Sleep Medicine and Physical Therapy

A Comprehensive Guide for Practitioners

Cristina Frange
Fernando Morgadinho Santos Coelho
Editors

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This book is dedicated to our families:

Matheus and Mauricio, Lucimar and Geraldo, Felício, and Ilza

Fernando, Ana Carolina, and Amanda

And to our patients

Foreword

The *Sleep Medicine and Physical Therapy* book justifies its subtitle with its content, as it really represents a comprehensive guide for physiotherapy practitioners dealing with the field of sleep. Through the chapters of the book, the authors, who are both recognized researchers and experts in sleep medicine, neurology and physiotherapy, excellently describe and illustrate the importance of sleep for overall health, sleep-related pathologies or disturbances and the role of physiotherapists in dealing with such issues.

Dealing with sleep and its disturbances is relatively a new area of work for physiotherapists, although they are in terms of their competencies known as experts in physical (in)activity, sedentary behavior, and exercise for all ages and specific vulnerable target groups. However, effective healthy lifestyle counselling must be multidisciplinary and must cover the entire 24-hour wake-sleep human cycle, which is why every physiotherapist as a health promoter must be able to provide not only counselling in preventing sedentary behavior and improving active lifestyle, but also in providing at least basic counselling around sleeping matters.

Studies have shown that regular sleep is associated with a better quality of life at all ages. On the other hand, sleep is associated with a number of physiological systems, such as memory consolidation, immune response, hormone and body temperature regulation, cardiovascular regulation, and many other important functions, so lack and poor quality of sleep are associated with detrimental health outcomes. Short sleep has been shown to impair cognitive and executive functions, and poor sleep is associated with poor mental health. Sufficient length of uninterrupted and deep enough sleep is thus important for quality of sleep.

During the current Covid-19 pandemic, it is especially important to sleep well and take care of our sleep order. Good sleep protects us from infections, facilitates the course of the disease and improves the immune response to the vaccine, and protects us from infection in the long run. It helps us manage stress and adapt effectively to the current situation.

Reading this book, you as a reader will get an overview about basic concepts of sleep and sleep medicine including why this is important for physical therapists. You will learn about physiotherapeutic management of sleep disturbances such as

insomnia, restless legs symptom and periodic limb movement of sleep, circadian rhythm sleep disturbances, sleep bruxism, obstructive and central sleep apnea, upper airway resistance syndrome, narcolepsy, excessive daytime sleepiness, and parasomnias. Furthermore, you will improve your knowledge about sleep in specific conditions across the lifespan including gender differences, neurological disease, and pain in relation to sleep. Of course, you as a reader will get familiar in more detail with various physiotherapeutic resources, methods, and techniques to improve sleep, such as exercise, hydrotherapeutic resources, optimizing behavior strategies, and sleep ergonomics. You will also learn more about evidence-based physiotherapy in sleep medicine (especially in sleep physiotherapy and sleep and musculoskeletal system). At the end, you will learn in detail about the subjective and objective sleep assessment in physical therapy practice. Overall, the content of this book constantly reminds you that sleep problems require multidisciplinary approaches.

So, as a physiotherapist, a national health promoter, a health educator, and a senior lecturer, I would highly recommend this excellent and one-of-a-kind literature to all physiotherapists (and also other related health professionals) around the globe, who are dealing with sleep problems in their everyday clinical or education practice. This is a professional book that every physiotherapist should own, read, and use.

Andrea Backović Juričan, World Physiotherapy Network for Health Promotion in Life and Work

Ljubljana, Slovenia Andrea Backović Juričan

Preface

Many of the ideas seen in this book were germinated in a discussion section held at the World Physical Therapy Congress (WCPT) in Geneva, Switzerland, in 2019, toghether with the routine of the Excessive Daytime Sleepiness and Hypersomnia Outpatient Clinic, several supervision meetings, and physical therapy sessions (between a neurologist and a physical therapist) in São Paulo (Brazil) were fundamental for ideas, brainstorming and clinical experiences shared from both of us to become a book.

There is a set of core ideas that underlies all the chapters in this book. Some of these ideas have been roughly investigated while others are more hypotheses until this moment. Indeed, the physiotherapeutic practices and the regulation of the profession, and education policies regarding sleep health may vary between countries and cultures. In Brazil, only recently the sleep health was stated as a role for the physical therapist. This book highlights many points of sleep medicine and discusses how physical therapists can help within the interdisciplinary approach and their role in sleep medicine. The mission of physiotherapists is to promote wellness, mobility, and independence developing people's abilities to move during the course of their lives. Physiotherapists also prevent and treat several issues related to pain, illness, disability and disease, sport and work-related injuries, aging, and inactivity.

Sleep and its disturbances are related to health in general. Sleep is an example of new areas that have been constantly developed into health sciences. Continuing education ensures that they keep up to date with the latest advances in physical therapy research and practice. This book will give a basic grounding in sleep medicine to physiotherapists, healthcare providers, and related specialties, as well as to younger professionals.

The book itself has been divided into seven main parts. The first part focuses on fundamental concepts of sleep, explaining sleep and discussing disturbances and other factors that impact a good night's sleep.

Part of sleep medicine history is remembered. The knowledge of our history is fundamental to understand the present approach and drive to beyond. The second part focuses on the basic conceptions of physical therapists' understanding and working in clinical practice and research with sleep. Both sides must be seen: sleep

impacting on rehabilitation/physical therapy and vice versa. The third part focuses on the most prevalent sleep disorders. There is a brief explanation of sleep diseases in each chapter, followed by evidence-based research and clinical reports by physicians, physical therapists, and other health professionals that already work with sleep issues. The fourth part focuses on specific particularities of sleep during childhood, adolescence, and old age, as well as differences between genders and women's phases during her lifespan. The clinical practice of many physiotherapists is to treat patients with pain and neurological conditions. We also debate about neurological diseases and pain, discussing the intrinsic relationship between sleep and pain/neurological diseases. In the fifth part, the chapters discuss physical therapy resources (exercise, hydrotherapy, ergonomics during sleep, and cognitive behavioral therapy) to improve sleep and to treat sleep disturbances.

There is much to grow in the interface between sleep and physical therapy field. It requires the improvement of basic sleep science knowledge, including experiment-based research (i.e., animal experiments). The sixth part explains the importance of basic research and its results from investigations on the musculoskeletal system and sleep (or lack of sleep). Finally, the seventh part focuses on subjective and objective tools to assess sleep and sleep disturbances. These tools provide useful information to practical clinics with fundamental importance in a interdisciplinary set of approaches.

The editorial process has been a pleasure due to intense work with many professionals who dedicated a lot of time and effort to this project. All these chapters have been written by experts in their respective areas, and we are extremely grateful for their contributions and willingness to donate their experience and time for this book. This book would not be possible without the authors and their wholehearted contributions and keeping up with deadlines.

We hope that this book will improve clinical practice, interdisciplinarity of healthcare professionals of many health professions and physiotherapists, and stimulate further researches in this important area. It is important always to take sleep into account on behalf of our patient's (and our) lives.

São Paulo, Brazil
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Cristina Frange
Fernando Morgadinho Santos Coelho

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Abbreviations

ACTH	adrenocorticotropic hormone
ADHD	attention deficit hyperactivity disorder
AHI	apnea hypopnea index
ARDS	ascending activator reticular system
ASD	autism spectrum disorder
ASV	adaptive servo-ventilation
BFD	biofeedback
BiPAP	bilevel ventilation
BMI	body mass index
BZD	benzodiazepines
CAI	central apnea index
CBT	cognitive-behavioral therapy
CBT-I	cognitive-behavioral therapy for insomnia
CBT-P	cognitive-behavioral therapy for pain
CBT-S	cognitive-behavioral therapy for sleep
CES	contingent electrical stimulation
CHF	congestive heart failure
CNS	central nervous system
CO_2	carbon dioxide
CRSWD	circadian rhythm sleep-wake disorders
CSB	Cheyne-Stokes breathing
CSF	cerebrospinal fluid
Ct	clinical trial
CT	computer assisted tomography
DSM-V	Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition
ECG	electrocardiogram
EDS	excessive daytime sleepiness
EEG	electroencephalogram
EMG	electromyogram
EOG	electrooculogram
ESS	Epworth sleepiness scale

FDA	Food and Drug Administration
GABA	gamma aminobutyric acid
GERD	gastroesophageal reflux disorder
GH	growth hormone
GHB	sodium oxybate
HCRT-1	hypocretin-1 or orexin
HF	heart failure
HI	hypopnea events
HLA	human leukocyte antigens
HPA	hypothalamus-pituitary-adrenal axis
Hz	hertz
IASP	International Association for the Study of Pain
ICF	International Classification of Functioning, Disability and Health
ICSD	International Classification of Sleep Disorders
ICSD-3	International Classification of Sleep Disorders, Third Edition
IGF-1	insulin-like growth factor 1
IRLSSGS	International RLS Study Group Scale
KLS	Kline-Levin syndrome
LVEF	left ventricular ejection fraction
MAD	mandibular advancement device
MENS	microcurrent electrical nerve stimulation
MMA	masticatory muscle activity
MRT	magnetic resonance tomography
MSLT	multiple sleep latency test
NCDs	non-communicable diseases
NIV	non-invasive ventilation
NREM	non-REM sleep
NT1	narcolepsy type 1
NT2	narcolepsy type 2
O_2	oxygen
OAI	obstructive apnea index
ODI	oxygen desaturation index
OFP	orofacial pain
OHS	obesity hypoventilation syndrome
OSA	obstructive sleep apnea
PAP	positive airway pressure therapy
PCO_2	pressure of arterial carbon dioxide
PLMD	periodic limb movement disorder
PLMDi	periodic limbs movement disorder index
PLMS	periodic limbs movement during sleep
PMR	progressive muscle relaxation
PO_2	pressures of arterial oxygen
PSG	polysomnography
PSQI	Pittsburgh Sleep Quality Index
PT	physical therapist or physiotherapist

