

Excessive daytime sleepiness

Sonolência excessiva

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Abstract

Sleepiness is a physiological function and can be defined as an increased propensity to fall asleep. However, excessive sleepiness or hypersomnia refer to an abnormal increase in the likelihood of falling asleep, dozing off or having sleep attacks when sleep is not desired. The main causes of excessive sleepiness are chronic sleep deprivation, obstructive sleep apnea syndrome, narcolepsy, movement disorders during sleep, circadian rhythm sleep disorders, use of illicit/prescription drugs and idiopathic hypersomnia. Social, familial, work, and cognitive impairment are among the consequences of hypersomnia. An increased risk of accidents has also been reported. The treatment of excessive sleepiness includes treating the primary cause, when identified. Sleep hygiene for sleep deprivation, continuous positive airway pressure for sleep apnea, dopaminergic agents and exercises for sleep-related movement disorders and phototherapy or melatonin for circadian disorders, as well as the use of stimulants in general, are the treatment modalities of choice.

Keywords: Sleep disorders; Disorders of excessive somnolence; Chronobiology disorders; Narcolepsy; Restless legs syndrome; Sleep apnea, obstructive

Resumo

A sonolência é uma função biológica, definida como uma probabilidade aumentada para dormir. Já a sonolência excessiva (SE), ou hipersonia, refere-se a uma propensão aumentada ao sono com uma compulsão subjetiva para dormir, tirar cochilos involuntários e ataques de sono, quando o sono é inapropriado. As principais causas de sonolência excessiva são a privação crônica de sono (sono insuficiente), a Síndrome da Apnéia e Hipopnéia Obstrutiva do Sono (SAHOS), a narcolepsia, a Síndrome das Pernas Inquietas/Movimentos Periódicos de Membros (SPI/MPM), Distúrbios do Ritmo Circadiano, uso de drogas e medicações e a hipersonia idiopática. As principais conseqüências são prejuízo no desempenho nos estudos, no trabalho, nas relações familiares e sociais, alterações neuropsicológicas e cognitivas e risco aumentado de acidentes. O tratamento da sonolência excessiva deve estar voltado para as causas específicas. Na privação voluntária do sono, aumentar o tempo de sono e higiene do sono, o uso do CPAP (Continuous Positive Airway Pressure) na Síndrome da Apnéia e Hipopnéia Obstrutiva do Sono, exercícios e agentes dopaminérgicos na Síndrome das Pernas Inquietas/Movimentos Periódicos de Membros, fototerapia e melatonina nos Distúrbios do Ritmo Circadiano, retiradas de drogas que causam sonolência excessiva e uso de estimulantes da vigília.

Descritores: Distúrbios do Sono; Sonolência Excessiva; Distúrbios do ritmo circadiano; Narcolepsia; Síndrome das pernas inquietas; Apnéia do sono tipo obstrutiva

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Introduction

Excessive sleepiness (ES) and sleep disorders (SDs) are prevalent in our society today. Recent information shows serious consequences of these problems. In 1990 in the USA, 200,000 car accidents were caused due to motorists falling asleep at the wheel. On the other hand, one-third of all fatal accidents involving truck drivers are related to ES while driving. Great disasters, such as: the Exxon Valdez, Bhopal, the Challenger, Chernobyl and Three Mile Island have been associated with lack of judgment and poor performance related to fatigue. Forty million Americans suffer from chronic SDs, 95% of which are neither properly diagnosed nor treated. In 1990, the costs directly related to ES and SDs in the USA were 15.9 billion dollars.¹

Definition

Sleepiness is a biological function, defined as an increased likelihood of falling asleep. However, ES, or hypersomnia, refers to an increased propensity to fall asleep and a subjective compulsion to sleep, as well as a tendency to take involuntary naps or suffer sleep attacks when sleep is not desired.² From 2% to 5% of the population is affected by ES, which has consequences for study and work, as well as for family and social relations. In addition, ES can result in neuropsychological changes, cognitive changes and an increased risk of accidents.

