclusion: "Repression of hostile feelings against the father caused the patients to react by acting out in a dream world with sleepwalking, the distorted fantasies they had about all authoritarian figures, such as fathers, officers and stern superiors." This same group published an article twelve years later with a new conclusion: "Sleepwalking, contrary to most belief, apparently has little to do with dreaming. In fact, it occurs when the sleeper is enjoying his most oblivious, deepest sleep—a stage in which dreams are not usually reported." More recent research has discovered that sleepwalking is actually a disorder of NREM (non-rapid eye movement) arousal. Acting out a dream is the basis for a REM (rapid eye movement) sleep disorder called REM Behavior Disorder (or REM Sleep Behavior Disorder, RSBD). More accurate data about sleep is due to the invention of technologies such as the electroencephalogram (EEG) by Hans Berger in 1924 and BEAM by Frank Duffy in the early 1980s.

Chapter 7

Delayed Sleep Phase Syndrome

Delayed sleep phase syndrome

ICD-10	G47.2
ICD-9	327.31
eMedicine	neuro/655
MeSH	D021081

Delayed sleep-phase syndrome (DSPS), also known as **delayed sleep-phase disorder** (DSPD) or **delayed sleep-phase type** (DSPT), is a circadian rhythm sleep disorder, a chronic disorder of the timing of sleep, peak period of alertness, the core body temperature rhythm, hormonal and other daily rhythms, compared to the normal population and relative to societal requirements. People with DSPS generally fall asleep some hours after midnight and have difficulty waking up in the morning.

Often, people with the disorder report that they cannot sleep until early morning, but fall asleep at about the same time every "night". Unless they have another sleep disorder such as sleep apnea in addition to DSPS, patients can sleep well and have a normal need for sleep. Therefore, they find it very difficult to wake up in time for a typical school or work day. If, however, they are allowed to follow their own schedules, e.g. sleeping from 4 a.m. to noon, they sleep soundly, awaken spontaneously, and do not experience excessive daytime sleepiness.

The syndrome usually develops in early childhood or adolescence. An adolescent version disappears in adolescence or early adulthood; otherwise DSPS is a lifelong condition. Depending on the severity, it can be to a greater or lesser degree treatable. Prevalence among adults, equally distributed among women and men, is approximately 0.15%, or 3 in 2,000.

DSPS was first formally described in 1981 by Dr. Elliot D. Weitzman and others at Montefiore Medical Center. It is responsible for 7–10% of patient complaints of chronic insomnia. However, as few doctors are aware of it, it often goes untreated or is treated inappropriately; DSPS is often misdiagnosed as primary insomnia or as a psychiatric condition. At its most severe and inflexible, it is an invisible disability.

Definition

According to the International Classification of Sleep Disorders (ICSD), the circadian rhythm sleep disorders share a common underlying chronophysiologic basis:

The major feature of these disorders is a misalignment between the patient's sleep pattern and the sleep pattern that is desired or regarded as the societal norm... In most circadian rhythm sleep disorders, the underlying problem is that the patient cannot sleep when sleep is desired, needed or expected.

The ICSD (page 128-133) diagnostic criteria for delayed sleep-phase syndrome are:

1. There is an intractable delay in the phase of the major sleep period in relation to the desired clock time, as evidenced by a chronic or recurrent complaint of inability to fall asleep at a desired conventional clock time together with the inability to awaken at a desired and socially acceptable time.
2. When not required to maintain a strict schedule, patients will exhibit normal sleep quality and duration for their age and maintain a delayed, but stable, phase of entrainment to local time.
3. Patients have little or no reported difficulty in maintaining sleep once sleep has begun.
4. Patients have a relatively severe to absolute inability to advance the sleep phase to earlier hours by enforcing conventional sleep and wake times.
5. Sleep-wake logs and/or actigraphy monitoring for at least two weeks document a consistent habitual pattern of sleep onsets, usually later than 2 a.m., and lengthy sleeps.
6. Occasional noncircadian days may occur (i.e., sleep is "skipped" for an entire day and night plus some portion of the following day), followed by a sleep period lasting 12 to 18 hours.
7. The symptoms do not meet the criteria for any other sleep disorder causing inability to initiate sleep or excessive sleepiness.
8. If any of the following laboratory methods is used, it must demonstrate a delay in the timing of the habitual sleep period: 1) Twenty-four-hour polysomnographic monitoring (or by means of two consecutive nights of polysomnography and an intervening multiple sleep latency test), 2) Continuous temperature monitoring showing that the time of the absolute temperature nadir is delayed into the second half of the habitual (delayed) sleep episode.

Some people with the abnormality adapt their lives to the delayed sleep phase, avoiding common business hours (e.g., 9 a.m. to 5 p.m.) as much as possible. They have the disorder, but for them it is not a disability. The ICSD's severity criteria, all of them "over at least a one-month period", are:

- Mild: Two hour delay associated with little or mild impairment of social or occupational functioning.
- Moderate: Three hour delay associated with moderate impairment.
- Severe: Four hour delay associated with severe impairment.

Some features of DSPS which distinguish it from other sleep disorders are:

- People with DSPS have at least a normal—and often much greater than normal—ability to sleep during the morning, and sometimes in the afternoon as well. In contrast, those with chronic insomnia do not find it much easier to sleep during the morning than at night.
- People with DSPS fall asleep at more or less the same time every night, and sleep comes quite rapidly if the person goes to bed near the time he or she usually falls asleep. Young children with DSPS resist going to bed before they are sleepy, but the bedtime struggles disappear if they are allowed to stay up until the time they usually fall asleep.
- DSPS patients can sleep well and regularly when they can follow their own sleep schedule, e.g. on weekends and during vacations.
- DSPS is a chronic condition. Symptoms must have been present for at least one month before a diagnosis of DSPS can be made.

Attempting to force oneself onto daytime society's schedule with DSPS has been compared to constantly living with 6 hours of jet lag; the disorder has, in fact, been referred to as "social jet lag". Often, sufferers manage only a few hours sleep a night during the working week, then compensate by sleeping until the afternoon on weekends. Sleeping in on weekends, and/or taking long naps during the day, may give people with the disorder relief from daytime sleepiness but may also perpetuate the late sleep phase.

People with DSPS can be called extreme night owls. They feel most alert and say they function best and are most creative in the evening and at night. DSPS patients cannot simply force themselves to sleep early. They may toss and turn for hours in bed, and sometimes not sleep at all, before reporting to work or school. Less extreme and more flexible night owls, and indeed morning larks, are within the normal chronotype spectrum.

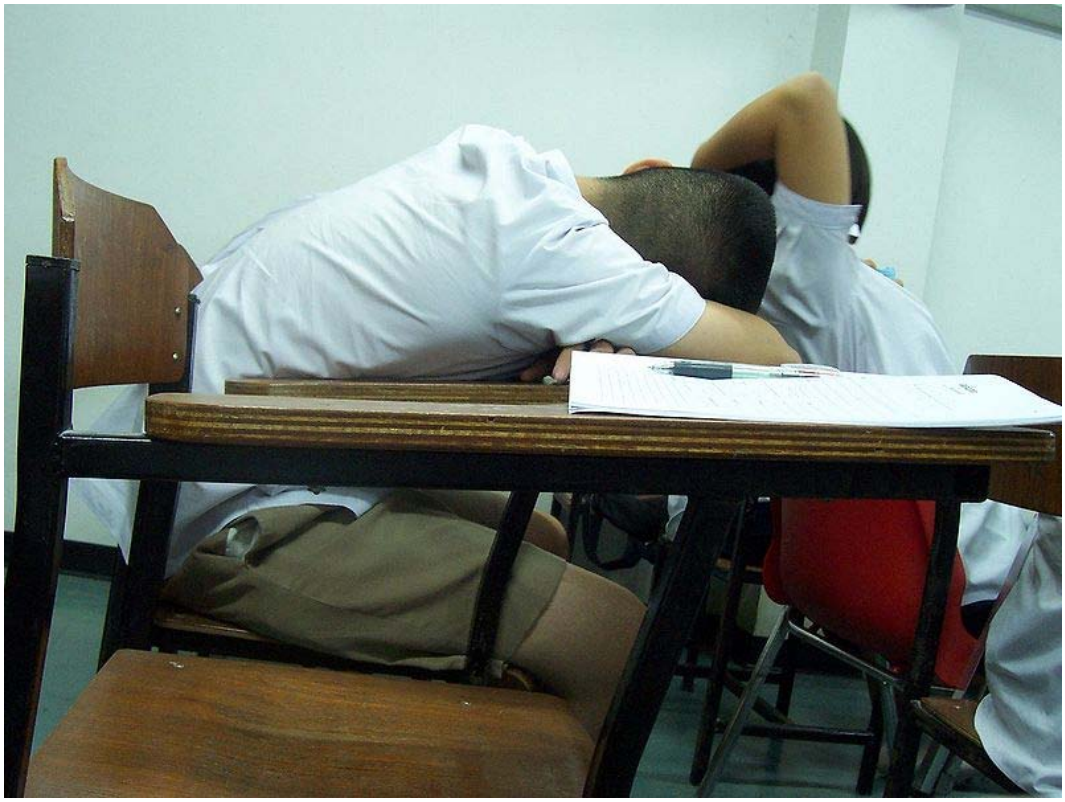
By the time DSPS patients seek medical help, they usually have tried many times to change their sleeping schedule. Failed tactics to sleep at earlier times may include maintaining proper sleep hygiene, relaxation techniques, early bedtimes, hypnosis, alcohol, sleeping pills, dull reading, and home remedies. DSPS patients who have tried using sedatives at night often report that the medication makes them feel tired or relaxed, but that it fails to induce sleep. They often have asked family members to help wake them

in the morning, or they have used several alarm clocks. As the syndrome occurs in childhood and is most common in adolescence, it is often the patient's parents who initiate seeking help, after great difficulty waking their child in time for school.

The current formal name established in the second edition of the International Classification of Sleep Disorders is **circadian rhythm sleep disorder, delayed sleep phase type**; the preferred common name is delayed sleep-phase disorder.

Prevalence

About 0.15% of adults, three in 2,000, have DSPS. Using the strict ICSD diagnostic criteria, a random study in 1993 of 7700 adults (aged 18–67) in Norway estimated the prevalence of DSPS at 0.17%. A similar study of 1525 adults (aged 15–59) in Japan estimated its prevalence at 0.13%.



Sleepy students

DSPS is not uncommon among teenagers; at least one study has indicated that the prevalence of DSPS among adolescents is as high as 7%. Among adolescents, boys predominate, while the gender distribution shows equal numbers of women and men in adults.

A marked delay of sleep patterns is a normal feature of the development of adolescent humans. According to Mary Carskadon, both circadian phase and homeostasis (the accumulation of sleep pressure during the wake period) contribute to a DSPS-like condition in post-pubertal as compared to pre-pubertal adolescents.

Physiology

DSPS is a disorder of the body's timing system—the biological clock. Individuals with DSPS might have an unusually long circadian cycle, might have a reduced response to the re-setting effect of daylight on the body clock and/or may respond overly to the delaying effects of evening light and too little to the advancing effect of light earlier in the day. In support of the increased sensitivity to evening light hypothesis, "the percentage of melatonin suppression by a bright light stimulus of 1,000 lux administered 2 hours prior to the melatonin peak has been reported to be greater in 15 DSPS patients than in 15 controls."

People with normal circadian systems can generally fall asleep quickly at night if they slept too little the night before. Falling asleep earlier will in turn automatically help to advance their circadian clocks due to decreased light exposure in the evening. In contrast, people with DSPS are unable to fall asleep before their usual sleep time, even if they are sleep-deprived. Sleep deprivation does not reset the circadian clock of DSPS patients, as it does with normal people.

People with the disorder who try to live on a normal schedule cannot fall asleep at a "reasonable" hour and have extreme difficulty waking because their biological clocks are not in phase with that schedule. Normal people who do not adjust well to working a night shift have similar symptoms (diagnosed as shift-work sleep disorder, SWSD).

In most cases, it is not known what causes the abnormality in the biological clocks of DSPS patients. DSPS tends to run in families, and a growing body of evidence suggests that the problem is associated with the hPer3 (human period 3) gene. There have been several documented cases of DSPS and non-24-hour sleep-wake syndrome developing after traumatic head injury.

There have been a few cases of DSPS developing into non-24-hour sleep-wake syndrome, a more severe and debilitating disorder in which the individual sleeps later each day. It has been suggested that, instead of (or perhaps in addition to) a reduced reaction to light in the morning, an abnormal *over-sensitivity* to light in the late evening might contribute to the odd non-circadian pattern.

Diagnosis

p.m.	Wed	Thu	Fri	Sat	Sun	Mon	Tue
a.m.	**Thu**	**Fri**	**Sat**	**Sun**	**Mon**	**Tue**	**Wed**

A **sleep diary** with nighttime in the middle and the weekend in the middle, the better to notice trends

DSPS is diagnosed by a clinical interview, actigraphic monitoring and/or a sleep diary kept by the patient for at least three weeks. When polysomnography is also used, it is primarily for the purpose of ruling out other disorders such as narcolepsy or sleep apnea. If a person can, on her/his own with just the help of alarm clocks and will-power, adjust to a daytime schedule, the diagnosis is not given.

DSPS is frequently misdiagnosed or dismissed. It has been named as one of the sleep disorders most commonly misdiagnosed as a primary psychiatric disorder. DSPS is often confused with: psychophysiological insomnia; depression; psychiatric disorders such as schizophrenia, ADHD or ADD; other sleep disorders; or school refusal. Practitioners of sleep medicine point out the dismally low rate of accurate diagnosis of the disorder, and have often asked for better physician education on sleep disorders.

Management

Treatment, a set of management techniques, is specific to DSPS. It is different from treatment of insomnia, and recognizes the patients' ability to sleep well on their own schedules, while addressing the timing problem. Success, if any, may be partial; for example, a patient who normally awakens at noon may only attain a wake time of 10 or 10:30 with treatment and follow-up. Being consistent with the treatment is paramount.

Before starting DSPS treatment, patients are often asked to spend at least a week sleeping regularly, without napping, at the times when the patient is most comfortable. It is important for patients to start treatment well-rested.

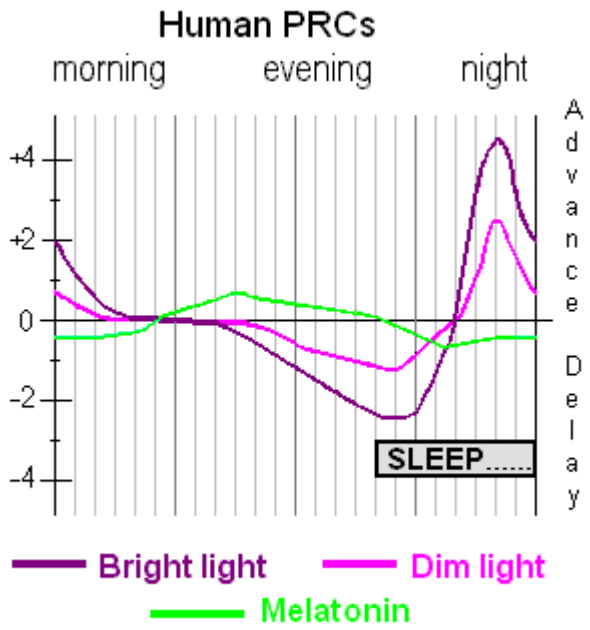
Treatments that have been reported in the medical literature include:

Light therapy (phototherapy) with a full spectrum lamp or portable visor, usually 10,000 lux for 30–90 minutes at the patient's usual time of spontaneous awakening, or shortly before (but not long before), which is in accordance with the phase response curve (PRC) for light. The use of an LED light therapy device can reduce this to 15–30 minutes. Sunlight can also be used. Only experimentation, preferably with specialist help, will show how great an advance is possible and comfortable. For maintenance, some patients must continue the treatment indefinitely, some may reduce the daily treatment to 15 minutes, others may use the lamp, for example, just a few days a week or just every third week. Whether the treatment is successful is highly individual. Light therapy generally requires adding some extra time to the patient's morning routine. Patients with a family history of macular degeneration are advised to consult with an eye doctor. The use of exogenous melatonin administration in conjunction with light therapy is common.