PTs	physiotherapists
QoL	quality of life
RBD	REM sleep behavior disorder
RCT	randomized controlled trial
RDI	respiratory disturbance index
REM	rapid eye movement
REML	REM sleep latency
RERA	respiratory effort related arousal
RLS	restless legs syndrome
RR	risk ratio
SB	sleep bruxism
SDB	sleep disordered breathing
SE	sleep efficiency
SL	sleep latency
SOL	sleep onset latency
SOREMP	periods of sleep onset REM periods
SPECT	single-photon emission computed tomography
Stage N1	stage NREM 1
Stage N2	stage NREM 2
Stage N3	stage NREM 3
Stage R	stage REM
Stage W	awake
SWS	slow wave sleep
TECSA	treatment-emergent central sleep apnea
TENS	transcutaneous electrical nerve stimulation
TMD	temporomandibular disorder
TST	total sleep time (sleep duration)
UA	upper airway
UARS	upper airway resistance syndrome
VLPO	ventrolateral pre-optic area
WASO	wake after sleep onset
WED	Willis-Ekbom disease
WHO	World Health Organization
WMT	wakefulness maintenance test

Part I
Basic Concepts

Sleep: Definition, Concept, New Area for Physical Therapy

Cristina Frange, Ana Carolina Aguilar, and Fernando Morgadinho Santos Coelho

Sleep is often characterized by a reversible reduction in consciousness, an increase in arousal threshold, behavioral quiescence, closed eyes, and a recumbent body posture. Sleep is an essential physiological phenomenon for the maintenance of homeostasis of our organism, being a state of intense brain activity. Yes, you read it right: intense activity! Sleep was considered a passive state until the discovery of rapid eye movements (REM) sleep in 1951, today called R stage [1]. At that time, and prior to that time, no distinction was seen between sleep and other states of quiescence such as comma, stupor, intoxication, hypnosis, anesthesia, and hibernation. Sleep represents an essential element for health and well-being, including cognitive performance, physiological processes, emotion regulation, physical development, and quality of life [2].

Sleep (and why we sleep) remains a scientific enigma and we do not know sleep functions precisely. We do know that we cannot survive without it. Many scientific investigations on the function of sleep have proposed a variety of theories: sleep serves an immune function, reduces caloric usage, restores brain energy stores, has a glymphatic function (house cleaning duties such as removal of extracellular amyloid-β from the brain), restores waking-induced performance degradation, and

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may also serve a neuronal/glial connectivity (plasticity) function [3]. In addition, we have many investigations on this active process providing daily restoration due to the production of fundamental anabolic hormones, involved in cellular growth and regeneration, such as growth hormone, testosterone, and prolactin [4].

Theories as to the function of sleep have naturally focused on the brain. The synaptic homeostasis theory [5], the brain energetic restoration theory [6], the memory consolidation theory [7], and the macromolecular biosynthesis theory [8] have all cited a central emphasis on the significance of sleep for the brain. Unforgettable, there is a famous declaration of sleep being a product "of the brain, by the brain, and for the brain" [9].

The effects of sleep and sleep deprivation on the body are hard to ignore. In humans, there are well characterized physiological and behavioral changes known to impact the pathophysiology of several diseases such as metabolic dysfunction [10], hypertension, stroke [11, 12], diabetes, neurocognitive diseases [13], heart diseases [14–17], musculoskeletal function [18], and altered immune function [19, 20]. Taken together, these comorbidities increase morbimortality associated with sleep and sleep deprivation [21]. Given this context, it is reasonable to suspect that sleep state impacts a broader array of peripheral tissues in addition to the brain. In this sense, transcriptional effects of sleep outspread further than the brain to include peripheral tissues [22].

In each specific tissue of our body, sleep seems to provide a temporal compartment to cope with the tissue-specific molecular consequences of wakefulness. Here is another point to consider: not only sleep is important but also the relationship between sleep and wakefulness is imperative. We need to broaden our vision beyond *what happens* withing our body *during* sleep, but also *what happens* to our body *prior to* and *after* sleep. Sleep prepares our body for the awake state, and the hormones (likewise the lack of some of them during the day) are responsible for many physiological processes.

The propensity to sleep is determined by two of the interviewed processes: the circadian and the homeostatic processes [23, 24]. The two intertwined process model postulates that the homeostatic process increases during waking and decreases during sleep, and interacts with a circadian process that is not directly dependent on sleep and waking. In the circadian process exists a timing mechanism of the body, where hormones are produced and released (e.g., glucocorticoids, melatonin, cortisol), influencing endocrine function. There are either fluctuations of core temperature, performance, muscle strength, rhythms in behavioral processes (e.g., locomotor activity and feeding). In humans, the circadian rhythm is about ±24 hours and, for our biological clocks to be effective, they must accurately keep time and adjust to environmental signals (e.g. light and dark cicles, feeding and fasting, activity and rest). In the homeostatic process, sleep pressure is increased as longer as we are awake, and consequently, there is an increase in adenosine, an endogenous hormone that promotes sleep [25]. Adenosine also dissipates during sleep, and thus induces wakefulness for the next day toghether with an orchestra of other hormones. That is, sleep is also regulated by the accumulation of its debt: the more the wakefulness, the more the need to sleep accumulates, until the moment when this accumulation becomes unbearable, and it is necessary to sleep (Fig. 1).

We sleep when these two processes are in tune: the circadian process indicating that it is the time to sleep, and the homeostatic process indicating that there is an accumulation of need for sufficient sleep. The interaction of both processes determines the time of sleeping and waking up.

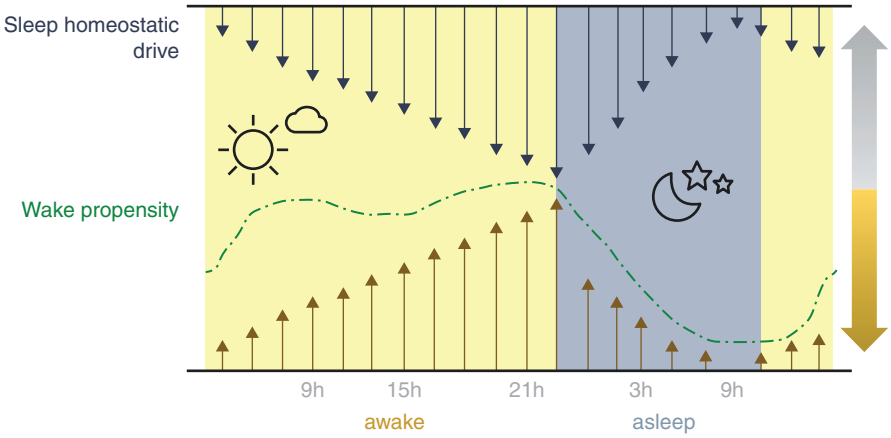

Fig. 1 Circadian and homeostatic processes of sleep. A two-process model of sleep. A linearly accumulating and dissipating homeostatic (Process S) drive to sleep counteracted by a circadian alerting signal that has approximately 24-hour birhythmicity (Process C). The homeostatic process represents a sleep pressure that accumulates in a nonlinear progression from the time of the last sleep episode. With a subsequent sleep episode, the signal strength representing the homeostatic process declines at an exponential rate. The circadian processes follow a nearly sinusoidal pattern, repeating independently of sleep episodes. Sleep and wakefulness are only maintained in a consolidated fashion when the signals from both processes must be appropriately aligned. (Adapted with permission from Ref. [26])

The desynchrony of these processes can lead to many diseases. According to the third International Classification of Sleep Disorders (ICSD-3), American Academy of Sleep Medicine (AASM) [14], there exists a variety of sleep disorders.[1]

[1] Insomnia: chronic insomnia disorder, short-term insomnia disorder, and other insomnia disorders such as excessive time in bed or short sleepers. Sleep-related breathing disorders: obstructive sleep apnea, central sleep apnea (primary, due to a medical disorder, with Cheyne-Stokes breathing, due to high-altitude periodic breathing, due to a medication or substance, treatment-emergent central sleep apnea, sleep-related hypoventilation disorders such as upper airway resistance syndrome, obesity hypoventilation syndrome, sleep-related hypoxemia, and snoring. Central disorders of hypersomnolence such as narcolepsy, idiopathic hypersomnia, Kleine-Levin syndrome, hypersomnia due to a medical disorder or a medication or substance, or associated with a psychiatric disorder, and insufficient sleep syndrome. Circadian rhythm sleep-wake disorders, such as delayed sleep-wake phase disorder, advanced sleep-wake phase disorder, irregular sleep-wake rhythm disorder, non-24-hour sleep-wake rhythm disorder, shift work disorder, jet lag disorder, circadian sleep-wake disorder, not otherwise specified. Parasomnias such as NREM-related parasomnias (disorders of arousal, confusional arousals, sleepwalking, sleep terrors, sleep-related eating disorder), REM-related parasomnias (REM sleep behavior disorder, recurrent isolated sleep paralysis, nightmare disorder), other parasomnias (exploding head syndrome, sleep-related hallucinations, sleep enuresis, parasomnia due to a medical disorder, due to a medication or substance), and somniloquy (sleep talking). Sleep related movement disorders (restless legs syndrome (also called Willis-Ekbom disease), periodic limb movement disorder, sleep bruxism, sleep related rhythmic movement disorder benign sleep myoclonus of infancy, propriospinal myoclonus at sleep onset, due to a medical disorder or a medication or substance).