The symptom known as ES has long been attributed to clinical depression, apathy or lassitude, as well as to negative personality traits. True ES, in which physiological sleepiness is not present, is not attributable to any particular condition. It should be distinguished from fatigue and apathy, conditions related to a number of physical and psychiatric illnesses (multiple sclerosis, lupus, cancer, infections, Parkinson's disease, cerebral vascular accidents, chronic fatigue syndrome, fibromyalgia, depression, etc).³ Fatigue is referred to as tiredness, lack of energy and exhaustion. It is generally induced by excessive activity and alleviated by rest. On the other hand, ES is referred to as a decreased capacity for performing physical and mental work, being, many times, incompletely relieved with rest or sleep, as well as being normally associated with SDs.⁴ These conditions often coexist in the same patients, despite being distinct clinical entities. The presence of fatigue or ES may indicate a psychiatric illness or even represent a worse prognosis of such an illness.

Causes

The main causes of ES are chronic sleep deprivation (insufficient sleep), obstructive sleep apnea-hypopnea syndrome (OSAHS), narcolepsy, restless legs syndrome (RLS)/periodic limb movements in sleep (PLMS), circadian rhythm disorders, use of illicit/prescription drugs and idiopathic hypersomnia.⁵

1. Chronic sleep deprivation

It is believed that, with the advent of electricity and consequently the use of televisions and computers, as well as higher demands on working hours, studies and social commitments, people are sleeping less and, as a consequence, complaining of ES.

2. OSAHS

This syndrome affects 2% to 4% of the population, especially overweight men over the age of 40.⁶ It is defined as recurrent episodes of upper airway obstruction during sleep, which

usually results in desaturation of oxyhemoglobin and, in cases of prolonged events, it results in hypercapnia. This obstruction may be partial (hypopnea) or total (apnea). The events end upon awakening.⁷ The diagnosis of OSAHS is made based on clinical and polysomnographic criteria: 1) excessive daytime sleepiness unexplained by other causes and; 2) two or more of the following symptoms and signs not explained by other conditions: asphyxia or difficulty in breathing during sleep, recurrent nocturnal awakenings, sensation of nonrestful sleep, daytime fatigue and difficulty in concentrating; 3) five or more obstructive respiratory events (apneas and hypopneas and awakenings related to respiratory efforts) per hour of sleep, recorded during all-night polysomnography.⁷ The severity of OSAHS is based on the degree of ES and on the number of obstructive events per hour of sleep.⁷

3. Narcolepsy

Narcolepsy is a rare condition (1/1000 individuals), presenting a higher incidence among individuals between 18 and 25 years of age, whose symptoms may precede the diagnosis by 20 years, on average.⁵ It may present classically as the following signs and symptoms: ES, cataplexy (loss of muscle tonus), sleep paralysis, hypnagogic hallucinations and fragmented sleep. It may be monosymptomatic, expressing itself only through ES, or oligosymptomatic, expressed through ES and cataplexy. The degree of ES is variable and the cataplexy attacks may involve several muscle groups. These are triggered by emotions, of which laughing is the most common.⁸ There is a genetic predisposition, meaning that 85% to 90% of the patients with narcolepsy have a specific allele of HLA II (12% to 28% of the general population has this allele). The presence of the allele is neither necessary nor sufficient. There is a family occurrence (1% to 4%), a concordance between twins of 17% to 25% and a deficiency in orexin (hypocretin) has been described in the liquor of these patients. Other immune, self-immune and environmental factors (stress, sleep deprivation, conflicts and family loss) may be involved.⁹ In the polysomnography, we found decreased latency for sleep onset and for REM sleep, as well as frequent awakenings. In the of multiple sleep latency test (MSLT), we observed average latency values less than or equal to 5 minutes and two or more sleep onsets in REM sleep in the five data sets.¹⁰