Dim lights in the evening, sometimes called darkness therapy. Just as bright light upon awakening should advance one's sleep-phase, bright light in the evening and night delays it. One might be advised to keep lights dim the last hours before bedtime and even wear sunglasses or amber-colored goggles. Attaining an earlier sleep onset, in a dark room with eyes closed, effectively blocks a period of phase-delaying light. An understanding of this is a motivating factor in treatment.

Chronotherapy, which is intended to reset the circadian clock by manipulating bedtimes. Often, chronotherapy must be repeated every few months to maintain results, and its safety is uncertain. It can be one of two types. The most common consists of going to bed two or more hours *later* each day for several days until the desired bedtime is reached. A modified chronotherapy (Thorpy, 1988) is called controlled sleep deprivation with phase advance, SDPA. One stays awake one whole night and day, then goes to bed 90 minutes *earlier* than usual and maintains the new bedtime for a week. This process is repeated weekly until the desired bedtime is reached.

Melatonin taken an hour or so before usual bedtime may induce sleepiness.



Phase response curves for light and for melatonin administration

Taken this late, it does not, of itself, affect circadian rhythms, but a decrease in exposure to light in the evening is helpful in establishing an earlier pattern. In accordance with its phase response curve (PRC), a very small dose of melatonin can also, or instead, be taken some hours earlier as an aid to resetting the body clock; it must then be so small as to not induce excessive sleepiness.

Side effects of melatonin may include disturbance of sleep, nightmares, daytime sleepiness and depression, though the current tendency to use lower doses has decreased such complaints. Large doses of melatonin can even be counterproductive: Lewy et al. provide support to the "idea that too much melatonin may spill over onto the wrong zone of the melatonin phase-response curve." The long-term effects of melatonin administration have not been examined. In some countries the hormone is available only by prescription or not at all. In the United States and Canada, melatonin is freely available as a dietary supplement. The prescription drug Rozerem (ramelteon) is a melatonin analogue that selectively binds to the melatonin MT_1 and MT_2 receptors and, hence, has the possibility of being effective in the treatment of DSPS.

A review by a US government agency found little difference between melatonin and placebo for most primary and secondary sleep disorders. The one exception, where melatonin is effective, is the "circadian abnormality" DSPS.

Modafinil (Provigil) is approved in the US for treatment of shift-work sleep disorder, which shares some characteristics with DSPS, and a number of clinicians are prescribing it for DSPS patients. Modafinil does not deal with underlying causes of DSPS, but it may improve a sleep-deprived patient's quality of life. Taking modafinil less than 12 hours

before the desired sleep onset time will likely exacerbate the symptoms by delaying the sleep/wake cycle.

Trazodone successfully treated DSPS in one elderly man.

Vitamin B_{12} was, in the 1990s, suggested as a remedy for DSPS/DSPD, and can still be found to be recommended by many sources. Several case reports were published. However, a review for the American Academy of Sleep Medicine in 2007 concluded that no benefit was seen from this treatment.

A strict schedule and good sleep hygiene are essential in maintaining any good effects of treatment. With treatment, some people with mild DSPS may sleep and function well with an early sleep schedule. Caffeine and other stimulant drugs to keep a person awake during the day may not be necessary, and should be avoided in the afternoon and evening, in accordance with good sleep hygiene. A chief difficulty of treating DSPS is in *maintaining* an earlier schedule after it has been established. Inevitable events of normal life, such as staying up late for a celebration or having to stay in bed with an illness, tend to reset the sleeping schedule to its intrinsic late times.

Prognosis

Adaptation to late sleeping times

Long-term success rates of treatment have seldom been evaluated. However, experienced clinicians acknowledge that DSPS is extremely difficult to treat. One study of 61 DSPS patients with mean sleep onset at about 3 a.m. and mean waking time of about 11:30 a.m., followed up with questionnaires to the subjects a year later. Good effect was seen *during* the 6-week treatment with a daily, very large dose (5 mg), of melatonin. Follow-up showed that over 90% had relapsed to pretreatment sleeping patterns within the year, 28.8% reporting that the relapse occurred within one week. The milder cases retained changes significantly longer than the more severe cases.

Working the evening or night shift, or working at home, makes DSPS less of an obstacle for some. Many of these people do not describe their pattern as a "disorder". Some DSPS individuals nap, even taking 4–5 hours of sleep in the morning and 4–5 in the evening. DSPS-friendly careers can include security work, work in theater, the entertainment industry, hospitality work in restaurants, hotels or bars, call center work, nursing, taxi or truck driving, the media, and freelance writing, translation, IT work, or medical transcription.

Some people with the disorder are unable to adapt to earlier sleeping times, even after many years of treatment. Sleep researchers have proposed that the existence of untreatable cases of DSPS be formally recognized as a "sleep-wake schedule disorder disability", an invisible disability.

Rehabilitation for DSPS patients includes acceptance of the condition, and choosing a career that allows late sleeping times, or running their own home business because it allows flexible hours. In a few schools and universities, students with DSPS have been able to arrange to take exams at times of day when their concentration levels may be good.

> “ Patients suffering from SWSD disability should be encouraged to accept the fact that they suffer from a permanent disability, and that their quality of life can only be improved if they are willing to undergo rehabilitation. It is imperative that physicians recognize the medical condition of SWSD disability in their patients and bring it to the notice of the public institutions responsible for vocational and social rehabilitation. ”

In the United States, the Americans with Disabilities Act requires that employers accommodate employees with sleeping disorders by providing appropriate accommodations. In the case of DSPS, this requires that the employer accommodate later working hours for jobs normally performed on a "9-to-5" work schedule.

Impact on patients

Lack of public awareness of the disorder contributes to the difficulties experienced by people with DSPS, who are commonly stereotyped as undisciplined or lazy. Parents may be chastised for not giving their children acceptable sleep patterns, and schools and workplaces rarely tolerate chronically late, absent, or sleepy students and workers, failing to see them as having a chronic illness.

> “ By the time DSPS sufferers receive an accurate diagnosis, they often have been misdiagnosed or labelled as lazy and incompetent workers or students for years. Misdiagnosis of circadian rhythm sleep disorders as psychiatric conditions causes considerable distress to patients and their families, and leads to some patients being inappropriately prescribed psychoactive drugs. For many patients, diagnosis of DSPS is itself a life-changing breakthrough. ”

As DSPS is so little-known and so misunderstood, support groups may be important for information and self-acceptance.

People with DSPS who force themselves to live on a normal 9-5 day "are not often successful and may develop physical and psychological complaints during waking hours, i.e. sleepiness, fatigue, headache, decreased appetite, or depressed mood. Patients with [Circadian Rhythm Sleep Disorders] often have difficulty maintaining ordinary social lives, and some of them lose their jobs or fail to attend school.

Comorbidity

In the DSPS cases reported in the literature, about half of the patients have suffered from clinical depression or other psychological problems, about the same proportion as among patients with chronic insomnia. According to the ICSD:

> “Although some degree of psychopathology is present in about half of adult patients with DSPS, there appears to be no particular psychiatric diagnostic category into which these patients fall. Psychopathology is not particularly more common in DSPS patients compared to patients with other forms of "insomnia." ... Whether DSPS results directly in clinical depression, or vice versa, is unknown, but many patients express considerable despair and hopelessness over sleeping normally again.”

A direct neurochemical relationship between sleep mechanisms and depression is another possibility.

It is conceivable that DSPS often has a major role in causing depression because it can be such a stressful and misunderstood disorder. A recent study from the University of California, San Diego found no association of bipolar disorder (history of mania) with DSPD, and it states that there may be

> “behaviorally-mediated mechanisms for comorbidity between DSPD and depression. For example, the lateness of DSPD cases and their unusual hours may lead to social opprobrium and rejection, which might be depressing...”

The fact that half of DSPS patients are not depressed indicates that DSPS is not merely a symptom of depression. Sleep researcher M. Terman has suggested that those who follow their internal circadian clocks may be less likely to suffer from depression than those try to live on a different schedule.

DSPS patients who also suffer from depression may be best served by seeking treatment for both problems. There is some evidence that effectively treating DSPS can improve the patient's mood and make antidepressants more effective.

Vitamin D deficiency has been linked to depression. As it is a condition which comes from lack of exposure to sunlight, anyone who does not get enough sunlight exposure during the daylight hours could be at risk.

Accommodations

United States

According to the Americans with Disabilities Act of 1990, "disability" is defined as a "physical or mental impairment that substantially limits one or more major life activities". "Sleeping" is defined as a "major life activity" in § 12102(2)(a) of the statute.

Chapter 8

Narcolepsy

Narcolepsy	
ICD-10	G47.4
ICD-9	347
OMIM	161400
DiseasesDB	8801
eMedicine	neuro/522
MeSH	D009290

Narcolepsy is a chronic sleep disorder, or dyssomnia, characterized by excessive daytime sleepiness (EDS) in which a person experiences extreme fatigue and possibly falls asleep at inappropriate times, such as while at work or at school. Narcoleptics usually experience disturbed nocturnal sleep and an abnormal daytime sleep pattern, which is often confused with insomnia. When a narcoleptic falls asleep they generally experience the REM stage of sleep within 10 minutes; whereas most people do not experience REM sleep until after 90 minutes.

Another problem that some narcoleptics experience is cataplexy, a sudden muscular weakness brought on by strong emotions (though many people experience cataplexy without having an emotional trigger). It often manifests as muscular weaknesses ranging from a barely perceptible slackening of the facial muscles to the dropping of the jaw or head, weakness at the knees, or a total collapse. Usually speech is slurred and vision is impaired (double vision, inability to focus), but hearing and awareness remain normal. In some rare cases, an individual's body becomes paralyzed and muscles become stiff.

Narcolepsy is a neurological sleep disorder. It is not caused by mental illness or psychological problems. It is most likely affected by a number of genetic abnormalities that affect specific biologic factors in the brain, combined with an environmental trigger during the brain's development, such as a virus.

The term *narcolepsy* derives from the French word *narcolepsie* created by the French physician Jean-Baptiste-Édouard Gélineau by combining the Greek νάρκη (*narkē*, "numbness" or "stupor"), and λῆψις (*lepsis*), "attack" or "seizure".

Signs and symptoms

The main characteristic of narcolepsy is excessive daytime sleepiness (EDS), even after adequate nighttime sleep. A person with narcolepsy is likely to become drowsy or fall asleep or just be very tired throughout the day, often at inappropriate times and places. Daytime naps may occur with little warning and may be physically irresistible. These naps can occur several times a day. They are typically refreshing, but only for a few hours. Drowsiness may persist for prolonged periods of time. In addition, nighttime sleep may be fragmented with frequent awakenings.

The classic symptoms of the disorder, often referred to as the "tetrad of narcolepsy," are cataplexy, sleep paralysis, hypnagogic hallucinations, and excessive daytime sleepiness. Other symptoms include automatic behaviors. These symptoms may not occur in all patients. Cataplexy is an episodic condition featuring loss of muscle function, ranging from slight weakness (such as limpness at the neck or knees, sagging facial muscles, or inability to speak clearly) to complete body collapse. Episodes may be triggered by sudden emotional reactions such as laughter, anger, surprise, or fear, and may last from a few seconds to several minutes. The person remains conscious throughout the episode. In some cases, cataplexy may resemble epileptic seizures. Sleep paralysis is the temporary inability to talk or move when waking (or less often, when falling asleep). It may last a few seconds to minutes. This is often frightening but is not dangerous. Hypnagogic hallucinations are vivid, often frightening, dreamlike experiences that occur while dozing, falling asleep and/or while awakening.

Automatic behavior means that a person continues to function (talking, putting things away, etc.) during sleep episodes, but awakens with no memory of performing such activities. It is estimated that up to 40 percent of people with narcolepsy experience automatic behavior during sleep episodes. Sleep paralysis and hypnagogic hallucinations also occur in people who do not have narcolepsy, but more frequently in people who are suffering from extreme lack of sleep. Cataplexy is generally considered to be unique to narcolepsy and is analogous to sleep paralysis in that the usually protective paralysis mechanism occurring during sleep is inappropriately activated. The opposite of this situation (failure to activate this protective paralysis) occurs in rapid eye movement behavior disorder.

In most cases, the first symptom of narcolepsy to appear is excessive and overwhelming daytime sleepiness. The other symptoms may begin alone or in combination months or

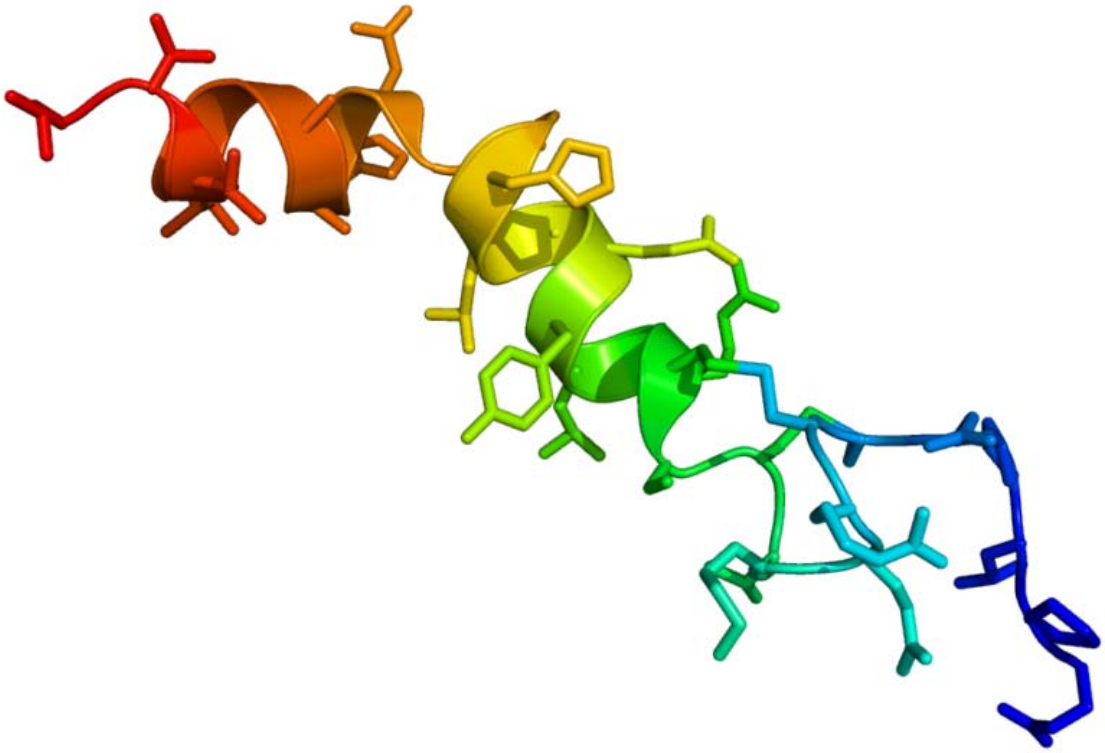
years after the onset of the daytime naps. There are wide variations in the development, severity, and order of appearance of cataplexy, sleep paralysis, and hypnagogic hallucinations in individuals. Only about 20 to 25 percent of people with narcolepsy experience all four symptoms. The excessive daytime sleepiness generally persists throughout life, but sleep paralysis and hypnagogic hallucinations may not.