The identification and classification of sleep stages are made by polysomnography examination (PSG, see Chap. 36 for more information). In PSG, the characteristics of each of the stages are well defined and measured through the electroencephalography (EEG) waves, according to their frequency and amplitude. Sleep has two separate stages, defined based on an assemblage of physiologic parameters: the R stage (REM sleep) and the non-REM stage (NREM). The NREM stage is further subdivided into stage 1 (N1), stage 2 (N2), and stage 3 (N3) sleep. A sleep cycle is composed of consecutive alternations between the NREM and R stage and lasts about 70–110 minutes each. Humans experience about 4 to 6 sleep cycles per night, with different proportions of each stage throughout the night (Fig. 2) [27] and vary according to age, sex, exposition to daylight, diseases, etc. In normal individuals, NREM sleep predominates in the first half of the night, while REM sleep is more frequent in the second half of the night. The schematic representation of sleep architecture (sleep structure, sleep pattern) can be seen in polysomnographic examination in the hypnogram, a graph that characterizes the sleep stages as a function of time (Fig. 3). There exists a protocol defined by the AASM for sleep scoring.

Normal sleep pattern begins at the N1 stage of NREM sleep, which constitutes the transition from wakefulness to sleep and is predominantly characterized by the transition from alpha rhythm to theta rhythm, from 4 to 7.5 Hz. From the time an individual goes to bed to sleep and the time he/she effectively starts to sleep is called sleep latency. During stage N1 sleep, the heart rate decreases and the eyes exhibit lenient movement. N1 sleep stage presents typical graphic elements in the EEG, such as the vertex waves (i.e., focal sharp transients' waves with duration <0.5 seconds, with greater amplitude (Fig. 4). The vertex waves progress through deeper NREM stages N2 and N3, before the first episode of REM sleep, which occurs about 80 to 100 minutes after N1. Here the time from the begining of sleep to the first REM sleep stage in a cycle is called REM sleep latency. Back to sleep pattern,

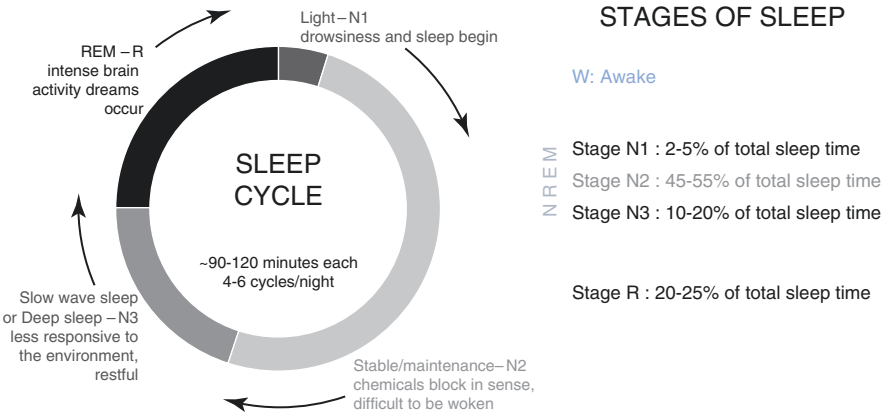

Fig. 2 Sleep "architecture," sleep pattern, sleep structure: distribution of sleep stages during the total sleep time/sleep duration, which is composed of 4–6 sleep cycles each night. A sleep cycle is composed of stages NREM: N1, N2, N3, and R

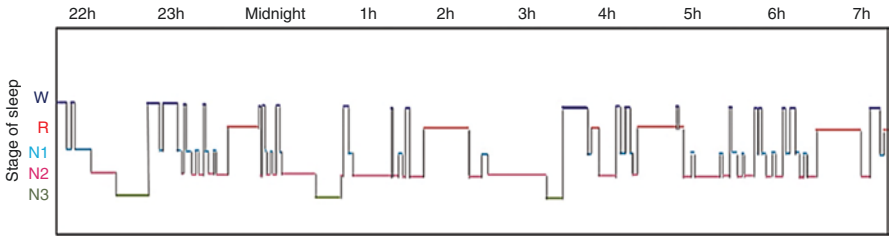

Fig. 3 Hypnogram representing the sleep pattern, extracted from the polysomnography exam. Note that the sleep stages repeat, although with different durations throughout the night. In addition, generally, the N3 stage is predominant in the first half of the night and the R stage in the second half of the night. (Image courtesy from Dr. Cristina Frange)

most of the night's sleep occurs in stage N2, characterized by slow waves (i.e., theta waves, with decreased frequency, low amplitude, and graphic elements such as sleep spindles and K-complexes) (Fig. 4), related to sleep maintenance [28]. Sleep spindles are bursts of neural oscillatory activity that are generated by the interplay of the thalamic reticular nucleus and other thalamic nuclei in a frequency range of 11–16 Hz (usually 12–14 Hz) with a duration of 0.5–1.5 seconds [29]. Sleep spindles are an EEG hallmark of NREM sleep and are believed to mediate many sleep-related functions, from memory consolidation to cortical development. K-complexes have the functions of suppressing cortical arousal in response to stimuli that the sleeping brain evaluates not to signal danger and supporting sleep-based memory consolidation [30]. At the N2 sleep stage, there are slow or absent eye movement and moderate muscle tone. The N3 stage of NREM sleep is composed of high amplitude waves, $\geq$75 μV – with low frequency <3.5 Hz (delta wave activity, that is why it is also called slow-wave sleep, deep sleep, or delta sleep (Fig. 4) – called delta waves, which makes it the "deepest" sleep, with a higher threshold for awakening and more intense brain synchronization seen in the EEG. Night terrors and sleepwalking can occur during N3 sleep. In NREM sleep, there is a regular decrease in ventilation, effectiveness of proprioceptive reflexes and chemoreceptors is maintained, and intercostal muscles are active. There is also maintenance of muscle tone of the upper airways, eurythmic decrease in heart rate, and regular decrease in blood pressure and cardiac output. Therefore, the EEG pattern in NREM sleep is commonly described as synchronous, with such characteristic waveforms as sleep spindles, K-complexes, and high-voltage slow waves. Finally, REM sleep is characterized by EEG activation, muscle atonia, and episodic bursts of rapid eye movements, presenting with a mixed frequency of fast brain waves, with theta and alpha waves, desynchronized, indicating (very) intense brain activity, with or without the presence of sawtooth waves (triangular, 2–6 Hz, with greater amplitude in central regions (Fig. 4)). In the REM sleep stage, there is muscle hypotonia (also called by some researchers as muscle atonia), as the brain blocks motor neurons; consequently, the body does not "act" the dreamed orders or waxes them. Brain activity is intense, similar (or even higher!) to the state of awakeness [25, 31]. REM sleep stage was once known (not anymore) as paradoxical sleep, exactly by the paradox