4. Restless Legs Syndrome/Periodic Limb Movements in Sleep

The PLMS phenomenon occurs more frequently in individuals over the age of 30, and the prevalence in this age range is 5%. For those over the age of 60, the prevalence reaches as high as 44%. Concomitant ES occurring as a consequence is seen in 11% of the patients. Of the patients with RLS, 80% present PLMS, although few individuals with PLMS have RLS.¹¹ The diagnostic criteria for PLMS include: insomnia, ES, limb movements are reported by the partner (even in asymptomatic patients), stereotyped limb movements with hallux extension (bending the legs at the knee and hip), polysomnography showing five or more episodes per hour of PLMS sleep (muscle contraction 25% above resting value, in a sequence of four or more movements, with a duration of 0.5 to 5 seconds each at 5- to 90-second intervals).¹⁰ The diagnostic criteria for RLS are clinical, referred to as an uncomfortable feeling in the legs, which leads to an irresistible urge to move them. It worsens with rest or sleep and improves with movement.¹⁰ The prevalence of RLS ranges from 5% to 15%. It is possible

that RLS and PLMS are related to conditions such as pregnancy, neuropathy, uremia, iron-deficiency anemia, withdrawal of benzodiazepines, use of tricyclic antidepressants and use of lithium.¹¹

5. Circadian Rhythm Disorders

Circadian rhythm disorders may lead to ES, especially if the individuals affected are obliged to synchronize with the environment.

In the delayed sleep phase syndrome, sleep is late compared to real time, resulting in difficulty in initiating sleep and in waking within the desired time frame. In the advanced sleep phase syndrome, the opposite is observed; sleep is early compared to real time, leading to ES in the early evening and early awakening. In the non-24 hour sleep-wake cycle syndrome, which is common among the blind, individuals tend to sleep at irregular times each day. In jet-lag syndrome, individuals who engage in transmeridian travel, crossing many time zones rapidly, have difficulty in maintaining sleep and present symptoms of ES, gastrointestinal disorders and psychosomatic disorders. In the shift-work sleep disorder, symptoms such as ES and fatigue, as well as gastrointestinal, cognitive and performance alterations, affect people who invert sleeping time due to night work.¹²⁻¹³

6. Drugs and medication

There is a possibility that ES is caused by the use of various medications, such as hypnotics, anticonvulsants, antidepressants, antihistamines, lithium, antipsychotics, antiparkinsonian drugs, and cardiovascular drugs.¹⁴

7. Idiopathic hypersomnia

Idiopathic hypersomnia is an illness of the central nervous system in which prolonged periods of sleep occur (one or two additional hours) with subsequent ES. It principally affects individuals of approximately 25 years of age. Polysomnography is normal and sleep onset latency is normally less than 10 minutes, and there is an increase in the amount of NREM sleep. The latency for REM sleep is normal. The MSLT shows a mean latency of less than 10 minutes and of less than 2 minutes for sleep onset in REM sleep.¹⁰

Consequences

From the point of view of cognitive performance, many are the alterations that may be directly related to losses caused by SDs, including: difficulty in fixing and maintaining attention; memory loss; loss in the ability to plan strategically; mild motor loss (more related to fine motor skills such as agility and precision); difficulty in controlling impulses and clouded thought. Our mental functioning is totally integrated; if there is loss in any one function, the performance in another may be affected to a greater or lesser degree.¹⁵ Several of these functions are found to be lower in fatigue and ES situations.

One of the most apparent changes of the increase in sleepiness is its effect on the state of alertness. The number of lapses of attention, for instance, evaluated in a test of sustained attention model, practically increases in a linear manner, combined with the number of vigilance hours. The frequency of lapses of attention also accompanies circadian fluctuation of body temperature throughout the day, in such a way that a significant reduction in alertness occurs in moments close to the minimum value of body temperature during the night.¹⁶ In addition to the circadian expression in alertness,