Although these are the common symptoms of narcolepsy, many people with narcolepsy also suffer from insomnia for extended periods of time. The symptoms of narcolepsy, especially the excessive daytime sleepiness and cataplexy, often become severe enough to cause serious problems in a person's social, personal, and professional life. Normally, when an individual is awake, brain waves show a regular rhythm. When a person first falls asleep, the brain waves become slower and less regular. This sleep state is called non-rapid eye movement (NREM) sleep. After about an hour and a half of NREM sleep, the brain waves begin to show a more active pattern again. This sleep state, called REM sleep (rapid eye movement sleep), is when most remembered dreaming occurs. Associated with the EEG-observed waves during REM sleep, muscle atonia is present (called REM atonia).

In narcolepsy, the order and length of NREM and REM sleep periods are disturbed, with REM sleep occurring at sleep onset instead of after a period of NREM sleep. Thus, narcolepsy is a disorder in which REM sleep appears at an abnormal time. Also, some of the aspects of REM sleep that normally occur only during sleep—lack of muscular control, sleep paralysis, and vivid dreams—occur at other times in people with narcolepsy. For example, the lack of muscular control can occur during wakefulness in a cataplexy episode; it is said that there is intrusion of REM atonia during wakefulness. Sleep paralysis and vivid dreams can occur while falling asleep or waking up. Simply put, the brain does not pass through the normal stages of dozing and deep sleep but goes directly into (and out of) rapid eye movement (REM) sleep.

This has several consequences. Night time sleep does not include as much deep sleep, so the brain tries to "catch up" during the day, hence EDS. People with narcolepsy may visibly fall asleep at unpredicted moments (such motions as head bobbing are common). People with narcolepsy fall quickly into what appears to be very deep sleep, and they wake up suddenly and can be disoriented when they do (dizziness is a common occurrence). They have very vivid dreams, which they often remember in great detail. People with narcolepsy may dream even when they only fall asleep for a few seconds.

Causes



A depiction of the neuropeptide **Orexin A**. People with narcolepsy often have a reduced number of neurons that produce this protein.

Although the cause of narcolepsy was not determined for many years after its discovery, scientists had discovered conditions that seemed to be associated with an increase in an individual's risk of having the disorder. Specifically, there appeared to be a strong link between narcoleptic individuals and certain genetic conditions. One factor that seemed to predispose an individual to narcolepsy involved an area of Chromosome 6 known as the HLA complex. There appeared to be a correlation between narcoleptic individuals and certain variations in HLA genes, although it was not required for the condition to occur. Certain variations in the HLA complex were thought to increase the risk of an auto-immune response to protein-producing neurons in the brain. The protein produced, called hypocretin or orexin, is responsible for controlling appetite and sleep patterns. Individuals with narcolepsy often have reduced numbers of these protein-producing neurons in their brains. In 2009 the autoimmune hypothesis was supported by research carried out at Stanford University School of Medicine.

The neural control of normal sleep states and the relationship to narcolepsy are only partially understood. In humans, narcoleptic sleep is characterized by a tendency to go

abruptly from a waking state to REM sleep with little or no intervening non-REM sleep. The changes in the motor and proprioceptive systems during REM sleep have been studied in both human and animal models. During normal REM sleep, spinal and brainstem alpha motor neuron depolarization produces almost complete atonia of skeletal muscles via an inhibitory descending reticulospinal pathway. Acetylcholine may be one of the neurotransmitters involved in this pathway. In narcolepsy, the reflex inhibition of the motor system seen in cataplexy is believed to be identical to that seen in normal REM sleep.

In 2004 researchers in Australia induced narcolepsy-like symptoms in mice by injecting them with antibodies from narcoleptic humans. The research has been published in the Lancet providing strong evidence suggesting that some cases of narcolepsy might be caused by autoimmune disease. Narcolepsy is strongly associated with HLA-DQB1*0602 genotype. There is also an association with HLA-DR2 and HLA-DQ1. This may represent linkage disequilibrium. Despite the experimental evidence in human narcolepsy that there may be an inherited basis for at least some forms of narcolepsy, the mode of inheritance remains unknown. Some cases are associated with genetic diseases such as Niemann-Pick disease or Prader-Willi syndrome.

Currently a link between GlaxoSmithKline's swine flu vaccine Pandemrix and childhood narcolepsy is being investigated due to increased prevalence of narcolepsy in Finnish and Swedish children after vaccinations. Finland's National Institute of Health and Welfare is recommending that Pandemrix vaccinations are suspended pending further investigation into 15 reported cases of recently vaccinated children developing narcolepsy.

In Finland in mid-November 2010, 37 cases of children's narcolepsy had been reported as suspected adverse events of Pandemrix. This can compared to normal average of 3 cases of children's narcolepsy per year.

Diagnosis

Diagnosis is relatively easy when all the symptoms of narcolepsy are present, but if the sleep attacks are isolated and cataplexy is mild or absent, diagnosis is more difficult. It is also possible for cataplexy to occur in isolation. Two tests that are commonly used in diagnosing narcolepsy are the polysomnogram and the multiple sleep latency test (MSLT). These tests are usually performed by a sleep specialist. The polysomnogram involves continuous recording of sleep brain waves and a number of nerve and muscle functions during nighttime sleep. When tested, people with narcolepsy fall asleep rapidly, enter REM sleep early, and may awaken often during the night. The polysomnogram also helps to detect other possible sleep disorders that could cause daytime sleepiness.

For the multiple sleep latency test, a person is given a chance to sleep every 2 hours during normal wake times. Observations are made of the time taken to reach various stages of sleep (sleep onset latency). This test measures the degree of daytime sleepiness and also detects how soon REM sleep begins. Again, people with narcolepsy fall asleep rapidly and enter REM sleep early.

Treatment

Treatment is tailored to the individual, based on symptoms and therapeutic response. The time required to achieve optimal control of symptoms is highly variable, and may take several months or longer. Medication adjustments are also frequently necessary, and complete control of symptoms is seldom possible. While oral medications are the mainstay of formal narcolepsy treatment, lifestyle changes are also important.

The main treatment of excessive daytime sleepiness in narcolepsy is central nervous system stimulants such as methylphenidate, amphetamine, methamphetamine, modafinil (Provigil), a new stimulant with a different pharmacologic mechanism, and/or armodafinil (Nuvigil). In Fall 2007 an alert for severe adverse skin reactions to modafinil was issued by the FDA. Other medications used are codeine and selegiline. Another drug that is used is atomoxetine (Strattera), a non-stimulant and norepinephrine reuptake inhibitor (NRI), that has little or no abuse potential. In many cases, planned regular short naps can reduce the need for pharmacological treatment of the EDS to a low or non-existent level.

Cataplexy and other REM-sleep symptoms are frequently treated with tricyclic antidepressants such as clomipramine, imipramine, or protriptyline, as well as other drugs that suppress REM sleep. Venlafaxine (branded as Effexor XR by Wyeth Pharmaceuticals), an antidepressant which blocks the reuptake of serotonin and norepinephrine, has shown usefulness in managing symptoms of cataplexy, however, it has notable side-effects including sleep disruption.

Another treatment option for narcolepsy is Xyrem (sodium oxybate) oral solution. Xyrem is a prescription medication manufactured by Jazz Pharmaceuticals, and is approved by the U.S. Food and Drug Administration (FDA) for the treatment of cataplexy associated with narcolepsy and Excessive Daytime Sleepiness (EDS) associated with narcolepsy. The American Academy of Sleep Medicine (AASM) recently recognized Xyrem as a standard of care for the treatment of cataplexy, daytime sleepiness, and disrupted sleep due to narcolepsy in its Practice Parameters for the Treatment of Narcolepsy and other Hypersomnias of Central Origin. These recommendations are based upon careful review of the medical literature, and the designation “standard” of care “reflects a high degree of clinical certainty” based on strong empirical evidence. Xyrem is the only medication specifically indicated and approved for cataplexy associated with narcolepsy. Xyrem has been shown to reduce symptoms of EDS associated with narcolepsy. While the exact mechanism of action is unknown, Xyrem is thought to improve the quality of nocturnal sleep by increasing the prevalence of slow wave (delta) sleep (as this is the time when the brain is least active and therefore most at rest and able to rebuild and repair itself physiologically). Xyrem appears to help sufferers much more effectively than the hypnotic class of medications typically used for insomnia (hypnotics tend to obstruct delta wave sleep), so it can be vital to be properly diagnosed as narcoleptic rather than insomniac.

Using stimulants to mask daytime sleepiness does not address the actual cause of the problem. Stimulants may provide some assistance with daytime activity, but the underlying cause will remain and potentially worsen over time due to the stimulant itself becoming an obstruction to delta wave sleep periods. Lifestyle changes involving reduced stress, more exercise (especially for overweight persons experiencing EDS caused by sleep apnea and snoring) and less stimulant intake (such as coffee and nicotine) are likely to be ideal forms of assistive treatment. Some people with narcolepsy have a nocturnal body clock and are helped by selecting an occupation that properly coincides with their body's natural sleep cycle (such as sleeping in the day and working at night). This allows sufferers to avoid the need to force themselves into the more common 9 to 5 schedule that their body is unable to maintain, and avoids the need to take stimulants to remain active during the times when their bodies are inclined to rest.

In addition to drug therapy, an important part of treatment is scheduling short naps (10 to 15 minutes) two to three times per day to help control excessive daytime sleepiness and help the person stay as alert as possible. Daytime naps are not a replacement for nighttime sleep, especially if a person's body is natively inclined towards a nocturnal life cycle. Ongoing communication between the health care provider, patient, and the patient's family members is important for optimal management of narcolepsy.

Finally, a recent study reported that transplantation of hypocretin neurons into the pontine reticular formation in rats is feasible, indicating the development of alternative therapeutic strategies in addition to pharmacological interventions.

Epidemiology

It is estimated that as many as 3 million people worldwide are affected by narcolepsy. In the United States, it is estimated that this condition afflicts as many as 200,000 Americans, but fewer than 50,000 are diagnosed. It is as widespread as Parkinson's disease or multiple sclerosis and more prevalent than cystic fibrosis, but it is less well known. Narcolepsy is often mistaken for depression, epilepsy, or the side effects of medications. It can also be mistaken for poor sleeping habits, recreational drug use, or laziness. Narcolepsy can occur in both men and women at any age, although its symptoms are usually first noticed in teenagers or young adults. There is strong evidence that narcolepsy may run in families; 8 to 12 percent of people with narcolepsy have a close relative with this neurologic disorder.

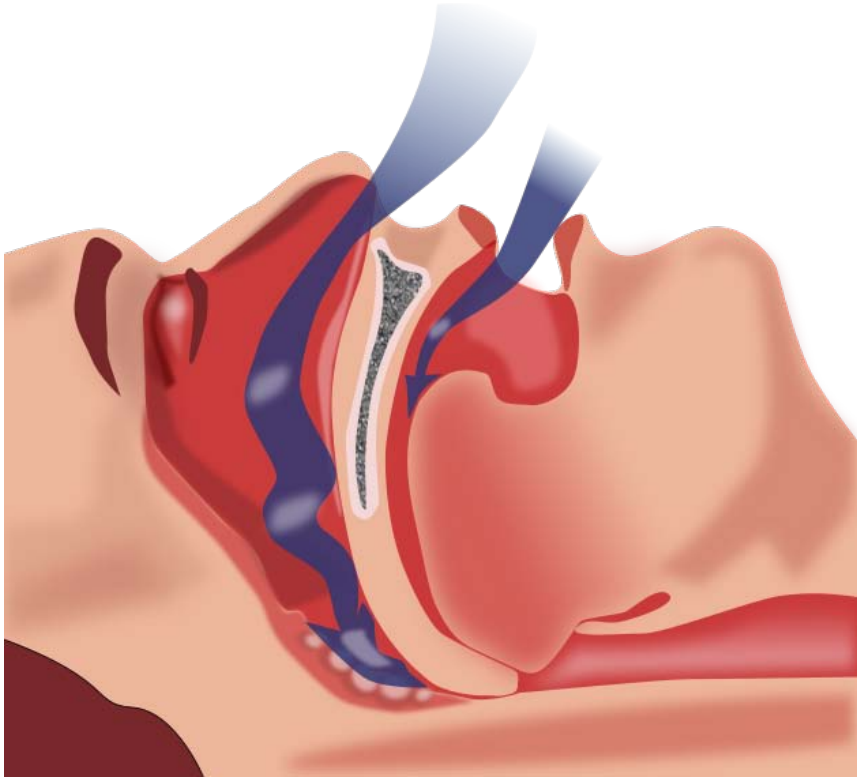
Narcolepsy has its typical onset in adolescence and young adulthood. There is an average 15-year delay between onset and correct diagnosis which may contribute substantially to the disabling features of the disorder. Cognitive, educational, occupational, and psychosocial problems associated with the excessive daytime sleepiness of narcolepsy have been documented. For these to occur in the crucial teen years when education, development of self-image, and development of occupational choice are taking place is especially damaging. While cognitive impairment does occur, it may only be a reflection of the excessive daytime somnolence.

The prevalence of narcolepsy is about 1 per 2,000 persons. It is a reason for patient visits to sleep disorder centers, and with its onset in adolescence, it is also a major cause of learning difficulty and absenteeism from school. Normal teenagers often already experience excessive daytime sleepiness because of a maturational increase in physiological sleep tendency accentuated by multiple educational and social pressures; this may be disabling with the addition of narcolepsy symptoms in susceptible teenagers. In clinical practice, the differentiation between narcolepsy and other conditions characterized by excessive somnolence may be difficult. Treatment options are currently limited. There is a paucity in the literature of controlled double-blind studies of possible effective drugs or other forms of therapy. Mechanisms of action of some of the few available therapeutic agents have been explored but detailed studies of mechanisms of action are needed before new classes of therapeutic agents can be developed. Narcolepsy is an underdiagnosed condition in the general population. This is partly because its severity varies from obvious to barely noticeable. Some people with narcolepsy do not suffer from loss of muscle control. Others may only feel sleepy in the evenings.