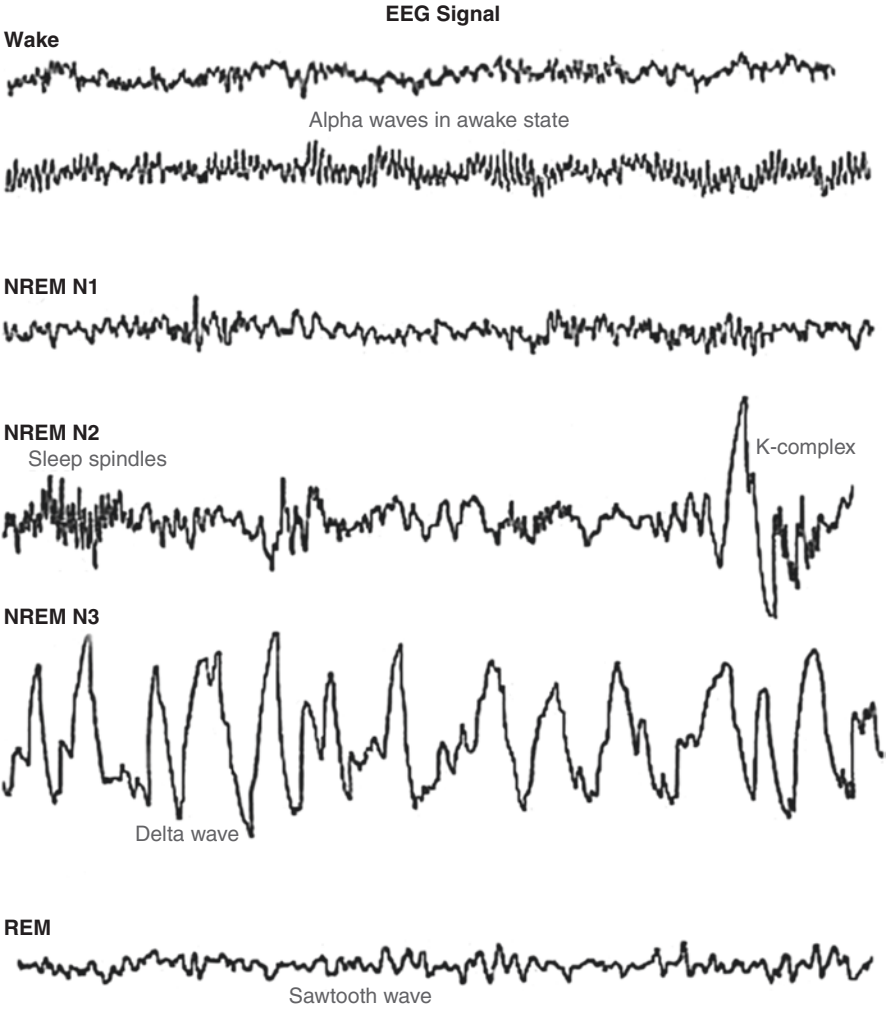

Fig. 4 Sleep stages and their brain waves acquired by electroencephalography in the polysomnography exam and its typical graphic elements

of being in a very intense activity of the mind and extreme relaxation of muscles. In REM sleep, ventilation is variable and quick, proprioceptive reflexes and chemoreceptors are abolished, intercostal muscles are inactive, hypotonia of the upper airway muscles is observed, heart rate becomes faster, and irregular oscillations of blood pressure and cardiac output occurs. Therefore, a quick definition of REM sleep is "an activated brain in a paralyzed body."

For the first sleep cycle, sleep does not always start in N1 and goes through N2, N3, and REM sleep stages. Individuals who are deprived of sleep, for example, may initiate sleep in the REM sleep stage, a condition called sleep rebound, a strategy of our organism to compensate for some functions of the body going directly to the

needed sleep stage. Sleep deprivation and issues regarding sleep may, in a long time, lead to sleep disorders comorbid with other diseases, with a negative impact on health and functioning.

In this sense, physiotherapists (PTs) are in an ideal position to promote health and wellness, prescribing physical activity and exercises, educating patients and clients to adopt a regular physical activity regimen, performing hands-on interventions consistent with the biopsychosocial paradigm, and educating patients and clients about sleep. PTs are in ideal position due to the nature of PT's scope of practice, having constant and persistent access to their patients and clients. As the profession changes and improve over time, based on scientific developments PTs practice in contemporary times include sleep health.

The World Health Organization (WHO) has an international classification of occupational professions, essentially reflecting the distinction of subgroups of the health workforce according to assumed differences in skill level and skill specialization required to fulfill the tasks and duties of jobs. PTs are under the classification of health professionals focused on the study, advise on, or provide preventive, curative, rehabilitative, and promotional health services based on an extensive body of theoretical and factual knowledge in diagnosis and treatment of disease, health difficulties and conditions:

> Physiotherapists assess, plan and implement rehabilitative programs that improve or restore human motor functions, maximize movement ability, relieve pain syndromes, and treat or prevent physical challenges associated with injuries, diseases, and other impairments. They apply a broad range of physical therapies and techniques such as movement, ultrasound, heating, laser, and other techniques. They may develop and implement programs for screening and prevention of common physical ailments and disorders.

On the one hand, for the patient, many diseases or conditions may ameliorate if sleep is properly assessed and treated (e.g., knowledge of sleep basics and the importance of sleep for health), as sleep has an imperative function in most of our body's systems, such as modulating pain and mood disorders (e.g., anxiety and depression), memory and learning (and include motor learning), cognitive function, immune function, cardiovascular health, and many more. So, adequate sleep with regard to amount and quality can aid within rehabilitation and physical therapy. On the other hand, PTs can perceive sleep issues in their patients, access and refer to physician and other health professionals, and treat the disturbance along with the physician and other health care providers in an interdisciplinary manner. Therefore, PTs can treat sleep disturbances by a variety of techniques, methods, and resources, addressed in the course of this book.

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Normal Sleep: Interindividual Differences and Sleep Variability

Maria Júlia Figueiró Reis

Normal sleep is characterized by multiple cycles of defined stages that comprise cerebral and behavioral features. Central nervous system (CNS) maturation and aging processes are intimately linked to changes in normal sleep patterns. Additionally, there are variations related to gender and individual night-by-night oscillations. These normal variants will be the matter of this chapter.

1 Circadian Rhythm and Homeostasis

Sleep-wake machinery is composed of two independent forces – circadian (C) and homeostatic (S) processes – that can be modulated by internal and external cues, leading to a nearly 24-hour cycle [1], as explained in Chap. 1. These cues include body temperature, light, physical exercise, among others [2]. Sleep onset normally occurs in association with body temperature decrease, while sleep offset occurs when temperature rises [3].

The homeostatic process is mediated mainly by adenosine, which is a direct product of the cleavage of adenosine triphosphate (ATP) in the synaptic cleft. ATP is coreleased with neurotransmitters and leads to the accumulation of adenosine in the extracellular space as neuronal activity is stimulated, leading to an increase in the drive to sleep by the end of the day [4]. On the other hand, it is believed that the circadian process promotes maximum wakefulness by that same time, to

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counterbalance homeostatic drive [1]. This system is mediated by the retinohypothalamic pathway, by which light stimuli are transduced to promote rhythm adjustment of the suprachiasmatic nucleus – also known as a master clock – by means of transcription of clock genes [5]. Also, there is a light-mediated continuous inhibition of melatonin release by the pineal gland. By twilight, as it becomes dimmer, there is a disinhibition of this pathway, leading to an increase in melatonin levels, which occurs about 2 hours before usual sleep onset [6]. Finally, at the end of the night, wake is promoted by a suprachiasmatic nucleus-mediated increase in cortisol levels around 2–3 hours before usual wake time, by the same time when the lowest core body temperatures are registered, and the peak of melatonin levels occurs [7].

Usually, some circadian preferences within healthy individuals are described, referred to as morningness-eveningness. On the other hand, chronotypes are defined as an activity/behavior measure: late types are more active and productive by night, whereas early types have increased activity in the morning hours [8]. Human populations, in the majority, show a slight tendency for late chronotypes.

Circadian rhythms have progressive expression in the course of development and the aging process is related to changes mainly in the entrainment of the master clock and gene expression. It has been demonstrated that human fetuses show circadian rhythms for cardiovascular function, behavior, and hormonal regulation. Cycles of heart rate and body temperature within the 24-hour period were demonstrated in both preterm and full-term infants. Cortisol rhythms appear approximately 2–4 months after birth, while melatonin secretion starts to cycle around 48 to 52 weeks post-conception [9].

2 Sleep Duration

Normal sleep duration in young adults varies from 7.5 to 8.5 hours, considering weekday and weekend nights, respectively. It is known that duration depends not only on volitional but also on genetic features. Circadian and homeostatic factors also contribute to bout length [3]. A recent meta-analysis suggests that this difference in sleep duration for weekend nights occurs only in age groups that have a school or work schedule during weekdays [10].

In childhood, most recommendations on normal sleep duration are based on expert consensus opinions. American National Sleep Foundation opinion is the most cited of them [11]. Sleep requirements normally decrease over the lifespan in healthy populations, and it is assumed that lower needs occur in older subjects (Fig. 1).

There are also defined criteria for sleep durations that are out of the recommended range, although without clear daytime dysfunction or sleep/wake complaints, putting these special cases as part of the normal range. Short sleepers are the ones who report to sleep six or fewer hours a day and long sleepers are the ones who need nine or more hours of sleep per day. The clinical significance of these patterns remains unclear [12]. Although some studies suggest an increase in morbidity in the extremes of sleep hours per day [13], they might be unable to distinguish genuine

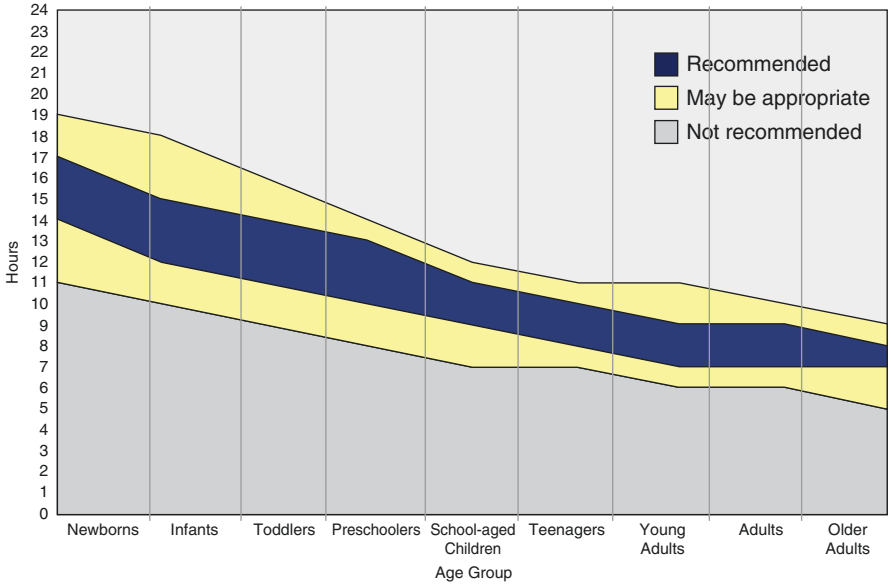

Fig. 1 Sleep duration recommendations across the lifespan. Note that there is a progressive decrease of average sleep needs over the lifespan, as assumed for this consensus. (Reprinted with permission from Hirshkowitz et al. [11])

short and long sleepers from individuals who present with a sleep pathology that leads to secondarily short or long periods of sleep [12].