some sleep components, with their duration and quality, are controlled by the circadian system and, therefore, depend on the moment that the system occurs during the day. In general, sleep during the day is shorter and more fragmented when compared to nocturnal sleep, representing a challenge for those who need to invert the sleep and vigilance pattern, as is the case of shift workers.¹⁷⁻¹⁹ The higher frequency of car accidents considered the result of sleepiness during the night and the higher proportion of accidents during night shift confirm the risks associated to ES resulting from the interaction between sleep restriction and circadian disorganization.^{17,20-22} In Brazil, the contribution of sleepiness in car accidents may be inferred by the study of de Mello et al:²³ 16% of the bus drivers interviewed confessed having fallen asleep while driving, whereas more than half of these drivers (58%) admitted to know another driver who slept while driving. Furthermore, among SDs, the obstructive sleep apnea syndrome is an important cause of ES and also frequently associated with an increased risk of accidents.²⁴⁻²⁷ In this context, Brazilian estimates show that both snoring and sleep apnea are common among split-shift workers.^{18-19,23}

According to this panorama, sleep restriction, circadian disorganization and SDs may act in a synergic manner, facilitating the occurrence of severe sleepiness and accidents. The importance of recognizing these factors as critical both to private and to public safety is evident, as well as considering the adoption of strategies as a priority.

Investigation of excessive sleepiness

Many procedures may be used for appropriate investigation of ES, among which are: clinical evaluation, keeping a sleep diary, subjective measurements and objective measurements.

During clinical evaluation, collecting a sleep history is essential for identifying the nature of the problem. The sleep-wake patterns of the patient should be evaluated, considering weekends and holidays, including an interview with the partner, in addition to the symptoms over a 24-hour period. The presence of psychiatric and psychopathological disorders, as well as of clinical or neurological diseases, should be investigated. Alcohol or drug use and its relationship with sleep patterns and ES should also be investigated. Information on type, dose and time of ingestion should be included in the investigation.

Sleep diaries are important instruments in the evaluation of ES. Two weeks of evaluation are indicated for the observation of circadian rhythms and sleep hygiene disorders. In addition to these, the determination of the presence of naps may also help in the characterization of sleep patterns. Sleep diaries should include bedtimes and rising times, as well as sleeping and waking times, sleep quality, awakenings during the night (time and duration), naps, the use of medication, etc.

Subjective measures may be used for evaluating the feeling of ES at a given moment or in daily situations. These are based on standardized questionnaires which should be completed by the patient. However, this may present a problem when the patient is unaware of his condition or has inaccurate perceptions regarding ES. Many sleepiness scales have been made available in the literature. However, the most frequently used are the Stanford Sleepiness Scale (SSS),²⁸ Karolinska Sleepiness Scale (KSS)²⁹ and Epworth Sleepiness Scale (ESS).³⁰ The SSS and KSS allow the evaluation of ES at the moment of application. The disadvantage is the fact that ES may vary from one moment to another. In these scales, the

patient must choose between the different descriptions and levels of ES (from totally awake to totally asleep) which best define his current state. The ESS, on the other hand, evaluates ES in several active and passive situations. The situations include: sitting and reading; watching TV; sitting in a public place; being a train, car or bus passenger (for one hour, non-stop); laying down in the afternoon to rest; sitting and talking to someone; sitting calmly after lunch, with no alcohol; while driving, but stuck in traffic for a few moments. The patient reports the chance of falling asleep in each of the situations described, scoring from 0 (no chance) to 3 (high chance). The reference values are: normal ES: from 0 to 6; limited ES: from 7 to 9; mild ES: from 10 to 14; moderate ES: from 15 to 20; severe ES: over 20.³¹ The ESS is simple and easy to apply and it is able to discriminate between patients with some SDs and normal individuals.³² It is relatively stable when reapplied in healthy controls, as well as being able to detect variations of ES in patients submitted to treatment, especially in patients with obstructive sleep apnea.³³ Some problems may be related to the ESS, such as ambiguity in some situations presented. Furthermore, ES may vary within the same situation, depending on the duration or moment of the day in which it occurs. Some of these limitations may be partly responsible for the low correlation found between the ESS and the objective evaluation of ES using the MSLT.³⁴⁻³⁵