Chapter 9

Obstructive Sleep Apnea

Obstructive sleep apnea



Obstructive sleep apnea

ICD-10	G47.3
ICD-9	327.23
eMedicine	ped/2114
MeSH	D012891

Obstructive sleep apnea (OSA) or **obstructive sleep apnea syndrome** is the most common type of sleep apnea and is caused by obstruction of the upper airway. It is characterized by repetitive pauses in breathing during sleep, despite the effort to breathe, and is usually associated with a reduction in blood oxygen saturation. These pauses in breathing, called **apneas** (literally, "without breath"), typically last 20 to 40 seconds.

The individual with OSA is rarely aware of having difficulty breathing, even upon awakening. It is recognized as a problem by others witnessing the individual during episodes or is suspected because of its effects on the body (*sequelae*). OSA is commonly accompanied with snoring.

Symptoms may be present for years, even decades without identification, during which time the sufferer may become conditioned to the daytime sleepiness and fatigue associated with significant levels of sleep disturbance. Persons who sleep alone without a long-term human partner may not be told about their sleep disorder symptoms.

Since the muscle tone of the body ordinarily relaxes during sleep, and since, at the level of the throat, the human airway is composed of walls of soft tissue, which can collapse, it is easy to understand how breathing can be obstructed during sleep. Although a very low level of obstructive sleep apnea is considered to be within the bounds of normal sleep, and many individuals experience episodes of obstructive sleep apnea at some point in life, a much smaller percentage of people are afflicted with chronic, severe obstructive sleep apnea.

Many people experience episodes of obstructive sleep apnea for only a short period of time. This can be the result of an upper respiratory infection that causes nasal congestion, along with swelling of the throat, or tonsillitis that temporarily produces very enlarged tonsils. The Epstein-Barr virus, for example, is known to be able to dramatically increase the size of lymphoid tissue during acute infection, and obstructive sleep apnea is fairly common in acute cases of severe infectious mononucleosis. Temporary spells of obstructive sleep apnea syndrome may also occur in individuals who are under the influence of a drug (such as alcohol) that may relax their body tone excessively and interfere with normal arousal from sleep mechanisms.

Signs and symptoms

Common signs of obstructive sleep apnea include unexplained daytime sleepiness, restless sleep, and loud snoring (with periods of silence followed by gasps). Less common symptoms are morning headaches; insomnia; trouble concentrating; mood changes such as irritability, anxiety and depression; forgetfulness; increased heart rate and/or blood pressure; decreased sex drive; unexplained weight gain; increased urination and/or nocturia; frequent heartburn or Gastroesophageal reflux disease; and heavy night sweats.

Adults

In adults, the most typical individual with obstructive sleep apnea syndrome suffers from obesity, with particular heaviness at the face and neck. Obesity is not always present with OSA; in fact, a significant number of adults with normal body mass indices (BMI) have decrease in muscle tone causing airway collapse and sleep apnea. The cause of the decreased tone is not presently understood. The hallmark symptom of obstructive sleep apnea syndrome in adults is excessive daytime sleepiness. Typically, an adult or adolescent with severe long-standing obstructive sleep apnea will fall asleep for very brief periods in the course of usual daytime activities if given any opportunity to sit or rest. This behavior may be quite dramatic, sometimes occurring during conversations with others at social gatherings.

The hypoxia (absence of oxygen supply) through OSA may cause changes in the neurons of the hippocampus and the right frontal cortex in the brain. Research through the use of neuro-imaging revealed evidence of hippocampal atrophy in people suffering from OSA. They found some OSA sufferers to have problems in mentally manipulating nonverbal information and executive function.

Children

Although this so called "hypersomnolence" (excessive sleepiness) may also occur in children, it is not at all typical of young children with sleep apnea. Toddlers and young children with severe obstructive sleep apnea instead ordinarily behave as if "over-tired" or "hyperactive." Adults and children with very severe obstructive sleep apnea also differ in typical body *habitus*. Adults are generally heavy, with particularly short and heavy necks. Young children, on the other hand, are generally not only thin, but may have "failure to thrive", where growth is reduced. Poor growth occurs for two reasons: the work of breathing is high enough that calories are burned at high rates even at rest, and the nose and throat are so obstructed that eating is both tasteless and physically uncomfortable. Obstructive sleep apnea in children, unlike adults, is often caused by obstructive tonsils and adenoids and may sometimes be cured with tonsillectomy and adenoidectomy.

This problem can also be caused by excessive weight in children. In this case, the symptoms are more like the symptoms adults feel: restlessness, exhaustion, and more.

Children with OSA may experience learning and memory deficits. OSA has also been linked to lowered childhood IQ scores.

Risk factors

Old age is often accompanied by muscular & neurological loss of ability of the airways. Premature aging is temporarily caused by chemical depressants; alcoholic drinks being the most common. Permanent premature airway aging may be caused by traumatic brain injury, or poor adherence to chemical and or speech-therapy treatments.

Individuals with decreased muscle tone, increased soft tissue around the airway, and structural features that give rise to a narrowed airway are at high risk for obstructive sleep apnea. Men, whose anatomy is typified by increased body mass in the torso and neck, are more typical sleep apnea sufferers, especially through middle age and older. Adult women suffer typically less frequently and to a lesser degree than men do, owing partially to physiology, but possibly to emerging links to levels of progesterone. Prevalence in post-menopausal women approaches that of men in the same age range. Women are also at a greater risk for developing OSA during pregnancy.

Obstructive sleep apnea also appears to have a genetic component; those with a family history of OSA are more likely to develop it themselves. Lifestyle factors such as smoking may also increase the chances of developing OSA as the chemical irritants in smoke tend to inflame the soft tissue of the upper airway and promote fluid retention, both of which can result in a narrower airway. An individual may also experience or exacerbate OSA with the consumption of alcohol, sedatives, or any other medication that increases sleepiness as most of these drugs are also muscle relaxants.

Causes

Most cases of OSA are believed to be caused by:

- old age (natural or premature),
- brain injury (temporary or permanent),
- decreased muscle tone,
- increased soft tissue around the airway (sometimes due to obesity), and
- structural features that give rise to a narrowed airway.

Decreased muscle tone can be caused by drugs or alcohol, or it can be caused by neurological problems or other disorders. Some people have more than one of these issues. There is also a theory that long-term snoring might induce local nerve lesions in the pharynx in the same way as long-term exposure to vibration might cause nerve lesions in other parts of the body. Snoring is a vibration of the soft tissues of the upper airways, and studies have shown electrophysiological findings in the nerves and muscles of the pharynx indicating local nerve lesions.

Craniofacial syndromes

There are patterns of unusual facial features that occur in recognizable syndromes. Some of these craniofacial syndromes are genetic, others are from unknown causes. In many craniofacial syndromes, the features that are unusual involve the nose, mouth and jaw, or resting muscle tone, and put the individual at risk for obstructive sleep apnea syndrome.

Down Syndrome is one such syndrome. In this chromosomal abnormality, several features combine to make the presence of obstructive sleep apnea more likely. The specific features in Down Syndrome that predispose to obstructive sleep apnea include: relatively low muscle tone, narrow nasopharynx, and large tongue. Obesity and enlarged tonsils and adenoids, conditions that occur commonly in the western population, are much more likely to be obstructive in a person with these features than without them. Obstructive sleep apnea does occur even more frequently in people with Down Syndrome than in the general population. A little over 50% of all people with Down Syndrome suffer from obstructive sleep apnea (de Miguel-Díez, et al. 2003), and some physicians advocate routine testing of this group (Shott, et al. 2006).

In other craniofacial syndromes, the abnormal feature may actually improve the airway, but its correction may put the person at risk for obstructive sleep apnea *after* surgery, when it is modified. Cleft palate syndromes are such an example. During the newborn period, all humans are obigate nasal breathers. The palate is both the roof of the mouth and the floor of the nose. Having an open palate may make feeding difficult, but generally does not interfere with breathing, in fact - if the nose is very obstructed an open palate may relieve breathing. There are a number of clefting syndromes in which the open palate is not the only abnormal feature, additionally there is a narrow nasal passage - which may not be obvious. In such individuals, closure of the cleft palate- whether by surgery or by a temporary oral appliance, can cause the onset of obstruction.

Skeletal advancement in an effort to physically increase the pharyngeal airspace is often an option for craniofacial patients with upper airway obstruction and small lower jaws (mandibles). These syndromes include Treacher Collins Syndrome and Pierre Robin Sequence. Mandibular advancement surgery is often just one of the modifications needed to improve the airway, others may include reduction of the tongue, tonsillectomy or modified uvulopalatoplasty.

Complication of pharyngeal flap surgery

Obstructive sleep apnea is a serious complication that seems to be most frequently associated with pharyngeal flap surgery, compared to other procedures for treatment of velopharyngeal inadequacy (VPI). In OSA, recurrent interruptions of respiration during sleep are associated with temporary airway obstruction. Following pharyngeal flap surgery, depending on size and position, the flap itself may have an "obturator" or obstructive effect within the pharynx during sleep, blocking ports of airflow and hindering effective respiration. There have been documented instances of severe airway obstruction, and reports of post-operative OSA continue to increase as healthcare

professionals (i.e. physicians, speech language pathologists) become more educated about this possible dangerous condition. Subsequently, in clinical practice, concerns of OSA have matched or exceeded interest in speech outcomes following pharyngeal flap surgery.

The surgical treatment for velopalatal insufficiency may cause obstructive sleep apnea syndrome. When velopalatal insufficiency is present, air leaks into the nasopharynx even when the soft palate should close off the nose. A simple test for this condition can be made by placing a tiny mirror at the nose, and asking the subject to say "P". This p sound, a plosive, is normally produced with the nasal airway closed off - all air comes out of the pursed lips, none from the nose. If it is impossible to say the sound without fogging a nasal mirror, there is an air leak - reasonable evidence of poor palatal closure. Speech is often unclear due to inability to pronounce certain sounds. One of the surgical treatments for velopalatal insufficiency involves tailoring the tissue from the back of the throat and using it to purposefully cause partial obstruction of the opening of the nasopharynx. This may actually *cause* obstructive sleep apnea syndrome in susceptible individuals, particularly in the days following surgery, when swelling occurs.

Pathophysiology

AHI	Rating
<5	Normal
5-15	Mild
15-30	Moderate
>30	Severe

Normal sleep/wakefulness in adults has distinct stages numbered 1 to 4, REM sleep, non-REM sleep (NREM) and consciousness. The deeper stages (3 to 4) of REM sleep are required for the physically restorative effects of sleep, and in pre-adolescents are the focus of release for human growth hormone. Stages 2 and REM, which combined are 70% of an average person's total sleep time, are more associated with mental recovery and maintenance. During REM sleep in particular, muscle tone of the throat and neck, as well as the vast majority of all skeletal muscles, is almost completely attenuated, allowing the tongue and soft palate/oropharynx to relax, and in the case of sleep apnea, to impede the flow of air to a degree ranging from light snoring to complete collapse. In the cases where airflow is reduced to a degree where blood oxygen levels fall, or the physical exertion to breathe is too great, neurological mechanisms trigger a sudden interruption of sleep, called a neurological arousal. These arousals rarely result in complete awakening, but can have a significant negative effect on the restorative quality of sleep. In significant cases of obstructive sleep apnea, one consequence is sleep deprivation due to the repetitive disruption and recovery of sleep activity. This sleep interruption in stages 3 and

4 (also collectively called slow-wave sleep), can interfere with normal growth patterns, healing, and immune response, especially in children and young adults.

Diagnosis

Diagnosis is often based on a combination of patient history and tests (lab- or home-based). These tests range, in decreasing order of cost, complexity and tethering of the patient (number and type of channels of data recorded), from lab-attended full polysomnography down to single-channel home recording. These categories are associated (in the USA) with insurance classification from Type I down to Type IV.

Polysomnography

Results of polysomnography in obstructive sleep apnea show pauses in breathing. As in central apnea, pauses are followed by a relative decrease in blood oxygen and an increase in the blood carbon dioxide. Whereas in central sleep apnea the body's motions of breathing stop, in obstructive sleep apnea the chest not only continues to make the movements of inhalation, the movements typically become even more pronounced. Monitors for airflow at the nose and mouth show efforts to breathe are not only present, but that they are often exaggerated. The chest muscles and diaphragm contract and the entire body may thrash and struggle.

Obstructive sleep apnea is the most common category of sleep-disordered breathing. The prevalence of OSA among the adult population in western Europe and North America has not been confidently established, but in the mid-1990s was estimated to be 3-4% of women and 6-7% of men.

An "event" can be either an apnea, characterised by complete cessation of airflow for at least 10 seconds, or a hypopnea in which airflow decreases by 50 percent for 10 seconds or decreases by 30 percent if there is an associated decrease in the oxygen saturation or an arousal from sleep (American Academy of Sleep Medicine Task Force, 1999). To grade the severity of sleep apnea, the number of events per hour is reported as the apnea-hypopnea index (AHI). An AHI of less than 5 is considered normal. An AHI of 5-15 is mild; 15-30 is moderate and more than 30 events per hour characterizes severe sleep apnea.

Home oximetry

In patients who are at high likelihood of having OSA, a randomized controlled trial found that home oximetry may be adequate and easier to obtain than formal polysomnography. High probability patients were identified by an Epworth Sleepiness Scale (ESS) score of 10 or greater and a Sleep Apnea Clinical Score (SACS) of 15 or greater.

Treatment

There are a variety of treatments for obstructive sleep apnea, depending on an individual's medical history, the severity of the disorder and, most importantly, the specific cause of the obstruction.

In acute infectious mononucleosis, for example, although the airway may be severely obstructed in the first 2 weeks of the illness, the presence of lymphoid tissue (suddenly enlarged tonsils and adenoids) blocking the throat is usually only temporary. A course of anti-inflammatory steroids such as prednisone (or another kind of glucocorticoid drug) is often given to reduce this lymphoid tissue. Although the effects of the steroids are short term, in most affected individuals, the tonsillar and adenoidal enlargement are also short term, and will be reduced on its own by the time a brief course of steroids is completed. In unusual cases where the enlarged lymphoid tissue persists after resolution of the acute stage of the Epstein-Barr infection, or in which medical treatment with anti-inflammatory steroids does not adequately relieve breathing, tonsillectomy and adenoidectomy may be urgently required.

Obstructive sleep apnea in children is sometimes due to chronically enlarged tonsils and adenoids. Tonsillectomy and adenoidectomy is curative. The operation may be far from trivial, especially in the worst apnea cases, in which growth is retarded and abnormalities of the right heart may have developed. Even in these extreme cases, the surgery tends to cure not only the apnea and upper airway obstruction, but allows normal subsequent growth and development. Once the high end-expiratory pressures are relieved, the cardiovascular complications reverse themselves. The postoperative period in these children requires special precautions.

The treatment for obstructive sleep apnea in adults with poor oropharyngeal airways secondary to heavy upper body type is varied. Unfortunately, in this most common type of obstructive sleep apnea, unlike some of the cases discussed above, reliable cures are not the rule.