3 Sleep Particularities in Childhood

Clear wakefulness and sleep states can already be defined around 27–28 weeks post-conception. By this time, active sleep (REM, R stage) corresponds to approximately 80% of total sleep time. By 40 weeks post-conception, active sleep is reduced to approximately 50% of total sleep time, counterbalanced by quiet (NREM) sleep. R stage is progressively reduced until ages 3–4 years, by which it corresponds to 20–25% of total sleep time, similar to adults [14].

In neonates, sleep usually begins with an active sleep (R stage), differently from older infants [15]. Along the first year, quiet (NREM) sleep sequences become progressively more prominent, with N3 predominance over other sleep stages in the first part of the night during early childhood. This can lead to one or more episodes of suppression of the R stage in the first sleep cycles [16, 17]. N3 amount gradually decreases to reach the adult pattern by the second decade of life [18].

Considering electroencephalogram (EEG) components linked to brain development, K-complexes and sleep spindles can first be seen in full-term infants around 2–3 months of age and are linked to thalamocortical maturation. Around 4–6 months of age, sleep stages N1 to N3 become more defined. N3 is important for growth hormone release and memory consolidation [14].

Newborns exhibit sleep cycles of 50 to 60 minutes, in contrast with the 90-minute cycle commonly seen in adults [15]. Sleep in newborns and infants is not usually continuous throughout the night and extends as multiple sleeping episodes during the daytime, a pattern characterized as polyphasic sleep, usually between 0 and 3 months from birth. As children get older, sleep gradually consolidates as a lower amount of longer-duration sleeping episodes, first maintaining the polyphasic pattern between 4 and 12 months, though with a tendency for nighttime consolidated sleep. Then, when they reach 4 years of age, sleep is characterized by the presence of one main event of consolidated sleep by night and one daytime nap, a pattern known as biphasic sleep. Finally, monophasic sleep usually begins by the age of 5 years, when daytime naps stop and sleep is commonly set by nighttime (for review see [19]).

Concerning circadian rhythms, children usually have a tendency for earlier bedtimes. However, between prepuberty and puberty, there is a shift in the sleep phase, which shows a tendency for delay. This tendency can be exacerbated by changes in lifestyle, social demands, and screen exposure. For that reason, considering school start times that are habitually early, adolescents tend to be chronically sleep-deprived [10, 20].

4 Sleep Particularities in Aging Process

Several meta-analyses have shown changes in sleep architecture, most of them occurring up to 60 years old. One of these studies has shown that there is a more remarkable decrease in N3 and an increase in wake after sleep onset (WASO) if compared to reductions of total sleep time and R stage over time. Sleep latency also increases up to 60 years old [21]. Sleep efficiency shows a progressive reduction over the entire lifespan, although there is a recent meta-analysis based on sleep reports showing that 25% of individuals aged 65 or more presented with a sleep efficiency of more than 95% [10, 21].

It has also been demonstrated that the N3 decline that occurs with age is more pronounced in men compared to women [22]. Nevertheless, a meta-analysis did not show the same trend for gender variation [21]. Additionally, a gender difference was demonstrated in N1 and N2 duration, with an increase of these stages restricted to male subjects. R stage had a discrete reduction in both genders, as well as sleep efficiency [22].

Normal elements of NREM sleep are also modified with age. On the contrary of what happens in childhood and adolescence, there is a reduction of K-complex and spindle density, as one gets older [23].

In healthy older individuals, there is a tendency to present with more fragmented sleep, in spite of normal latencies to get back to sleep [24]. Although this happens even without sleep pathologies like sleep-disordered breathing, there is a marked effect of respiratory disturbance index (RDI) on sleep fragmentation, with an increase of arousal index as the severity of RDI progresses. There is also a slightly higher effect in favor of men, who show greater arousal indexes compared

to women. RDI was also associated with a greater decrease in the N3 stage in men compared to women and with a discrete reduction in the R stage that occurred in both genders [22]. Despite this pattern of sleep disruption, a recent meta-analysis suggests that older individuals with obstructive sleep apnea present with less excessive daytime sleepiness compared to younger ones [25]. Periodic limb movements during sleep might also play an important role in sleep fragmentation [26].

Besides changes evidenced in sleep architecture, there is also a circadian component in the process of aging. Studies suggest that there is a reduction in the amplitude of cycles seen in body temperature, some hormones, and sleep-wake rhythm over time. There is also a tendency for phase advancing [27]. This can be partly explained by the fact that entrainment to light might be impaired, as there are changes in lens color in healthy aging [28], thinning of retinal nerve fiber layer, decrease in melanopsin retinal ganglion cells in the context of neurodegeneration [29], and altered clock gene expression. It has been suggested that Parkinson's and Alzheimer's diseases might have a link with single nucleotide polymorphisms in BMAL1 and CLOCK, previously demonstrated clock genes [30].

Plus, there are several structural changes in the visual pathways that could in part justify changes in the entrainment capacity of the circadian rhythms. Aging is associated with ocular tissue degenerative processes such as cataracts, which could reduce response to blue light [31]. Besides, neuroimaging studies in the old ones suggest that response to blue light is impaired in brain areas related to alertness, attention, and visual and executive function [32].

The older ones also show a reduced ability to phase-shift, which might result from loss of rhythmic function within the suprachiasmatic nucleus. Loss of function of this structure might also be related to the increased quantity of sleep throughout the 24-hour period that usually occurs in normal aging [27].

Finally, recent studies are progressively demonstrating links between disordered sleep or changes in sleep architecture and cognitive decline. It has been demonstrated that both N3 and R sleep stages, which normally degrade among the elderly, have important roles in memory consolidation. Spindles have also been implied in this matter, and the manifestation of spindle up-states in NREM sleep appears to have functional significance [33]. Amnestic mild cognitive impairment has been linked to the reduction of slow-wave sleep and sleep efficiency among the elderly [34]. Recently, it has been demonstrated that the slow-wave sleep-dependent glymphatic system promotes the clearance of neurotoxic substances such as tau protein and amyloid-beta (Aβ), suggesting the pathogenesis by which sleep deprivation or N3 reduction in late life might lead to human neurodegenerative disease [35].

Indeed, there is recent data suggesting a beneficial role in terms of delay in cognitive decline secondary to Trazodone use, a known enhancer of the N3 stage, although it is not clear if this is a result of better overall sleep quality or an effect over N3 itself [36]. Some advances have been made in this area, with the in vitro demonstration of reduced Tau amyloidogenesis after administration of Trazodone over SH-SY5Y cell line and 1N4R isoform of tau protein [37].

Differential aspects of normal sleep that occur within the aging process are summarized in Table 1.

Table 1 Sleep in childhood and aging. Note the main differential elements in the macro and microstructure of sleep across the aging process

Children	Older ones
Increased percentage of R stage (up to 3–4 years of age)	Progressive reduction of R stage
Increased percentage of N3 (up to the second decade of life)	Progressive reduction of N3 stage leading to probable cognitive implications
Progressive consolidation into a monophasic sleep	Progressive return to a polyphasic pattern
A tendency for phase delay in adolescence	A tendency for phase advance
An increased amount of spindles and K-complexes	Reduction in spindles and K-complexes
Difficulty in waking up in the N3 stage of the first sleep cycle	Sleep fragmentation + increase in WASO

R Stage rapid eye movement stage, *WASO* wake after sleep onset

5 Final Considerations

There is a wide range of individual variations within the concept of normality. Ontogeny also adds a component of difficulty in analyzing the patient sleep complaints – or the absence of them. Knowing to interpret such subtlety can help clinicians and researchers to adequately predict outcomes and plan clinical interventions.

Although a lot has been made to elucidate the causes and consequences of changes in sleep architecture, sleep duration, and circadian patterns, there are still unanswered questions. Defining subgroup analyses that comprise the different normal variants will help to better understand this challenging field and to build an adequate epidemiological database for clinical support.

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Brief History of Sleep Medicine and Its Importance for Overall Health

Monica Levy Andersen and Sergio Tufik

Sleep has been a target of human imagination since ancient times, a period when inexplicable happenings, such as dreams and sleepwalking, were surrounded by mysticism. With the development of science, our knowledge became more refined and new investigation methods were conceived, resulting in the current level of understanding. This knowledge, however, is not yet complete, seen that some elementary problems, such as the evolutive origins of sleep, its biological causes, and the main question of why we sleep, remain unsolved.