Polysomnography, the MSLT and the Maintenance of Wakefulness Test (MWT) may be used for the objective evaluation of ES. As well as allowing the recording of multiple physiological variables during one night of sleep, polysomnography is an essential tool for the evaluation of nocturnal sleep patterns and diagnosis of SDs.³⁶⁻³⁷ It should be indicated for patients reporting ES, except for those with ES clearly associated with sleep deprivation or use of medication. The gold standard for the objective quantification of ES is the MSLT, the most utilized test for this matter. Both the MSLT and the MWT evaluate sleep onset in 4 or 5 polygraphic recordings per day, at 2-hour intervals, normally following nocturnal polysomnography. Whereas the MSLT evaluates the length of time the patients takes to sleep in a sleep-inducing situation and to have early REM sleep (essential for the diagnosis of narcolepsy), the MWT measures the ability to stay awake. This may explain why the correlation between the two tests is low (0.41).³⁸ On the other hand, MWT better reflects ES after treatment.³⁹ The minimum parameters for sleep staging, as proposed by Rechtschaffen & Kales, are used for recording in both tests (1968).⁴⁰ The set up includes the recording of the electroencephalogram (EEG), electro-oculogram and submental electromyogram. The EEG must include electrodes in the central regions, referenced by the mastoid or contralateral earlobe (C3-A2 and C4-A1). The inclusion of electrodes in the occipital regions (O1 and O2) may be very useful for the identification of sleep onset (alpha rhythm extinction). The individual should be awakened at the usual time, put on normal and comfortable clothes and have breakfast, avoiding caffeinated substances. At approximately 2

hours (from 1.5 to 3 hours) after arousal, the first record is made. During the intervals between the tests, the patient should leave the room, not being allowed to sleep or take any stimulant substance. In the case of smokers, it is advised not to smoke 30 minutes prior to the start of each record. The most essential differences between the tests are as follows: in the MSLT, the record should always be made when the patient is laying comfortably in the recording room, a silent and dark environment. Prior to the initiating of the recording, the patient is instructed not to resist sleep; in the MWT, the record is made when the patient is sitting in a comfortable chair in a low-light environment and instructed to resist sleep. The sleep onset criteria (Table 1) and the normative values for the MSLT depend on the approach of the researcher, although average latencies of less than 5 minutes are considered abnormal (Table 2). The normative values for the MWT are more well-established: in a 20-minute test, sleep latency of less than 11 minutes is considered abnormal.⁴¹ In the attempt to avoid false negatives and false positives, some precautions must be taken. The patient may be instructed to sleep and wake at regular and consistent times for one to two weeks prior to the exam. A sleep diary detailing sleep times, use of stimulants, use of alcohol and nap taking may be useful. Medication acting on the central nervous system (antidepressants, benzodiazepines, hypnotics, stimulants, alcohol, etc.) should be withdrawn, and it is essential to wait at least 14 days after the discontinuation of medication before administering the MSLT.

Table 1 – Characteristics of the multiple sleep latency test and the maintenance of wakefulness test

	Number of recordings	Criteria for sleep onset	Criteria for finalizing each recording
MSLT ^{35,42-43}	4 – 5	- First epoch of sleep ⁴² - First of 3 consecutive epochs of stage 1 or first epoch of any other stage of sleep ^{35,43}	- 15 minutes after sleep onset ^{35,42} - After 10 minutes of continuous sleep ⁴³ - After 20 minutes if no sleep occurs ^{35,42-43}
MWT ⁴¹	4	First of 3 consecutive epochs of stage 1 or first epoch of any other sleep stage	- After sleep onset - After 20 (or 40) minutes if no sleep occurs

MSLT: multiple sleep latency test; MWT: maintenance of wakefulness test

These measures aim to avoid the rebound of any sleep phase, as well as to avoid a false-negative result if the individual is using any drug that alters sleep architecture (for example, antidepressants suppress REM sleep). The occurrence of REM sleep after 10-15 minutes of sleep onset is defined as early REM sleep (sleep-onset REM period). At least two recorded incidents of early REM sleep are required for the diagnosis of narcolepsy.