Some treatments involve lifestyle changes, such as avoiding alcohol and medications that relax the central nervous system (for example, sedatives and muscle relaxants), losing weight, and quitting smoking. Some people are helped by special pillows or devices that keep them from sleeping on their backs, or oral appliances to keep the airway open during sleep. For those cases where these conservative methods are inadequate, doctors can recommend continuous positive airway pressure (CPAP), in which a face mask is attached to a tube and a machine that blows pressurized air into the mask and through the airway to keep it open. There are also surgical procedures intended to remove and tighten tissue and widen the airway, but none are reproducibly successful. Some individuals may need a combination of therapies to successfully treat their sleep apnea.

Physical intervention

The most widely used current therapeutic intervention is *positive airway pressure* whereby a breathing machine pumps a controlled stream of air through a mask worn over the nose, mouth, or both. The additional pressure splints or holds open the relaxed muscles, just as air in a balloon inflates it. There are several variants:

- (CPAP), or *continuous positive airway pressure*, in which a computer controlled air flow generator, generates an airstream at a constant pressure. This pressure is prescribed by the patient's physician, based on an overnight test or titration. Newer CPAP models are available which slightly reduce pressure upon exhalation to increase patient comfort and compliance. CPAP is the most common treatment for obstructive sleep apnea.
- (VPAP), or *variable positive airway pressure*, also known as bilevel or BiPAP, uses an electronic circuit to monitor the patient's breathing, and provides two different pressures, a higher one during inhalation and a lower pressure during exhalation. This system is more expensive, and is sometimes used with patients who have other coexisting respiratory problems and/or who find breathing out against an increased pressure to be uncomfortable or disruptive to their sleep.
- (APAP), or *automatic positive airway pressure*, is the newest form of such treatment. An APAP machine incorporates pressure sensors and a computer which continuously monitors the patient's breathing performance. It adjusts pressure continuously, increasing it when the user is attempting to breathe but cannot, and decreasing it when the pressure is higher than necessary. Although FDA approved, these devices are still considered experimental by many, and are not covered by most insurance plans under a APAP specific code. Auto CPAP machines can be covered at rate of a CPAP machine.

A second type of physical intervention, a Mandibular advancement splint (MAS), is sometimes prescribed for mild or moderate sleep apnea sufferers. The device is a mouthguard similar to those used in sports to protect the teeth. For apnea patients, it is designed to hold the lower jaw slightly down and forward relative to the natural, relaxed position. This position holds the tongue farther away from the back of the airway, and may be enough to relieve apnea or improve breathing for some patients. The FDA accepts only 16 oral appliances for the treatment of sleep apnea. A listing is available at its website.

Oral appliance therapy is less effective than CPAP, but is more 'user friendly'. Side-effects are common, but rarely is the patient aware of them.

Pharmaceuticals

There are no effective drug-based treatments for obstructive sleep apnea that have FDA approval. However, a clinical trial of mirtazapine, has shown early promise at the University of Illinois at Chicago. This small, early study found a 50% decrease in occurrence of apnea episodes and 28% decrease in sleep disruptions in 100% of patients

(twelve patients) taking them. Nonetheless, due to the risk of weight gain and sedation (two risk factors and consequences of sleep apnea) it is not recommended. An effort to improve the effects of mirtazapine by combining it with another existing medication was cancelled during Phase IIa trials in 2006. Dr. David Carley and Dr. Miodrag Radulovacki, the sleep researchers who were behind the initial clinical trial of mirtazapine are now working on a new treatment that consists of two other existing medications taken off-label together for treatment of sleep apnea.

Other serotonin effecting agents that have been explored unsuccessfully as a treatment for apnea include fluoxetine, tryptophan and protriptyline.

Oral administration of the methylxanthine theophylline (chemically similar to caffeine) can reduce the number of episodes of apnea, but can also produce side effects such as heart palpitations and insomnia. Theophylline is generally ineffective in adults with OSA, but is sometimes used to treat central sleep apnea, and infants and children with apnea.

When other treatments do not completely treat the OSA, drugs are sometimes prescribed to treat a patient's daytime sleepiness or somnolence. These range from stimulants such as amphetamines to modern anti-narcoleptic medicines. The anti-narcoleptic medicine modafinil is seeing increased use in this role as of 2004.

In most cases, weight loss will reduce the number and severity of apnea episodes. In the morbidly obese, a major loss of weight (such as what occurs after bariatric surgery) can sometimes cure the condition.

Neurostimulation

Some researchers believe that OSA is at root a neurological condition, in which nerves that control the tongue and soft palate fail to sufficiently stimulate those muscles, leading to over-relaxation and airway blockage. A few experiments and trial studies have explored the use of pacemakers and similar devices, programmed to detect breathing effort and deliver gentle electrical stimulation to the muscles of the tongue.

This is not a common mode of treatment for OSA patients as of 2004, but it is an active field of research.

Surgical intervention

A number of different surgeries are available to improve the size or tone of a patient's airway. For decades, tracheostomy was the only effective treatment for sleep apnea. It is used today only in rare, intractable cases that have withstood other attempts at treatment. Modern operations employ one or more of several options, tailored to each patient's needs. Success rates are directly proportional to the accuracy in the initial diagnosis of the site of obstruction.

- Nasal surgery, including turbinectomy (removal or reduction of a nasal turbinate), or straightening of the nasal septum, in patients with nasal obstruction or congestion which reduces airway pressure and complicates OSA.
- Tonsillectomy and/or adenoidectomy in an attempt to increase the size of the airway.
- Removal or reduction of parts of the soft palate and some or all of the uvula, such as uvulopalatopharyngoplasty (UPPP) or laser-assisted uvulopalatoplasty (*LAUP*). Modern variants of this procedure sometimes use radiofrequency waves to heat and remove tissue.
- Reduction of the tongue base, either with laser excision or radiofrequency ablation.
- *Genioglossus Advancement*, in which a small portion of the lower jaw that attaches to the tongue is moved forward, to pull the tongue away from the back of the airway.
- *Hyoid Suspension*, in which the hyoid bone in the neck, another attachment point for tongue muscles, is pulled forward in front of the larynx.
- *Maxillomandibular advancement* (MMA). MMA is the most effective sleep apnea surgical procedure currently available, with reduction of the AHI to less than 15 in over 90% of patients, and reduction of AHI to <5 in ~45% of patients. MMA was once thought to be fairly invasive, but has shown to be less painful, in general, than a UPPP soft palate procedure. The associated surgical risks are low, including bleeding, infection, malocclusion, and permanent numbness. In general, patient perceptions of surgical outcome have been very favorable.

The role of surgery in the treatment of sleep apnea has been questioned repeatedly as the long term success rate of the procedures has come into question. Surgery is generally only effective in obstructive sleep apnea where the obstruction can be effectively removed. The patient's age, weight and other factors may make them a bad candidate for surgery. Many sleep specialists still regard positive air pressure treatment as the gold standard.

Special situation: surgery and anesthesia in patients with sleep apnea

Many drugs and agents used during surgery to relieve pain and to depress consciousness remain in the body at low amounts for hours or even days afterwards. In an individual with either central, obstructive or mixed sleep apnea, these low doses may be enough to cause life-threatening irregularities in breathing.

Use of analgesics and sedatives in these patients postoperatively should therefore be minimized or avoided.

Surgery on the mouth and throat, as well as dental surgery and procedures, can result in postoperative swelling of the lining of the mouth and other areas that affect the airway. Even when the surgical procedure is designed to improve the airway, such as tonsillectomy and adenoidectomy or tongue reduction - swelling may negate some of the effects in the immediate postoperative period.

Individuals with sleep apnea generally require more intensive monitoring after surgery for these reasons.

Alternative treatments

One study showed that playing the didgeridoo may reduce snoring and daytime sleepiness due to obstructive sleep apnea. Since obstructive sleep apnea is sometimes caused by low tone (hypotonicity) in the muscles of the throat, playing the didgeridoo may improve symptoms of sleep apnea by exercising muscles of the throat and increasing tone.

A study published in 2009 tested the effect of a set of oropharyngeal exercises developed from exercises used by speech-language pathologists to improve swallowing function. Participants with moderate obstructive sleep apnea who performed the exercises every day showed a significant decrease in snoring frequency, snoring intensity, daytime sleepiness, sleep quality score, neck circumference, and apnea-hypopnea index (events per hour) when compared with a control group who performed sham exercises. The improvement in OSA shown by this group was comparable to the improvement shown in patients who use oral appliances to treat OSA.

Although this study was not designed to determine which specific exercises were beneficial, an editorial response to this study in the same journal argues that only 2 of the set of exercises were likely capable of effecting the improvements they reported. These 2 exercises included sucking the tongue upward against the palate for a total of 3 minutes throughout the day, and inflating a balloon by blowing forcefully and then breathing in deeply through the nose, repeated 5 times without removing the balloon from the mouth. The tongue exercise is intended to increase the strength of tongue protrusion, and the balloon exercise is intended to increase the strength of the pharyngeal wall. Although more research is needed to clarify the effects of oropharyngeal exercise on OSA, this recent study suggests a promising new approach to treating OSA.

Positional treatments

Many people benefit from sleeping at a 30 degree elevation of the upper body or higher, as if in a recliner. Doing so helps prevent the gravitational collapse of the airway. Lateral positions (sleeping on a side), as opposed to supine positions (sleeping on the back), are also recommended as a treatment for sleep apnea, largely because the gravitational component is smaller than in the lateral position. A 30 degree elevation of the upper body can be achieved by sleeping in a recliner, an adjustable bed, or a bed wedge placed under the mattress. This approach can easily be used in combination with other treatments and may be particularly effective in very obese people.

Prognosis

Although it takes some trial and error, most patients find a combination of treatments which reduce apnea events and improve their overall health, energy, and well-being.

Without treatment, the sleep deprivation and lack of oxygen caused by sleep apnea increases health risks such as cardiovascular disease, high blood pressure, stroke, diabetes, clinical depression, weight gain and obesity.

The most serious consequence of untreated obstructive sleep apnea is to the heart. In severe and prolonged cases, there are increases in pulmonary pressures that are transmitted to the right side of the heart. This can result in a severe form of congestive heart failure (*cor pulmonale*).

Elevated arterial pressure (commonly called high blood pressure) can be a consequence of obstructive sleep apnea syndrome. When high blood pressure is caused by OSA, it is distinctive in that, unlike most cases of high blood pressure (so-called essential hypertension), the readings do *not* drop significantly when the individual is sleeping. Stroke is associated with obstructive sleep apnea. Sleep apnea sufferers also have a 30% higher risk of heart attack or death than those unaffected.

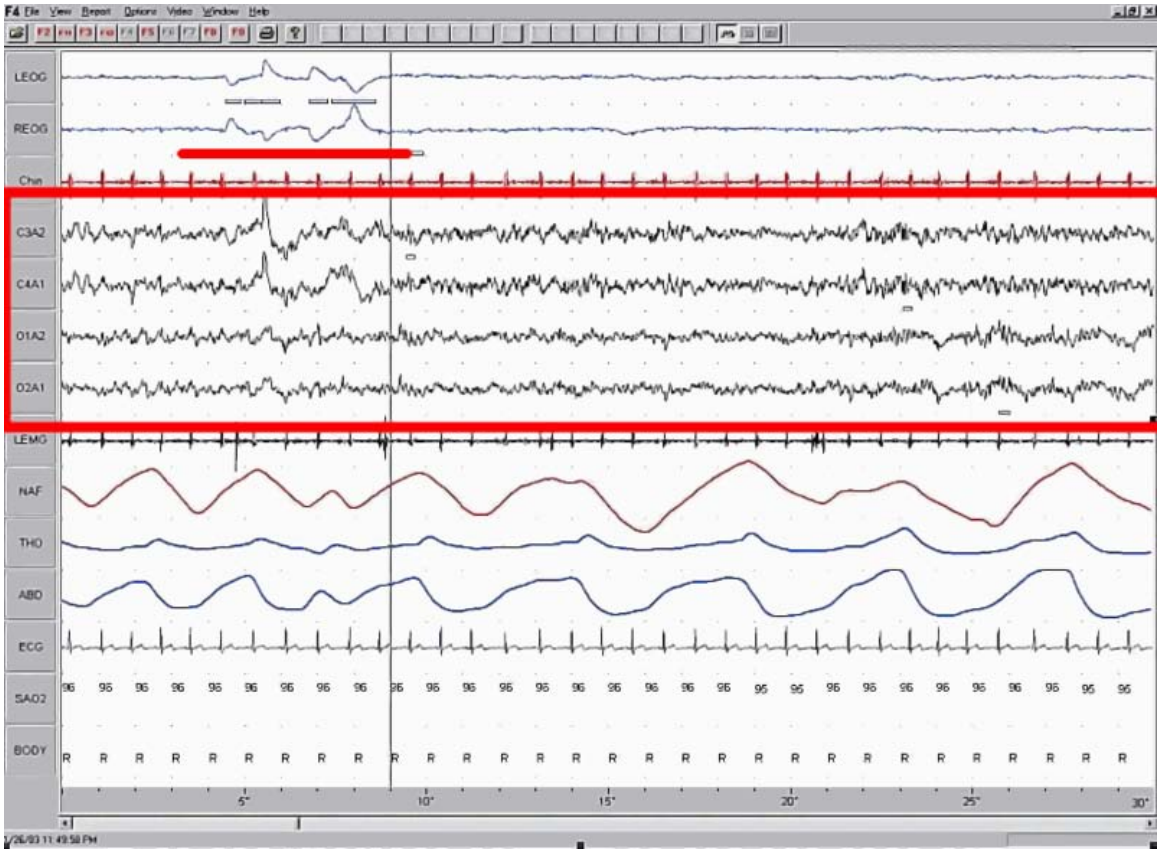
Many studies indicate that it is the effect of the "fight or flight" response on the body that happens with each apneic event that increases these risks. The fight or flight response causes many hormonal changes in the body; those changes, coupled with the low oxygen saturation level of the blood, cause damage to the body over time.

Epidemiology

OSA is a common condition in many parts of the world. If studied carefully in a sleep lab by polysomnography, approximately 1 in 5 American adults has at least mild OSA. OSA is more frequent than central sleep apnea.

Chapter 10

Polysomnography



Polysomnographic record of REM sleep. EEG highlighted by red box. Eye movements highlighted by a red line.

Polysomnography (PSG), also known as a **sleep study**, is a multi-parametric test used in the study of sleep and as a diagnostic tool in sleep medicine. The test result is called a **polysomnogram**, also abbreviated PSG. The name is derived from Greek and Latin roots: the Greek πολύς (*polus* for "many, much", indicating many channels), the Latin *somnus* ("sleep"), and the Greek γράφειν (*graphein*, "to write").

Polysomnography is a comprehensive recording of the biophysiological changes that occur during sleep. It is usually performed at night, when most people sleep, though some labs can accommodate shift workers and people with circadian rhythm sleep disorders and do the test at other times of day. The PSG monitors many body functions including brain (EEG), eye movements (EOG), muscle activity or skeletal muscle activation (EMG) and heart rhythm (ECG) during sleep. After the identification of the sleep disorder sleep apnea in the 1970s, the breathing functions respiratory airflow and respiratory effort indicators were added along with peripheral pulse oximetry.

Indications

Polysomnography is used to diagnose, or rule out, many types of sleep disorders including narcolepsy, periodic limb movement disorder (PLMD), REM behavior disorder, parasomnias, and sleep apnea. It is often ordered for patients with complaints of daytime fatigue or sleepiness that may be caused by interrupted sleep. Although it is not directly useful in diagnosing circadian rhythm sleep disorders, it may be used to rule out other sleep disorders.