Proper tools to study sleep were not available for a long time, making it a particularly elusive physiological process when compared to more tangible ones, such as blood flow and pulmonary respiration. It was only by the middle of the nineteenth century that the development of adequate techniques happened. Initially, auditory and tactile stimuli were employed to measure the depth of sleep (see [1]), but the true revolution in sleep neurology was reached with the discovery of electrooculography by Hans Berger in 1929 (see [2]). This technique, which measures neuroelectric activity, later established the basis for modern electroencephalograms (EEG).

With this new tool, it was possible, for the first time, to measure neuroencephalic activity during sleep, which led to numerous discoveries about its mechanisms and disorders. An important finding was that encephalic neurons trigger at different levels of synchrony, forming patterns or waves with distinct frequencies and amplitudes. These patterns are measured in Hertz (Hz) and are classified, by convention, as delta (slowest waves), theta, alpha, beta, and gamma (fastest waves).

Another elementary discovery was that human sleep occurs in phases, characterized according to different patterns detected by EEG, as described in the previous chapters.

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The discovery of REM sleep and NREM sleep, and their wave frequencies took place mainly in Europe and the United States during the first half of the twentieth century [3].

Historically, pioneers such as Kleitman, Aserinsky, Dement, and Jouvet established the development of sleep medicine. Aserinsky and Kleitman discovered that eye movements were present during particular periods of sleep by observing their own children asleep [4]. Dement and colleagues demonstrated that brain waves were distinct during sleep and that specific brain waves were associated with these distinct eye movements during sleep. They reported that periods of eye movement repeated at frequent intervals of nearly 100 min during nighttime sleep [5]. Jouvet and Michel lengthened the previous work and found that, in association with eye movements and brainwaves, there was an absence of muscle tone during certain sleep periods [6]. By 1961, they considered sleep into two different states: telencephalic sleep (slow-wave) and rhombencephalic sleep (paradoxical sleep, known nowadays as REM sleep or R stage). The monitoring of eye movements, brain waves, and muscle tone during sleep permitted the examination of sleep and its variety of sleep patterns. Dement created the "Association for the Psycho-Physiology of Sleep," which turned into the "Association of Professional Sleep Societies" (APSS). The primary goal of APSS was to create the new field "sleep medicine," as many physicians did not understand this need at that time. The first attempt to systematize the sleep disturbances occurred in 1972, in the APSS annual reunion, which showed the "loneliness" of the few individuals who wanted to create a new research disciple. Dement started working together with a neurologist, Guilleminault, which was visionary about this new discipline. He had been studying sleep apnea in Europe, and although sleep apnea was discovered back in 1965, Guilleminault was the first to describe obstructive sleep apnea as a clinical syndrome. In 1973, Guilleminault and his colleagues reported pediatric cases of obstructive sleep apnea (OSA) based on their studies of normal-weight subjects [7, 8]. In the winter of 1976 in Chicago, a new society, the Association of Sleep Disorder Centers (ASDC), was created (and its name changed after 2000 to the American Academy of Sleep Medicine (AASM) as we know it today). In 1979, the first "Diagnostic Classification of Sleep and Arousal Disorders" was published after 3 years of research by a "nosology committee" under the chairing of Roffwarg [9]. This early nosology was the antecedent to the following versions of the International Classification of Sleep Disorders (ICSD). Before the 1980s, the only effective treatment for severe OSA was a chronic tracheostomy, which was highly functional by that time. This treatment was then replaced by two new procedures: surgery (uvulopalatopharyngoplasty) and mechanical ventilation (equipment that eliminated the need to perform a tracheostomy, which used positive pressure on airways, developed by Sullivan and colleagues using his mother's old vacuum cleaner) [10]. The positive results from the use of continuous positive airway pressure treatment for OSA were (even being loudly and uncomfortable) and still are a success. In this sense, many physicians, health care providers, and researchers, in five or six centers, created an association of individuals interested in the clinical aspect of sleep.

The first textbooks on sleep medicine appeared in the 1980s, such as the first edition of Principles and Practice of Sleep Medicine [11], by Kryger, Roth, and Dement, a must-read book for everyone who wants to understand the basics of sleep. The sleep medicine field advanced enormously during this decade and followed one throughout the world. In the 1990s, the National Sleep Foundation and other organizations for patients were established.

Many of these studies were conducted on human beings, but sleep patterns were soon discovered in cats, dogs, monkeys, and other mammals, besides birds and reptiles. Some of these species are used to this day in sleep research, but this field has benefited greatly due to the use of experimental models with rats, allowing the intense development of knowledge in the area.

The prominence of this species in sleep science was due to the 1970s discovery that its short-wave sleep presents three phases, as do human beings, which allowed the knowledge acquired with it to be extrapolated to humans with more precision than any other species. This property made rats excellent models, which were quickly adopted in sleep laboratories around the world. Currently, rats have contributed to the publication of more than 12,500 indexed articles [12], placing them as the most used model in sleep science.

What makes this discovery even more interesting is the fact that it was entirely conducted in Brazil, having been published in 1970 by Professor Cesar Timo-Iaria's research group [13]. Professor Timo-Iaria was a pioneer in sleep science, having established the first Brazilian sleep research group in the 1960s. Doing science at the time was not easy: access to bibliography was difficult, the techniques were relatively primitive compared to today, there were several difficulties with the importation of equipment and reagents, and today's simplest things, such as statistical analysis, were done by hand using slide rules and mechanical calculators. There were also similar and more experienced research groups in other countries, which added an international competitive factor to the endeavor. Regardless, the group prevailed and accomplished astounding success in their research, a testimony to the competence of all involved. Today, Brazil is on its fifth generation of scientists dedicated to sleep and it leads scientific article production by the Web of Science platform as the field continues to grow, not only in basic science but also in medicine.

Sleep science started in Brazil with Prof. Timo-Iaria and evolved with other prominent scientists, such as Professor Katsumura Hoshino and others, but it only reached maturity with Professor Sergio Tufik, who currently bears the recognition of being the international researcher with the greatest productivity in the world in the field. During his career, he established one of the most active international sleep research groups, founded the Brazilian Sleep Society, consolidated sleep medicine as an academic course in health undergraduate courses, and founded *the Instituto do Sono* (Sleep Institute), a world-renowned philanthropic institution. Professor Tufik's effort has been pivotal for the dissemination of sleep as a health factor in the population, and the practice of sleep medicine in Brazil owes much to his activities [14].

In addition to attending to the general population, conducting scientific investigations, and promoting educational and conscientization campaigns, *Instituto do*

Sono is responsible for the research Sleep Epidemiology in the City of São Paulo, designated EPISONO Project. Epidemiological studies permit the assessment of the prevalence of pathologies in the general population through a representative sample of individuals. In the case of sleep science, they also allow other measurements, including the average duration of sleep, the quality of sleep, its impact during the vigil, and the prevalence of sleep disorders. EPISONO's first edition, concentrated in the city of São Paulo, was done in 1986, followed by three more editions in 1995, 2007 [15, 16] and 2018/2019, which allowed the longitudinal assessment of sleep patterns in the city.

In the 2007 edition, the largest and most complete so far, EPISONO recruited 1042 subjects for polysomnography, actigraphy, blood tests, genetic exams, and questionnaires [16]. The results indicated that 42% of São Paulo's population suffered from snoring, 24% registered frequent nightmares, and 9% and 3% had bruxism and sleepwalking, respectively [17]. The most common sleep disorder was sleep obstructive apnea, with a prevalence of 32.8% [18].

The 2007 EPISONO was one of the largest epidemiological sleep investigations in the world to utilize a modern and complete methodology, which provided invaluable data referring to populational habits and sleep disorders prevalence, thus allowing the realization of conscientization campaigns and the implementation of public policies specifically aimed at these patients. In the case of sleep obstructive apnea, for example, it was detected that its prevalence was 5–10 times higher than previously described [19], demonstrating the importance of employing adequate methodology in this type of research.

1 Sleep Medicine

Human beings consume one-third of their lives sleeping, an activity that leaves them inert for about 8 hours every day and drastically decreases their reaction capacity, making them vulnerable to predators and to other environmental factors, which lead us to question the evolutive importance of sleep in terms of its physiological utility. Today, it is known that this state is fundamental for the maintenance of organic systems, besides being responsible for numerous cognitive and homeostatic processes, such as metabolic clearance of the brain and the recovery of the musculoskeletal, nervous, and immune systems.

Another function of sleep is to conserve energy by reducing physical activity, besides the maintenance of encephalic energetic homeostasis. This happens through metabolic dynamics specific to REM sleep and depends upon regulatory mechanisms of energetic molecules such as adenosine triphosphate, glucose, and glycogen [19].

Several studies pointed out that the occurrence of infections or exposure to microbiotic antigens alters sleep patterns [19]. It is also known that the incidence of sleep results in improved immune response, while the lack of sleep impairs

the response to infections [20]; for example, patients that slept better after a round of hepatitis A vaccine obtained superior results in the establishment of immune memory against the viral antigen [21]. These data show the importance of sleep in the response against infections and in the patient's recovery after disease.

Another proposed function for sleep is the clearance of metabolites originated from cell activity, removing them from the cerebrospinal fluid and leading them to the bloodstream [22], in a process denominated "glymphatic function" (in reference to the analogous function of the lymphatic system). The glymphatic activity of sleep is responsible for cleaning products originated from the vigil period which, besides protecting the brain against neurotoxic compounds, results in the decrease of osmotic pressure in the extracellular medium due to the presence of these metabolites [23]. It has been proposed that the correct function of the glymphatic process may prevent against Alzheimer's disease, as one of its causes is the accumulation of beta-amyloid peptides in the cerebrospinal fluid [24].