Considering the pros and cons of the various instruments currently available in the literature, all may be used with

Table 2 – Normative Values for the multiple sleep latency test

Average sleep latency	< 5 minutes	5-8 minutes	> 8-10 minutes	> 10-15 minutes	> 15 minutes
	Abnormal ^{42,44-45}	Pathological limit ⁴⁴ Abnormal ⁴⁵ "Grey area" undefined ⁴² Moderate sleepiness ¹⁰	Normal ^{10,42,44} "Grey area" ⁴² Moderate sleepiness ¹⁰	Normal ^{10,42,44-45} Mild sleepiness ¹⁰	Normal ^{10,42,44-45}

reasonable safety for the evaluation of ES in different types of patients and approaches.

Treatments

The treatment of ES must be specific for the underlying cause. The inadequate amount of sleep must be approached with measures of sleep hygiene, so that the amount and quality of sleep may be recuperated.

For OSAHS, general measures such as losing weight, avoiding alcohol and sedatives, giving preference to the lateral decubitus, treating otorhinolaryngologic diseases and treating gastroesophageal reflux, are required.⁴⁶ The main treatment for OSAHS is continuous positive airway pressure, which has been shown to improve excessive daytime sleepiness, systemic arterial hypertension, quality of life and cognition.⁴⁷ The use of devices that promote the advance of the jaw and of surgeries are reserved for certain types of patients.⁴⁶

The treatment of narcolepsy includes sleep hygiene measures, programmed naps and continuous use of medication, among which are stimulants such as modafinil, methylphenidate, dexamphetamines and pemoline. These will be approached later. The use of antidepressants is more recent. Studies involving the use of sodium oxybate for the treatment of cataplexy are currently being conducted.^{5,8,14}

Regular aerobic exercises, iron supplementation when needed and withdrawal of medications that exacerbate periodic movements are recommended in RLS/PLMS. Specific pharmacological treatment consists of the use of dopaminergic agents (levodopa, pergolide) and dopaminergic agonists (pramipexole, ropinirole), opioids, carbamazepine, clonazepam and clonidine.^{5,11}

For the treatment of circadian rhythm disorders, sleep hygiene, phototherapy (2000 to 10,000 lux, at times predetermined by the type of disorder) and use of melatonin (0.5 to 10 mg) have been recommended.^{5,12}

Idiopathic hypersomnolence is treated with stimulants.⁵ The stimulants include a class of several medications including amphetamine (2.5 mg/day), methylphenidate (5 mg/day), pemoline (discontinued due to risk of hepatic insufficiency) and, more recently, a new stimulant, more specific for alertness, modafinil (100 to 300 mg/day). The main effects of this class of medication are decreased sleep time and increased alertness. Individuals under the effect of these drugs present better performance, less fatigue and decreased sleepiness, as well as improved mood and cognition. The main collateral effects are insomnia, euphoria, anorexia, headache, increased arterial pressure and higher cardiac frequency. Both expected and undesired effects depend on the type of medication, dose, patient age and previous state of health. The medication is contra-indicated for patients with glaucoma, uncompensated cardiovascular disease, hyperthyroidism, use of monoamine oxidase inhibitors, psychoactive states, uncontrolled convulsions, etc.^{5,14}

Modafinil has been used as the treatment of choice in narcolepsy and idiopathic hypersomnia.⁴⁸ However, this medication has been used in several studies to treat sleepiness and fatigue related to neurological and psychiatric diseases, attention deficit, split-shift work⁴⁹ and residual sleepiness in OSAHS under treatment with continuous positive airway pressure.⁵⁰⁻⁵¹ This medication has advantages over others in that it affects more specific areas of the brain, causing less mood alteration, little cardiovascular change, low tolerance and minimal dependence.

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