Mechanism

A polysomnogram will typically record a minimum of twelve channels requiring a minimum of 22 wire attachments to the patient. These channels vary in every lab and may be adapted to meet the doctor's requests. There is a minimum of three channels for the EEG, one or two measure airflow, one or two are for chin muscle tone, one or more for leg movements, two for eye movements (EOG), one or two for heart rate and rhythm, one for oxygen saturation and one each for the belts which measure chest wall movement and upper abdominal wall movement. The movement of the belts is typically measured with piezoelectric sensors or respiratory inductance plethysmography. This movement is equated to effort and produces a low-frequency sinusoidal waveform as the patient inhales and exhales. Because movement is equated to effort, this system of measurement can produce false positives. It is possible, especially during obstructive apneas, for effort to be made without measurable movement.

Wires for each channel of recorded data lead from the patient and converge into a central box, which in turn is connected to a computer system for recording, storing and displaying the data. During sleep the computer monitor can display multiple channels continuously. In addition, most labs have a small video camera in the room so the technician can observe the patient visually from an adjacent room.

The electroencephalogram (EEG) will generally use six "exploring" electrodes and two "reference" electrodes, unless a seizure disorder is suspected, in which case more electrodes will be applied to document the appearance of seizure activity. The exploring electrodes are usually attached to the scalp near the frontal, central (top) and occipital (back) portions of the brain via a paste that will conduct electrical signals originating from the neurons of the cortex. These electrodes will provide a readout of the brain

activity that can be "scored" into different stages of sleep (N1, N2, N3 which combined are referred to as NREM sleep, and Stage R which is rapid eye movement sleep or REM, and Wakefulness). The EEG electrodes are placed according to the International 10-20 system.

The electrooculogram (EOG) uses two electrodes; one that is placed 1 cm above the outer canthus of the right eye and one that is placed 1 cm below the outer canthus of the left eye. These electrodes pick up the activity of the eyes in virtue of the electropotential difference between the cornea and the retina (the cornea is positively charged relative to the retina). This helps to determine when REM sleep occurs, of which rapid eye movements are characteristic, and also essentially aids in determining when sleep occurs.

The electromyogram (EMG) typically uses four electrodes to measure muscle tension in the body as well as to monitor for an excessive amount of leg movements during sleep (which may be indicative of periodic limb movement disorder, PLMD). Two leads are placed on the chin with one above the jaw line and one below. This, like the EOG, helps determine when sleep occurs as well as REM sleep. Sleep generally includes relaxation and so a marked decrease in muscle tension occurs. A further decrease in skeletal muscle tension occurs in REM sleep. A person becomes partially paralyzed to make acting out of dreams impossible, although people that do not have this paralysis can suffer from REM behavior disorder. Finally, two more leads are placed on the anterior tibialis of each leg to measure leg movements.

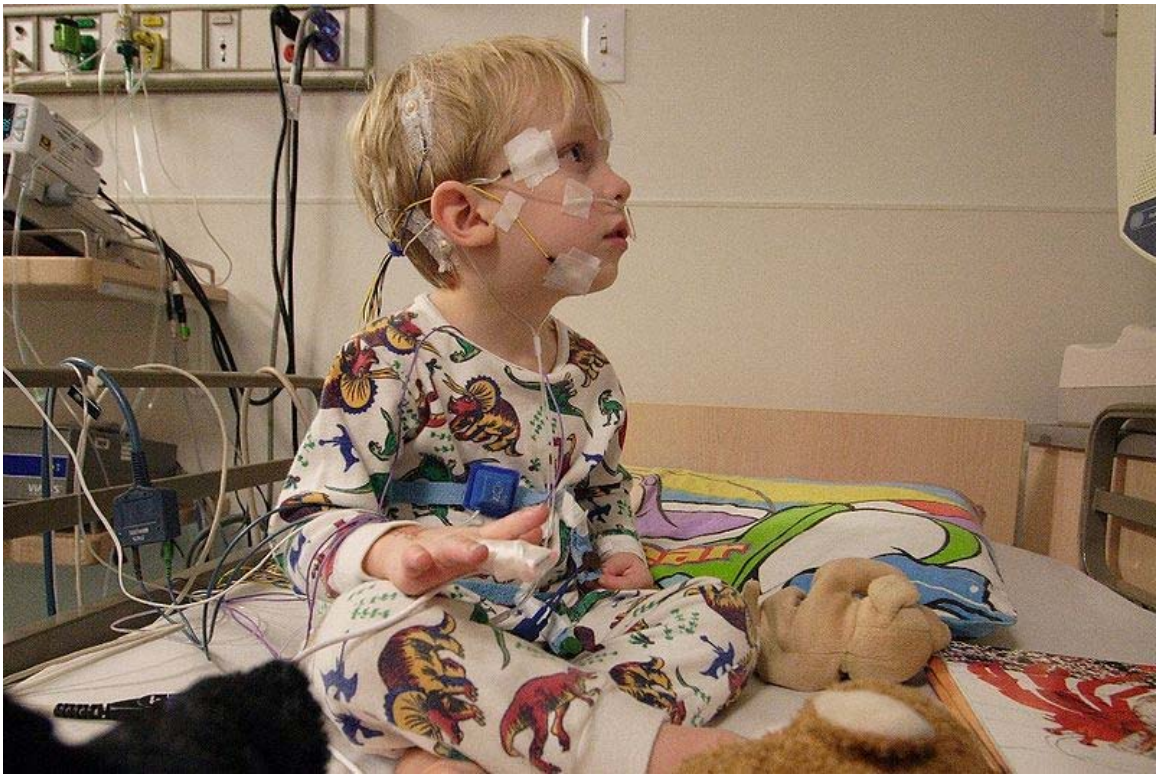
Though a typical electrocardiogram (ECG or EKG) would use ten electrodes, only two or three are used for a polysomnogram. They can either be placed under the collar bone on each side of the chest, or one under the collar bone and the other six inches above the waist on either side of the body. These electrodes measure the electrical activity of the heart as it contracts and expands, recording such features as the "P" wave, "QRS" complex, and "T" wave. These can be analyzed for any abnormalities that might be indicative of an underlying heart pathology.

Nasal and oral airflow can be measured using pressure transducers, and/or a thermocouple, fitted in or near the nostrils; the pressure transducer is considered the more sensitive. This allows the clinician/researcher to measure the rate of respiration and identify interruptions in breathing. Respiratory effort is also measured in concert with nasal/oral airflow by the use of belts. These belts expand and contract upon breathing effort. However, this method of respiration may also produce false positives. Some patients will open and close their mouth while obstructive apneas occur. This forces air in and out of the mouth while no air enters the airway and lungs. Thus, the pressure transducer and thermocouple will detect this diminished airflow and the respiratory event may be falsely identified as a hypopnea, or a period of reduced airflow, instead of an obstructive apnea.

Pulse oximetry determines changes in blood oxygen levels that often occur with sleep apnea and other respiratory problems. The pulse oximeter fits over a finger tip or an ear lobe.

Snoring may be recorded with a sound probe over the neck, though more commonly the sleep technician will just note snoring as "mild", "moderate" or "loud" or give a numerical estimate on a scale of 1 to 10. Also, snoring indicates airflow and can be used during hypopneas to determine whether the hypopnea may be an obstructive apnea.

Procedure



Pediatric polysomnography patient.

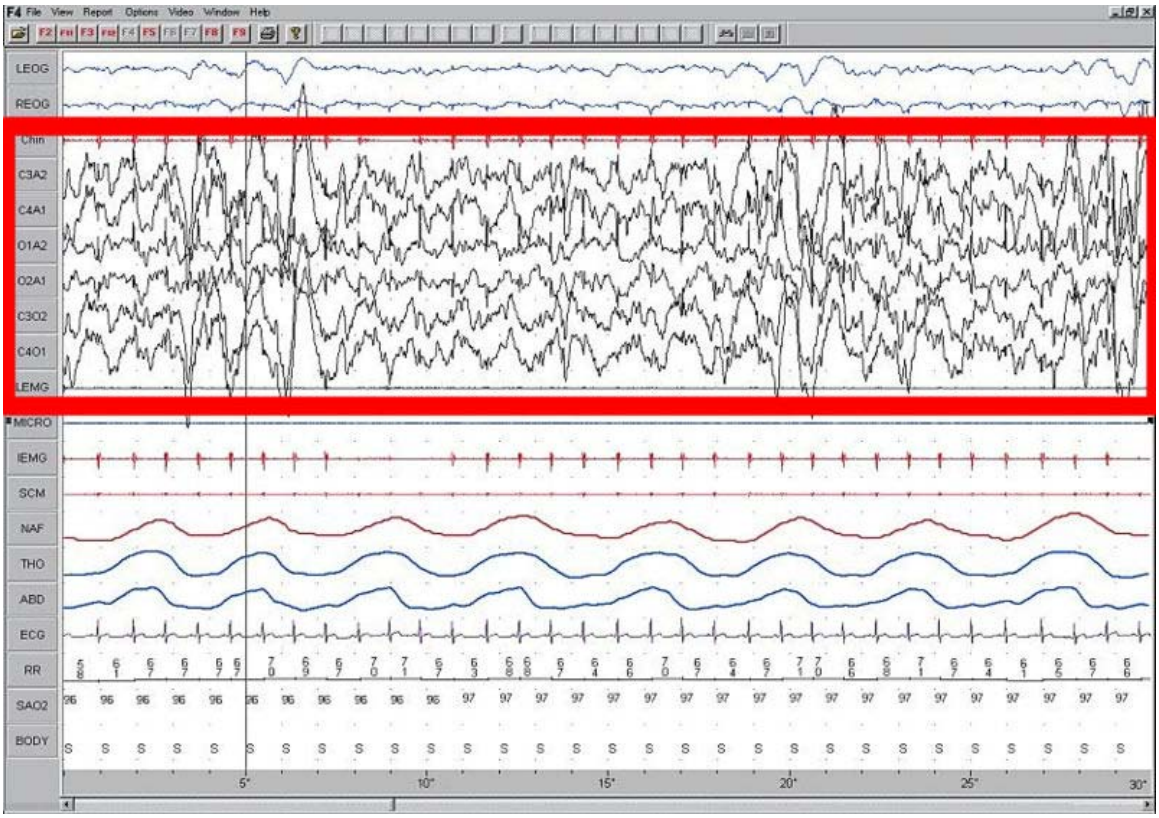
For the standard test the patient comes to a sleep lab in the early evening, and over the next 1–2 hours is introduced to the setting and "wired up" so that multiple channels of data can be recorded when he/she falls asleep. The sleep lab may be in a hospital, a free-standing medical office, or in a hotel. A sleep technician should always be in attendance and is responsible for attaching the electrodes to the patient and monitoring the patient during the study.

During the study, the technician observes sleep activity by looking at the video monitor and the computer screen that displays all the data second by second. In most labs the test is completed and the patient is discharged home by 7 a.m. unless a Multiple Sleep Latency Test (MSLT) is to be done during the day to test for excessive daytime sleepiness.

Most recently, physicians may prescribe home studies to enhance patient comfort and reduce expense. The patient is given instructions after a screening tool is used, uses the

equipment at home and returns it the next day. Most screening tools consist of an airflow measuring device (thermistor) and a blood oxygen monitoring device (pulse oximeter). The patient would sleep with the screening device for one to several days, then return the device to the physician. The physician would be able to retrieve data from the device and could make assumptions based on the information given ex. series of drastic blood oxygen desaturations during night periods may indicate some form of respiratory event(apnea). The equipment monitors, at a minimum, oxygen saturation.

Interpretation



Stage 4 sleep. EEG highlighted by red box.

After the test is completed a "scorer" analyzes the data by reviewing the study in 30 second "epochs".

The score consists of the following information:

- Onset of sleep from time the lights were turned off; this is called "sleep onset latency" and normally is less than 20 minutes. (Note that determining "sleep" and "awake" is based solely on the EEG. Patients sometimes feel they were awake when the EEG shows they were sleeping. This may be because of sleep state misperception, drug effects on brain waves, or individual differences in brain waves.)

- Sleep efficiency: the number of minutes of sleep divided by the number of minutes in bed. Normal is approximately 85 to 90% or higher.
- Sleep stages; these are based on 3 sources of data coming from 7 channels: EEG (4 channels usually), EOG (2) and chin EMG (1). From this information each 30-second epoch is scored as "awake" or one of 4 sleep stages: 1, 2, 3, and REM or Rapid Eye Movement sleep. Stages 1–3 are together called non-REM sleep. Non-REM sleep is distinguished from REM sleep, which is altogether different. Within non-REM sleep, stage 3 is called "slow wave" sleep because of the relatively wide brain waves compared to other stages; another name for stage 3 is "deep sleep". By contrast, stage 1 and 2 are "light sleep". The figures show stage 3 sleep and REM sleep; each figure is a 30-second epoch from an overnight PSG.

  (The percentage of each sleep stage varies by age, with decreasing amounts of REM and deep sleep in older people. The majority of sleep at all ages (except infancy) is Stage 2. REM normally occupies about 20-25% of sleep time. Many factors besides age can affect both the amount and percentage of each sleep stage, including drugs (particularly anti-depressants and pain meds), alcohol taken before bed time, and sleep deprivation.)

- Any breathing irregularities; mainly apneas and hypopneas. Apnea is a complete or near complete cessation of airflow for at least 10 seconds followed by an arousal and/or 3% oxygen desaturation; hypopnea is a 50% decrease in airflow for at least 10 seconds followed by an arousal and/or 3% oxygen desaturation. (Medicare requires a 4% desaturation in order to include the event in the report.)
- "Arousals" are sudden shifts in brain wave activity. They may be caused by numerous factors, including breathing abnormalities, leg movements, environmental noises, etc. An abnormal number of arousals indicates "interrupted sleep" and may explain a person's daytime symptoms of fatigue and/or sleepiness.
- Cardiac rhythm abnormalities.
- Leg movements.
- Body position during sleep.
- Oxygen saturation during sleep.

Once scored, the test recording and the scoring data are sent to the sleep medicine physician for interpretation. Ideally, interpretation is done in conjunction with the medical history, a complete list of drugs the patient is taking, and any other relevant information that might impact the study such as napping done before the test.

Once interpreted, the sleep physician writes a report which is sent to the referring physician, usually with specific recommendations based on the test results.

Example of summary report

Mr. J----, age 41, 5′8″ tall, 265 lbs., came to the sleep lab to rule out obstructive sleep apnea. He complains of some snoring and daytime sleepiness. His score on the Epworth

Sleepiness Scale is elevated at 15 (out of possible 24 points), affirming excessive daytime sleepiness (normal is <10/24).

This single-night diagnostic sleep study shows evidence for obstructive sleep apnea (OSA). For the full night his apnea+hypopnea index was elevated at 18.1 events/hr. (normal <5 events/hr; this is "moderate" OSA). While sleeping supine, his AHI was twice that, at 37.1 events/hr. He also had some oxygen desaturation; for 11% of sleep time his SaO2 was between 80% and 90%.

Results of this study indicate Mr. J---- would benefit from CPAP. To this end, I recommend that he return to the lab for a CPAP titration study.