Sleep is intimately related to cognitive and behavioral functions. Sleep deprivation impairs decision-making, reduces speed and precision when performing tasks, causes fatigue, and negatively affects the mood [25]. On the other hand, the incidence of sleep recovers these impaired functions in a way directly proportional to the time spent sleeping [26]. At the cellular level, it has been proposed that the quality of sleep maintains neuronal plasticity in a way that improves memory consolidation and learning [27]. These effects are not static and depend upon factors such as the patient's age and type of experience before sleeping, but they demonstrate the general importance of sleep upon cognition and in the maintenance of mental health.

Bearing in mind sleep's physiological functions and the negative consequences of its deprivation, it is fundamental to point out the importance of sleep hygiene to our health. This concept involves the habits practiced by each individual in order to preserve the quality and efficiency of sleep, including the regular practice of exercises, good nutrition, noise reduction at the time of sleep, and avoidance of caffeine, nicotine, and alcohol consumption, among others (see Chap. 31 for more info). Sleep hygiene is becoming more and more important within the clinical context due to the fact that it has a very low financial cost, is promptly available, and has the potential to significantly improve the quality of life. Laboral impositions and the prevalence of electronic media affect the circadian rhythm of a great portion of the population, leading to deregulation of sleep and of the biological clock, which may become public health issues. Information campaigns about sleep are relatively easy to realize and have an extensive reach when compared to medical consultations and individualized pharmacological treatments, which makes them an important tool in sleep medicine and public health [28]. It is important to point out that there are numerous disorders for which sleep hygiene may not be enough. These have several biological origins (including physiological, psychological, and genetic), and, therefore, need proper therapies. In these cases, sleep hygiene may be indicated as ancillary treatment.

2 Final words

Reference to healthy habits usually implies good nutrition or the practice of physical exercises, but one should bear in mind that care with his or her sleep is equally important. Fortunately, we have observed an increase in the population's awareness about sleep practices, partly due to the growth of science in this area and partly due to the promotion of this knowledge to the population. In this context, the education of health professionals about the importance of sleep is critical, as they act at the front line of the clinical practice and establish direct contact with the patients.

We must point out that the knowledge of sleep disorders by professionals is essential, as their prevalence among the general population is greater than previously thought. Because they occur during the night, away from the clinic, they may easily go unnoticed by the patient and by the health professional. A critical look is necessary for their identification, as well as the patient's forwarding to a specialized professional for exams and proper treatment. This book aims to educate health practictioners about sleep and its disorders, and we expect to help them become better and more conscientious professionals on this so-important factor to human health.

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Part II
Sleep Medicine for the Physical Therapist

Basic Principles of Sleep Physiotherapy Practice

Cristina Frange, Cristina Staub, and Stavros Stathopoulos

According to the World Physiotherapy, the global body for national physiotherapy associations, physiotherapists (PTs) provide services that develop, maintain, and restore people's maximum movement and functional ability. They can help people at any stage of life when movement and function are threatened by aging, injury, diseases, disorders, conditions, or environmental factors.

PTs help people maximize their quality of life, looking at physical, psychological, emotional, and social well-being. They work in the health spheres of promotion, prevention, treatment, and rehabilitation. PTs are qualified and professionally required to:

1. Undertake a comprehensive examination/assessment of the patient/client or needs of a client group
2. Evaluate the findings from the examination/assessment to make clinical judgments regarding patients/clients

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3. Formulate a diagnosis, prognosis, and plan
4. Provide consultation within their expertise and determine when patients/clients need to be referred to another healthcare professional
5. Implement a physiotherapist intervention/treatment program
6. Determine the outcomes of any interventions/treatments
7. Make recommendations for self-management

According to the American Physical Therapy Association (APTA) of the position of house delegates updated in 2020:

> Physical therapists are part of an interdisciplinary team of licensed health services providers in prevention and management of sleep impairments and promotion of healthy sleep behaviors. The PTs role includes using the best available evidence and standards of practice to screen for sleep dysfunction; identify impairments related to sleep dysfunction; implement and progress therapeutic interventions to address impairments that interfere with sleep; educate society, patients and clients, caregivers and providers on healthy sleep behaviors and the relationship between sleep, pain, physical activity, function, health, and well-being; monitor and, if indicated, manage sleep quality and quantity in patients and clients to enhance physical therapy outcomes, and refer to sleep medicine professionals as indicated.

Contemporary PTs, who are function specialists and movement experts, need to understand the impact of the sleep deprivation and disorders singularity on the health and well-being of the patients they attend. In this sense, knowledge about sleep (function, physiology, duration, etc.) and skills to screen sleep disorders and to promote quality sleep are important components for PTs to promote (and treat) health and wellness. Sleep must be listed within our priorities and be part of the anamnesis and of clinical practice. PTs must guise at the topic sleep more precisely – in research, in education, and in everyday practice [1, 2]. Therefore, the regulations/practice of physical therapy in each country is different and depends on the governmental system and health care system. PTs must respect local, regional and cultural differences and act within our scope of practice, in an interdisciplinary manner, and focused on patient-centered care.

1 Why PTs May Treat Sleep Disturbances

A network for Health Promotion in Life and Work (HPLW) has been established into World Physiotherapy. It encourages the members to forward with their health promotion strategies and share views and ideas which can be implemented for sustainable development of various problems such as sleep problems.

Sleep has a vital role in life. In fact, sleep is a behavior that occupies plenty of time in our lives. To be more specific, one-third of our life is spent asleep. In this sense, it must have an imperative function – or many functions, that we don't know yet for sure. However, we know that we cannot survive without sleep. Sleep is an important protagonist of the proper functioning of most, if not all, body systems. We know it because of much scientific evidence on lack of sleep, or disturbed sleep

stages from experimental, epidemiological, longitudinal, and trial investigations that showed that we cannot survive without sleep. In fact, since the 1960s, a variety of investigations using animal models have been conducted in order to study the effects of sleep deprivation on the system or organs and to see which would fail first [3–5]. The researchers found for example that after 2 weeks of sleep deprivation, the rodents died from massive multi-organ failure. The cause of death was not clear: the deterioration in appearance, skin lesions, and changes in brain activity resisted simple explication. Several organs failed, and not just one, as they expected to see. These experiments led a group of researchers to investigate the role of immune function in different organs and systems, and they started to investigate in humans the purpose of sleep. Until now we know that sleep is a biological necessity and that extended sleep loss reliably produces a syndrome of specific substantial physiological changes. Sleep functions are still a mystery. Impaired sleep affects our overall health.

Lack of sleep (both in appropriate quantity and quality) and circadian misalignment have been implicated in numerous adverse health outcomes and can lead to several physiological, neuropsychological, and mental health changes.

2 How PTs May Treat Sleep Disturbances

The physical therapy session, beyond being an external cue for the alignment of the peripheral oscillators, is also capable of adding to the sleep pressure, by many biochemicals endogenously induced during exercise and diverse PTs techniques. PTs' diagnoses are often based on single time point assessments during the day, ignoring circadian influences on physiology. Even when time is considered, using (external) clock time, it ignores the large interindividual differences in internal timing (chronotypes: morning, evening, and intermediate types; amount of sleep needed: short, intermediate, and long sleepers). These themes must be addressed by PTs in order to optimize not only sleep but also rehabilitation in physical therapy practice.

PTs as experts in movement and exercise and with a thorough knowledge of risk factors and pathology and their effects on all systems are the ideal professionals to promote, guide, and manage physical and exercise activities and efforts [6].

PTs are protagonists in promoting wellness, mobility, and independence, in a broad range of diseases. Why not sleep? As we have seen, all of our systems depend on the sleep-wake cycle, either in health or in disease. PTs can help with health promotion and with the prevention of disease conditions by enhancing sleep quantity and improving sleep quality.

In this context, to incorporate sleep health in PTs practice, we must address prevention, health promotion, and wellness interventions: evaluate general sleep health and screen for risk of sleep disorders; refer to a physician when a suspected disorder requires diagnosis and further investigation; arrange for sleep hygiene education; prescribe an appropriate and individualized exercise program to increase homeostatic sleep pressure and also breathing exercises for some

patients; provide relaxation exercises for patients; contemplate positioning therapies for patients to promote sleep quality; refer to bed mobility issues; break the sleep-pain cycle.

In addition to the above-mentioned role, PTs jointly can assist in the reversal of the growing global epidemic of lifestyle allied diseases, now known as non-communicable diseases (NCDs), such as physical inactivity and lack of sleep in our 24×7 plugged society. Several studies attest that a large amount of sedentary time increases the risk of cardiovascular disease [7], especially when the sedentary time is prolonged, that is, for subsequent long periods [8–10]. Physical inactivity is a frequent behavior adopted by the patient due to functional, cognitive, pain, or dependence on activities of daily living within many disease conditions that course along with sleep disturbances.

PTs as health professionals with expertise in prescribing physical activity and individualized exercise regimens for health can significantly help to decrease the global burden of morbidity and mortality of such diseases. However, as members of the interdisciplinary team, PTs collaborate with significant health professionals to implement universal programs to address this global epidemic (Fig. 1).