"Split night" study

The above report mentions CPAP as treatment for obstructive sleep apnea. CPAP is continuous positive airway pressure and is delivered via a mask to the patient's nose or the patient's nose and mouth. (Some masks cover one, some both). CPAP is typically prescribed after the diagnosis of OSA is made from a sleep study (*i.e.*, after a PSG test). To determine the correct amount of pressure and the right mask type and size, and also to make sure the patient can tolerate this therapy, a "CPAP titration study" is recommended. This is the same as a "PSG", but with the addition of the mask applied, so the technician can increase the airway pressure inside the mask as needed, until all, or most, of the patient's airway obstructions are eliminated.

The above report recommends Mr. J---- return for a CPAP titration study, which means a return to the lab for a second all-night PSG (this one with the mask applied). Often, however, when a patient manifests OSA in the first 2 or 3 hours of the initial PSG, the technician will interrupt the study and apply the mask right then and there; the patient is woken up and fitted for a mask. The rest of the sleep study is then a "CPAP titration." When both the diagnostic PSG and a CPAP titration are done the same night, the entire study is called "Split Night".

The split-night study has these advantages:

1. The patient only has to come to the lab once, so it is less disruptive than is coming two different nights;
2. It is "half as expensive" to whoever is paying for the study.

The split-night study has these disadvantages:

1. There is less time to make a diagnosis of OSA (Medicare requires a minimum of 2 hours of diagnosis time before the mask can be applied); and
2. There is less time to assure an adequate CPAP titration. If the titration begins with only a few hours of sleep left, the remaining time may not assure a proper CPAP titration, and the patient may still have to return to the lab.

Because of costs, more and more studies for "sleep apnea" are attempted as split-night studies when there is early evidence for OSA. (Note that both types of study, with and without a CPAP mask, are still polysomnograms.) When the CPAP mask is worn, however, the flow-measurement lead in the patient's nose is removed. Instead, the CPAP machine relays all flow-measurement data to the computer.

Example of summary report from a "split night" study

Mr. B____, age 38, 6 ft. tall, 348 lbs., came to the Hospital Sleep Lab to diagnose or rule out obstructive sleep apnea. This polysomnogram consisted of overnight recording of left and right EOG, submental EMG, left and right anterior EMG, central and occipital EEG, EKG, airflow measurement, respiratory effort and pulse oximetry. The test was done without supplemental oxygen. His latency to sleep onset was slightly prolonged at 28.5 minutes. Sleep efficiency was normal at 89.3% (413.5 minutes sleep time out of 463 minutes in bed).

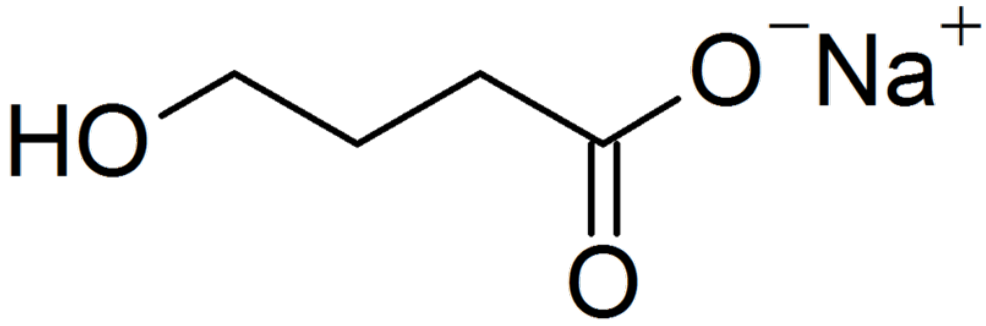
During the first 71 minutes of sleep Mr. B____ manifested 83 obstructive apneas, 3 central apneas, 1 mixed apnea and 28 hypopneas, for an elevated apnea+hypopnea index (AHI) of 97 events/hr (*"severe" OSA). His lowest SaO_2 during the pre-CPAP period was 72%. CPAP was then applied at 5 cm H_2O, and sequentially titrated to a final pressure of 17 cm H_2O. At this pressure his AHI was 4 events/hr. and the low SaO_2 had increased to 89%. This final titration level occurred while he was in REM sleep. Mask used was a Respironics Classic nasal (medium-size).

In summary, this split night study shows severe OSA in the pre-CPAP period, with definite improvement on high levels of CPAP. At 17 cm H_2O his AHI was normal at 4 events/hr. and low SaO_2 was 89%. Based on this split night study I recommend he start on nasal CPAP 17 cm H_2O along with heated humidity.

Chapter 11

Xyrem

Sodium oxybate



Systematic (IUPAC) name	
Sodium 4-hydroxybutanoate	
Identifiers	
CAS number	502-85-2
ATC code	None
PubChem	CID 23663870
ChemSpider	9983 ✓
KEGG	D05866 ✗
Chemical data	
Formula	C4H7NaO3
Mol. mass	126.09 grams/mole
SMILES	eMolecules & PubChem
Pharmacokinetic data	
Bioavailability	25%

Protein binding	1%
Half-life	0.5 to 1 hour.
Excretion	Almost entirely by biotransformation to carbon dioxide, which is then eliminated by expiration
Therapeutic considerations	
Licence data	EMA:(sodium oxybate) oral solution&searchType=Name&jsenabled=true Link, US Daily Med:(sodium oxybate) solution link
Pregnancy cat.	B(US)
Legal status	Schedule III (CA) CD (Benz) POM (UK) Schedule III (US) Rx Only
Routes	Oral

Xyrem (**sodium oxybate**) is a prescription medication manufactured by Jazz Pharmaceuticals, and is approved by the U.S. Food and Drug Administration (FDA) for the treatment of cataplexy associated with narcolepsy and Excessive Daytime Sleepiness (EDS) associated with narcolepsy. Sodium oxybate is the sodium salt of γ-hydroxybutyric acid.

The American Academy of Sleep Medicine (AASM) recommends Xyrem as a standard of care for the treatment of cataplexy, daytime sleepiness, and disrupted sleep due to narcolepsy in its Practice Parameters for the Treatment of Narcolepsy and other Hypersomnias of Central Origin. These recommendations are based upon careful review of the medical literature, and the designation "standard" of care "reflects a high degree of clinical certainty" based on strong empirical evidence.

Xyrem is a prescription medication used to treat narcolepsy, which is a rare medical condition that has been documented worldwide, with a prevalence ranging from 0.002% in Israel to 0.18% in Japan. Prevalence in the US is approximately 0.05%. The pentad of clinical symptoms includes: Excessive Daytime Sleepiness (EDS), cataplexy, hypnagogic hallucinations, sleep paralysis, and fragmented sleep. EDS and cataplexy are the most common daytime symptoms of narcolepsy.

Development

Xyrem is designated as an orphan drug, which is a pharmaceutical agent that has been developed specifically to treat a rare medical condition, the condition itself being referred to as an orphan disease. The assignment of orphan status to a disease and to any drugs developed to treat it is a matter of public policy in many countries, and has resulted in medical breakthroughs that may not have otherwise been achieved due to the economics

of drug research and development. In the last 20 years efforts have been made to encourage companies to develop orphan drugs. The Orphan Drug Act in the US (1983) was succeeded by similar legislation in Japan (1985), Australia (1997), and the European Community (2000).

The development of Xyrem (sodium oxybate) oral solution as a prescription medication was initiated by the Office of Orphan Products Development (OOPD). The OOPD is a department of the FDA dedicated to promoting the development of products that demonstrate promise for the diagnosis and/or treatment of rare diseases or conditions.

- In 1994, the OOPD petitioned a pharmaceutical company called Orphan Medical to investigate sodium oxybate as a potential treatment for narcolepsy.
- In 1996, Orphan Medical submitted an Investigational New Drug Application (IND) to the FDA and began Phase I, II, and III clinical trials to investigate the safety and efficacy of sodium oxybate.
- In 2000, Orphan Medical submitted a New Drug Application (NDA) to the FDA for Xyrem. Xyrem was granted "Priority Review", which is an expedited review process given to products that offer a major advance in treatment or treatment where no adequate therapy exists.
- In 2002, Xyrem received approval from the FDA for the treatment of cataplexy in patients with narcolepsy.
- In 2005, Xyrem was acquired by Jazz Pharmaceuticals when they purchased Orphan Medical. Later that year, Xyrem was granted a second indication by the FDA for the treatment of EDS in patients with narcolepsy. Also that year Xyrem was approved for the treatment of cataplexy in patients with narcolepsy by Health Canada's Therapeutic Products Directorate, and for the same indication in adult patients by the European Medicines Agency for the European Union (EU) and the Swiss Agency for Therapeutic Products, Swissmedic.
- In 2006, Xyrem received an expanded indication for narcolepsy with cataplexy in the EU.
- In 2010, Jazz Pharmaceuticals completed two Phase III clinical trials investigating sodium oxybate for the treatment of fibromyalgia. Fibromyalgia is a complex musculoskeletal disorder clinically characterized by widespread pain usually accompanied by fatigue, insomnia, and dyscognition. The company submitted a New Drug Application (NDA) to the FDA; approval was refused in October.

There are also ongoing tests to see if Xyrem could prove helpful with other medical conditions, such as Parkinson's disease, chronic fatigue syndrome (ME), schizophrenia, binge eating, essential tremor and other non-Parkinson's movement disorders.

Mechanism of action

According to the FDA, the precise mechanism of action for the prescription medication Xyrem is unknown.

Cost

Orphan drugs by their nature are very specialized and have relatively few patients to spread the costs associated with bringing them to market. The average cost of a specialty drug in the US is $2,875 per month or $34,500 annually, however drug prices vary by country.

In European Union (EU) countries, the government either provides national health insurance (as in the UK and Italy) or strictly regulates quasi-private social insurance funds (as in Germany, France, and the Netherlands). These government agencies are the sole purchaser (or regulator) of medical goods and services and have the power to set prices. The cost of pharmaceuticals, including Xyrem, tend to be lower in these countries.

In the US, the cost of Xyrem is $975 (180 mL bottle, 500 mg/mL) and the effective dose range is 6–9 grams per night which equates to $1,950–2,925 per month. Xyrem is covered by most insurance plans including Medicare and Medicaid and approximately 90% of Xyrem patients have a flat monthly co-pay. 75% of Xyrem insurance copays are less than $50 and 42% are less than $25 for a one-month supply. The manufacturer offers a coupon program for the small number of patients with larger co-pays. Some insurance companies may require physicians to fill out an insurance form called a Prior Authorization as part of the prescribing process. Additionally, the manufacturer offers a Patient Assistance Program to patients that do not have insurance and are unable to afford their Xyrem prescription. Approximately 8% of Xyrem patients currently participate in this program and receive their prescription for free.

Existing US Patents on Xyrem prevent other companies from manufacturing it as a drug. Xyrem is protected by US Patents 6472431, and 6780889 In total, Xyrem is protected by eight patents related to the product's formulation and Jazz Pharmaceuticals' distribution system. These patents expire from 2019 to 2024.

Distribution

A number of measures have been put in place by Xyrem's manufacture to ensure that it is used safely and appropriately. Xyrem requires a prescription and can only be obtained through a restricted distribution program, called the "Xyrem Success Program". This restricted distribution program is required by the FDA as part of a Risk Management Program (RMP) to manage product safety and prevent abuse.

The program involves many risk management components, such as:

- Physician education
- Registration
- Patient education
- Detailed patient surveillance

The program includes a single centralized pharmacy with a toll-free number.

Initial dosages are set by the prescribing physician. Each bottle of Xyrem is shipped with a graduated syringe (measured in grams) and two dosing cups. Each night, the patient mixes two doses with 60 ml of water (sometimes substituted with a calorie-free beverage to cover the unpleasant taste of the medication). The first dose is taken at bedtime, and the second is taken 2.5 to 4 hours later.

Safety

Xyrem has been safely used by patients with narcolepsy for more than seven years. A recent analysis evaluated the postmarketing safety of Xyrem (Wang et al. 2009), including rates of abuse, dependence, and withdrawal, using a conservative application of the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria to all worldwide Xyrem adverse event cases containing reporting terminology related to abuse or misuse. The analysis included cases reported to the manufacture from market introduction in 2002 through March 2008. Using the DSM-IV criteria, the analysis found the following rates of abuse, dependence, and withdrawal of the approximately 26,000 patients who used Xyrem during this period:

- Abuse – 10 cases (0.04%)
- Dependence – 4 cases (0.016%)
- Withdrawal symptoms after discontinuation – 8 cases (0.031%; including 3 of the previous 4 dependence cases)

The analysis also found 2 confirmed cases (0.008%) of sodium oxybate–facilitated sexual assault; in both cases the women knew that they were taking sodium oxybate. In addition, there were 21 deaths (0.08%) in patients receiving sodium oxybate treatment, with 1 death known to be related to sodium oxybate, and 3 cases (0.01%) of traffic accidents involving drivers taking sodium oxybate. The extremely low rates of abuse, dependence, withdrawal, and assault found in this analysis suggest that after seven years of commercial availability, Xyrem use is largely appropriate and confined to patients with legitimate therapeutic needs.

In the US, Xyrem is classified as a Schedule III controlled substance for medicinal use under the Controlled Substances Act, with illicit use subject to Schedule I penalties. Examples of other schedule III products in the US include vicodin, tylenol with codeine, and testosterone. In Canada and the European Union (EU), it is classified as a Schedule III and a Schedule IV controlled substance, respectively.

Adverse effects

Xyrem is generally well-tolerated by most patients. The most common side effects reported in clinical trials include nausea, dizziness, headache, vomiting, sleepiness, and bed-wetting. Some patients treated with Xyrem have also experienced moderate to

significant weight loss. This may be due to the fact that Xyrem improves sleep architecture and increases the length of deep sleep stages, resulting in increased production of human growth hormone (GH) and changes in energy metabolism.

Use by athletes

Xyrem has been instrumental in allowing cyclist Franck Bouyer to resume his career and is the only treatment for narcolepsy approved by the World Anti-Doping Agency.

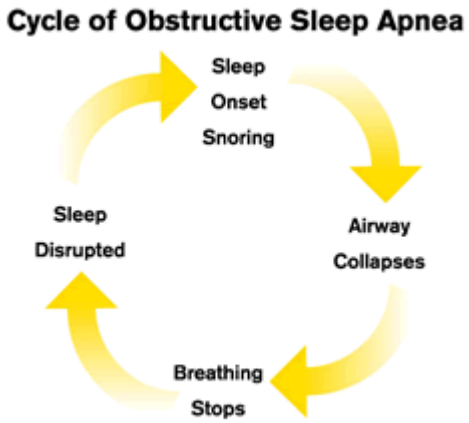
Chapter 12

Positive Airway Pressure

A typical CPAP machine houses the air pump in a case lined with sound-absorbing material for quieter operation. A hose carries the pressurized air to a face mask or nasal pillow.

The Sullivan V Plus, a typical mid-1990s CPAP (the mask is more modern).

A typical full face CPAP mask.



CPAP therapy breaks the cycle of OSA

Positive airway pressure (**PAP**) is a method of respiratory ventilation used primarily in the treatment of sleep apnea, for which it was first developed. PAP ventilation is also commonly used for those who are critically ill in hospital with respiratory failure, and in newborn infants (neonates). In these patients, PAP ventilation can prevent the need for tracheal intubation, or allow earlier extubation. Sometimes patients with neuromuscular diseases use this variety of ventilation as well. CPAP is an acronym for "continuous positive airway pressure", a variation of the PAP system which was first developed by Professor Colin Sullivan at Royal Prince Alfred Hospital in Sydney, Australia, in 1981.

Indications

The main indications for positive airway pressure are congestive heart failure and chronic obstructive pulmonary disease. There is some evidence of benefit for those with hypoxia and community acquired pneumonia.

PAP ventilation is often used for patients who have acute type 1 or 2 respiratory failure. Usually PAP ventilation will be reserved for the subset of patients for whom oxygen delivered via a face mask is deemed insufficient or deleterious to health. Usually, patients on PAP ventilation will be closely monitored in an intensive care unit, high dependency unit, coronary care unit or specialist respiratory unit.

The most common conditions for which PAP ventilation is used in hospital are congestive cardiac failure and acute exacerbation of obstructive airway disease, most notably exacerbations of COPD and asthma. It is not used in cases where the airway may be compromised, or consciousness is impaired. CPAP is also used to assist premature babies with breathing in the NICU setting.

The mask required to deliver CPAP must have an effective seal, and be held on very securely. The "nasal pillow" mask maintains its seal by being inserted slightly into the

nostrils and being held in place by various straps around the head. Some full-face masks "float" on the face like a hover-craft, with thin, soft, flexible "curtains" ensuring less skin abrasion, and the possibility of coughing and yawning. Some people may find wearing a CPAP mask uncomfortable or constricting. Breathing out against the positive pressure resistance (the expiratory positive airway pressure component, or EPAP) may also unpleasant to some patients. These factors lead to inability to continue treatment due to patient intolerance in about 20% of cases where it is initiated. Some machines have C-Flex pressure relief technology that makes sleep therapy more comfortable by reducing pressure at the beginning of exhalation and returning to therapeutic pressure just before inhalation. The level of pressure relief varies based on the patient's expiratory flow and which of the three C-Flex settings has been selected, making breathing out against the pressure less difficult. Those who suffer an anxiety disorder or claustrophobia are more likely to be unable to tolerate PAP treatment. Sometimes medication will be given to assist with the anxiety caused by PAP ventilation.

Unlike PAP used at home to splint the tongue and pharynx, PAP is used in hospital to improve the ability of the lungs to exchange oxygen and carbon dioxide, and to decrease the work of breathing (the energy expended moving air into and out of the alveoli). This is because:

- During inspiration, the inspiratory positive airway pressure, or IPAP, forces air into the lungs—thus less work is required from the respiratory muscles.
- The bronchioles and alveoli are prevented from collapsing at the end of expiration. If these small airways and alveoli are allowed to collapse, significant pressures are required to re-expand them. This is because of the Young–Laplace equation (which explains why the hardest part of blowing up a balloon is the first breath).
- Entire regions of the lung that would otherwise be collapsed are forced and held open. This process is called recruitment. Usually these collapsed regions of lung will have some blood flow (although reduced). Because these areas of lung are not being ventilated, the blood passing through these areas is not able to efficiently exchange oxygen and carbon dioxide. This is called ventilation–perfusion (or V/Q) mismatch. The recruitment reduces ventilation–perfusion mismatch.
- The amount of air remaining in the lungs at the end of a breath is greater (this is called the functional residual capacity). The chest and lungs are therefore more expanded. From this more expanded resting position, less work is required to inspire. This is due to the non-linear compliance–volume curve of the lung.

Disadvantages

A major issue with CPAP is non-compliance. Studies showed that some users either abandon the use of CPAP, and/or use CPAP for only a fraction of the nights .

Prospective PAP candidates are often reluctant to use this therapy, since the nose mask and hose to the machine look uncomfortable and clumsy, and the airflow required for

some patients can be vigorous. Some patients will develop nasal congestion while others may experience rhinitis or a runny nose. Some patients adjust to the treatment within a few weeks, others struggle for longer periods, and some discontinue treatment entirely. However, studies show that cognitive behavioral therapy at the beginning of therapy dramatically increases compliance—up to 148%. While PAP side effects are a nuisance, serious side effects are very uncommon. Furthermore, research has shown that PAP side effects are rarely the reason patients stop using PAP. There are reports of dizziness, sinus infections, bronchitis, dry eyes, dry mucosal tissue irritation, ear pain, and nasal congestion secondary to CPAP use.

PAP manufacturers frequently offer different models at different price ranges, and PAP masks have many different sizes and shapes, so that some users need to try several masks before finding a good fit. These different machines may not be comfortable for all users, so proper selection of PAP models may be very important in furthering adherence to therapy.

Beards, mustaches, or facial irregularities may prevent an air-tight seal. Where the mask contacts the skin must be free from dirt and excess chemicals such as skin oils. Shaving before mask-fitting may be necessary.

The CPAP mask can act as an orthodontic headgear and move the teeth and the upper and/or lower jaw backward. This effect can increase over time and may or may not cause TMD disorders in some patients. These facial changes have been dubbed "Smashed Face Syndrome".

Mechanism of action

Continuous pressure devices

Fixed-pressure CPAP

A continuous positive airway pressure (CPAP) machine was initially used mainly by patients for the treatment of sleep apnea at home, but now is in widespread use across intensive care units as a form of ventilation. Obstructive sleep apnea occurs when the upper airway becomes narrow as the muscles relax naturally during sleep. This reduces oxygen in the blood and causes arousal from sleep. The CPAP machine stops this phenomenon by delivering a stream of compressed air via a hose to a nasal pillow, nose mask, full-face mask, or hybrid, splinting the airway (keeping it open under air pressure) so that unobstructed breathing becomes possible, therefore reducing and/or preventing apneas and hypopneas. It is important to understand, however, that it is the air pressure, and not the movement of the air, that prevents the apneas. When the machine is turned on, but prior to the mask being placed on the head, a flow of air comes through the mask. After the mask is placed on the head, it is sealed to the face and the air stops flowing. At this point, it is only the air pressure that accomplishes the desired result. This has the additional benefit of reducing or eliminating the extremely loud snoring that sometimes accompanies sleep apnea.

The CPAP machine blows air at a prescribed pressure (also called the titrated pressure). The necessary pressure is usually determined by a sleep physician after review of a study supervised by a sleep technician during an overnight study (polysomnography) in a sleep laboratory. The titrated pressure is the pressure of air at which most (if not all) apneas and hypopneas have been prevented, and it is usually measured in centimetres of water (cm/H_2O). The pressure required by most patients with sleep apnea ranges between 6 and 14 cm/H_2O. A typical CPAP machine can deliver pressures between 4 and 20 cm/H_2O. More specialised units can deliver pressures up to 25 or 30 cm/H_2O.

CPAP treatment can be highly effective in treatment of obstructive sleep apnea. For some patients, the improvement in the quality of sleep and quality of life due to CPAP treatment will be noticed after a single night's use. Often, the patient's sleep partner also benefits from markedly improved sleep quality, due to the amelioration of the patient's loud snoring.

Given that sleep apnea is a chronic health issue which commonly doesn't go away, ongoing care is usually needed to maintain CPAP therapy. Based on the study of cognitive behavioral therapy (referenced above), ongoing chronic care management is the best way to help patients continue therapy by educating them on the health risks of sleep apnea and providing motivation and support.

Automatic positive airway pressure

"Automatic positive airway pressure" (APAP, AutoPAP, AutoCPAP) automatically *titrates*, or tunes, the amount of pressure delivered to the patient to the minimum required to maintain an unobstructed airway on a breath-by-breath basis by measuring the resistance in the patient's breathing, thereby giving the patient the precise pressure required at a given moment and avoiding the compromise of fixed pressure.

Bi-level pressure devices

- "VPAP" or "BiPAP" (variable/bilevel positive airway pressure) provides two levels of pressure: inspiratory positive airway pressure (IPAP) and a lower expiratory positive airway pressure (EPAP) for easier exhalation. (Some people use the term BPAP to parallel the terms APAP and CPAP.)
    - Modes
        - **S** (Spontaneous) – In spontaneous mode the device triggers IPAP when flow sensors detect spontaneous inspiratory effort and then cycles back to EPAP.
        - **T** (Timed) – In timed mode the IPAP/EPAP cycling is purely machine-triggered, at a set rate, typically expressed in breaths per minute (BPM).
        - **S/T** (Spontaneous/Timed) – Like spontaneous mode, the device triggers to IPAP on patient inspiratory effort. But in spontaneous/timed mode a "backup" rate is also set to ensure that

patients still receive a minimum number of breaths per minute if they fail to breathe spontaneously.

Components

- Flow generator (PAP machine) provides the airflow
- Hose connects the flow generator (sometimes via an in-line humidifier) to the interface
- Interface (nasal or full face mask, nasal pillows, or less commonly a lip-seal mouthpiece) provides the connection to the user's airway

Optional features

- Humidifier adds moisture to low humidity air
    - Heated: Heated water chamber that can increase patient comfort by eliminating the dryness of the compressed air. The temperature can usually be adjusted or turned off to act as a passive humidifier if desired. In general, a heated humidifier is either integrated into the unit or has a separate power source (i.e. plug).
    - Passive: Air is blown through an unheated water chamber and is dependent on ambient air temperature. It is not as effective as the heated humidifier described above, but still can increase patient comfort by eliminating the dryness of the compressed air. In general, a passive humidifier is a separate unit and does not have a power source.
- Mask liners: Cloth-based mask liners may be used to prevent excess air leakage and to reduce skin irritation and dermatitis.
- Ramp may be used to temporarily lower the pressure if the user does not immediately sleep. The pressure gradually rises to the prescribed level over a period of time that can be adjusted by the patient and/or the DME provider.
- Exhalation pressure relief: Gives a short drop in pressure during exhalation to reduce the effort required. This feature is known by the trade name C-Flex or A-Flex in some CPAPs made by Respironics and EPR in ResMed machines.
- Flexible chin straps may be used to help the patient not breathe through the mouth (full-face masks avoid this problem), thereby keeping a closed pressure system. The straps are elastic enough that the patient can easily open his mouth if he feels that he needs to. Modern straps use a quick-clip instant fit. Velcro-type adjustments allow quick sizing, before or after the machine is turned on.
- Data logging records basic compliance info or detailed event logging, allowing the sleep physician (or patient) to download and analyse data recorded by the machine to verify treatment effectiveness.
- Automatic altitude adjustment versus manual altitude adjustment.
- DC power source versus AC power source.

Such features generally increase the likelihood of PAP tolerance and compliance.

Care and maintenance

As with all durable medical equipment, proper maintenance is essential for proper functioning, long unit life and patient comfort. The care and maintenance required for PAP machines varies with the type and conditions of use, and are typically spelled out in a detailed instruction manual specific to the make and model.

Most manufacturers recommend that the end user perform daily and weekly maintenance. Units must be checked regularly for wear and tear and kept clean. Poorly connected, worn or frayed electrical connections may present a shock or fire hazard; worn hoses and masks may reduce the effectiveness of the unit. Most units employ some type of filtration, and the filters must be cleaned or replaced on a regular schedule. Sometimes HEPA filters may be purchased or modified for asthma or other allergy clients. Hoses and masks accumulate exfoliated skin, particulate matter, and can even develop mold. Humidification units must be kept free of mold and algae. Because units use substantial electrical power, housings must be cleaned without immersion.

In cold climates, humidified air may require insulated and/or heated air hoses. These may be bought ready-made, or modified from commonly available materials (aluminium foil and bubble-wrap insulation. Noisy machines may be distanced from the sleeper by extension hoses between the machine and the sleeping person).

Modifications are usually needed by the end-user. Straps are easily twisted wrongly (add hot-melt glue or silicone rubber on the "wrong" side). Fittings and buttons are invisible or without adequate sensation in the darkness of the night, so use bright tape or other fittings (self-adhesive children's earrings, masking tape, etc.) to help prevent mistakes.

Portability

Since continuous compliance is an important factor in the success of treatment, it is of importance that patients who travel have access to portable equipment. Progressively, PAP units are becoming lighter and more compact, and often come with carrying cases. Dual-voltage power supplies permit many units to be used internationally.

Long-distance travel or camping presents special considerations. Most airport security inspectors have seen the portable machines, so screening rarely presents a special problem. Increasingly, machines are capable of being powered by the 400-Hz power supply used on most commercial aircraft and include manual or automatic altitude adjustment. Some machines allow power-inverter and/or car-battery powering, but polarity of the connecting cables needs consideration.

Some patients on PAP therapy also use supplementary oxygen. When provided in the form of bottled gas, this can present an increased risk of fire and is subject to restrictions. (Commercial airlines generally forbid passengers to bring their own oxygen.) As of November 2006, most airlines permit the use of oxygen concentrators.

Availability

CPAP flow generator in the back to the left, connected to a 1500 gram preterm newborn by a hose and kept in place on the patient with an improvised interface: a diaper.

In many countries, PAP machines are only available by prescription. A sleep study at an accredited sleep lab is usually necessary before treatment can start. This is because the pressure settings on the PAP machine must be tailored to a patient's treatment needs. A sleep medicine doctor, who may also be trained in respiratory medicine, psychiatry, neurology, paediatrics, family practice or otolaryngology (ear, nose and throat), will interpret the results from the initial sleep study and recommend a pressure test. This may be done in one night (a split study with the diagnostic testing done in the first part of the

night, and CPAP testing done in the later part of the night) or with a follow up second sleep study during which the CPAP titration may be done over the entire night. With CPAP titration (split night or entire night), the patient wears the CPAP mask and pressure is adjusted up and down from the prescribed setting to find the optimal setting.

- In the United States, PAP machines are often available at large discounts online, but a patient purchasing a PAP personally must handle the responsibility of securing reimbursement from his or her insurance or Medicare. Many of the internet providers that deal with insurance such as Medicare will provide upgraded equipment to a patient even if he or she only qualifies for a basic PAP. In some locations a government programme, separate from Medicare, can be used to claim a reimbursement for all or part of the cost of the PAP device.
- In the United Kingdom, PAP machines are available on National Health Service prescription after a diagnosis of sleep apnea or privately from the internet provided a prescription is supplied.
- In Australia, PAP machines can be bought from the Internet or physical stores. There is no requirement for a doctor's prescription, however many suppliers will require a referral. Low-income earners who hold a Commonwealth Health Care Card should enquire with their state's health department about programmes that provide free or low-cost PAP machines. Those who have private health insurance may be eligible for a partial rebate on the cost of a CPAP machine and the mask. Superannuation may be released for the purchase of essential medical equipment such as PAP machines, on the provision of letters from two doctors, one of whom must be a specialist, and an application to the Australian Prudential Regulation Authority (APRA).
- In Canada, CPAP units are widely available in all provinces. Funding for the therapy varies from province to province. In the province of Ontario, the Ministry of Health's Assistive Devices Program will fund a portion of the cost of a CPAP unit based on a sleep study in an approved sleep lab showing Obstructive Sleep Apnea Syndrome and the signature of an approved physician on the application form. This funding is available to all residents of Ontario with a valid health card once every 5 years.