PTs are able to work with sleep disorders and also to identify sleep disturbances in their patients, which can impact rehabilitation in many, if not most areas, exacerbating and perpetuating the negative outcomes. Sleep is often changed in individuals with a range of different illnesses. For instance, sleep is altered in neurologic conditions, such as stroke [11], multiple sclerosis [12], Duchenne muscular dystrophy [13], spinal cord injury [14], Parkinson's disease [15], dementia [16], and Alzheimer's disease [17]. These patients often receive PT treatment, and we must optimize their sessions via improving sleep. Furthermore, sleep may impact their ability to learn and influence recovery. Sleep disturbances are also quite common in people with diverse pain conditions [18, 19], such as back pain [20], fibromyalgia [21], and orofacial pain [22]. Assessing and treating sleep disturbances may improve pain conditions and diseases. Additionally, post-operative conditions [23], musculoskeletal disorders [24], and orthopedic illnesses, including osteoarthritis [25], ankylosing spondylitis [26], rotator cuff tear [27], and trauma [28] share negative impact of sleep. These were just some examples of the daily PT practice in different settings that have an interaction with sleep. Thus, PTs must address and focus on integrating sleep health in wellness and health promotion interventions such as the following:

1. A good sleeping posture for a restful sleep
2. The type and number of pillows to be used that relate to how the shoulders are to the neck, the sleeping position, the personal preferences to correctly allign the body
3. Avoiding stress
4. Finding the best mattress that best suits their needs
5. Checking the duvet's tog rating
6. Checking the temperature of the room as it can affect sleep
7. Providing information on what time to go to bed and wake up according to sleep needs and circadian preferences (routine)

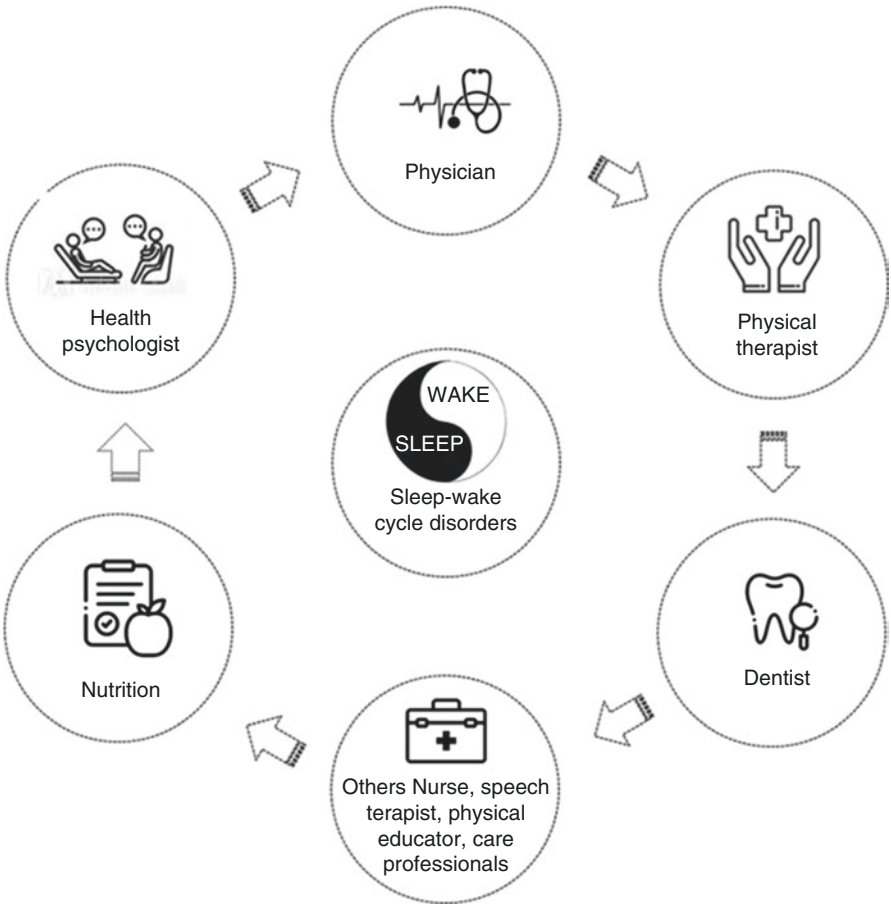

Fig. 1 The interplay between the physiotherapist and health professionals

8. Referring the patient/client to the best time of exercising and/or physical activity
9. Educating about sleep, naps, aging, and disease-specific sleep

PTs can assess sleep via objective or subjective measures. Objective measures are reckoned to be the gold standard in the assessment of specific sleep-related outcome measures. Polysomnography, actigraphy, multiple sleep latency test (MSLT), and maintenance of wakefulness test (MWT) are disease specific. Subjective measures of sleep include sleep questionnaires, sleep diaries/logs, rating scales on the estimated level of sleepiness, and hardware devices (best described in "Objective Assessment of Sleep" and "Subjective Assessment of this book" chapters of this book). These assessment tools and examinations can provide a broad overview of the of hours of sleep, the consistency in sleep, sleep propensity, and disease-specific complaints. They are also a quick and cost-effective way to estimate sleep variables.

Given the context, there are many opportunities for PTs to provide sleep health education and to treat sleep disorders and conditions in their patients/clients that will be discussed in this book.

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Sleep Physiology and Neuroendocrinology for Physiotherapists

Priscila Farias Tempaku

Far from being a simple absence of wakefulness, sleep is characterized by an active, regulated, consciousness, and metabolically distinct state, essential for the health and well-being of several species. Sleep has an important modulatory effect on neuroendocrine, metabolic, and immunological functions that will be discussed in this chapter and are summarized in Table 1.

The three main states of the sleep-wakefulness cycle (i.e., wakefulness, NREM, and R stages) are usually identified based on electroencephalogram (EEG) rhythms, muscle tone level, and in the presence of eye movements [1]. However, the physiological definition and the understanding of these states cannot disregard the evaluation of respiratory, cardiovascular, and metabolic parameters, which are under the integrated control of the autonomic and endocrine systems [2].

This definition goes beyond the standard, largely based on the level of cortical and somatomotor activity of the brain. The hypothalamus plays a fundamental role in this complex integrative activity [3], in arousal, and in regulating transitions between sleep and waking states, which are critical for the maintenance of body homeostasis and for both the survival of the body (fight or flight response) and reproduction. This activity leads to the formation of bodily functions, largely based on external and internal sensory information, according to the physiological meaning and objectives of the different behavioral states [2, 3].

The neural fundamentals of the sleep-wake cycle involve interactions between sleep-promoting areas, such as the anterior hypothalamus, and waking systems [4]. During sleep, gabaergic and glycinergic neurons located in the ventrolateral preoptic area of the anterior hypothalamus are activated and the alternation between REM and NREM sleep is controlled by the multiple cell populations located in the hypothalamus, basal forebrain, and brainstem [5]. Transitions for wakefulness

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Table 1 Main effects of NREM and REM sleep stages on physiological processes

Physiological process	NREM sleep	REM sleep
Airway resistance	Increases in relation to wakefulness	Increases and varies in relation to wakefulness
Appetite regulation	Increased levels of ghrelin	Decreased levels of ghrelin
Brain activity	Decreases from wakefulness	Increases in motor and sensory areas, while other areas are similar to NREM
Body temperature	It is set at a lower set point than wake, tremors initiated at a lower temperature than during wakefulness	Not regulated, there is no shaking or sweating and the temperature fluctuates in response to the environment
Blood flow to the brain	Decreases from wakefulness	Increases from NREM, depending on brain region
Blood pressure	Decreases in relation to wakefulness	Increases by up to 30% and varies in relation to NREM sleep
Breathing	Decreases in relation to wakefulness	Increases and varies from NREM, but may show brief interruptions
Gastrointestinal function	Decrease of peristaltic amplitude and swallowing rate in relation to wakefulness	Absence of peristaltic amplitude and swallowing rate
Growth hormone	Low levels	High levels
Heart rate	Decreases in relation to wakefulness	Increases and varies in relation to NREM sleep
Muscle tone	Similar to wakefulness	Absent
Renal function	Decrease in urinary volume and flow in relation to wakefulness	Decreased urinary volume and flow in relation to NREM sleep
Respiration	Decreases from wakefulness	Increases and varies from NREM, but may show brief stoppages; coughing suppressed
Sexual arousal	Occurs infrequently	Greater than NREM
Sympathetic nerve activity	Decreases from wakefulness	Increases significantly from wakefulness

involve the reactivation of neurons promoting wakefulness, which in turn inhibit the sleep-promoting circuits [4]. The secretion of several sleep-related hormones also shows distinct patterns throughout the night as evidenced in Fig. 1.

During NREM sleep, physiological regulation acts favoring the maintenance of body homeostasis. NREM sleep is a state of minimal energy expenditure and motor activity, during which cardiovascular, respiratory and thermoregulatory variables are driven by the autonomic nervous system at a lower level compared to wakefulness and are kept stable by autonomic reflexes [2].

In contrast, during REM sleep, sleep posture control is lost, the autonomic nervous system is highly unstable, centrally driven heart rate and blood pressure outbreaks occur, breathing becomes irregular, and thermoregulation is suspended or

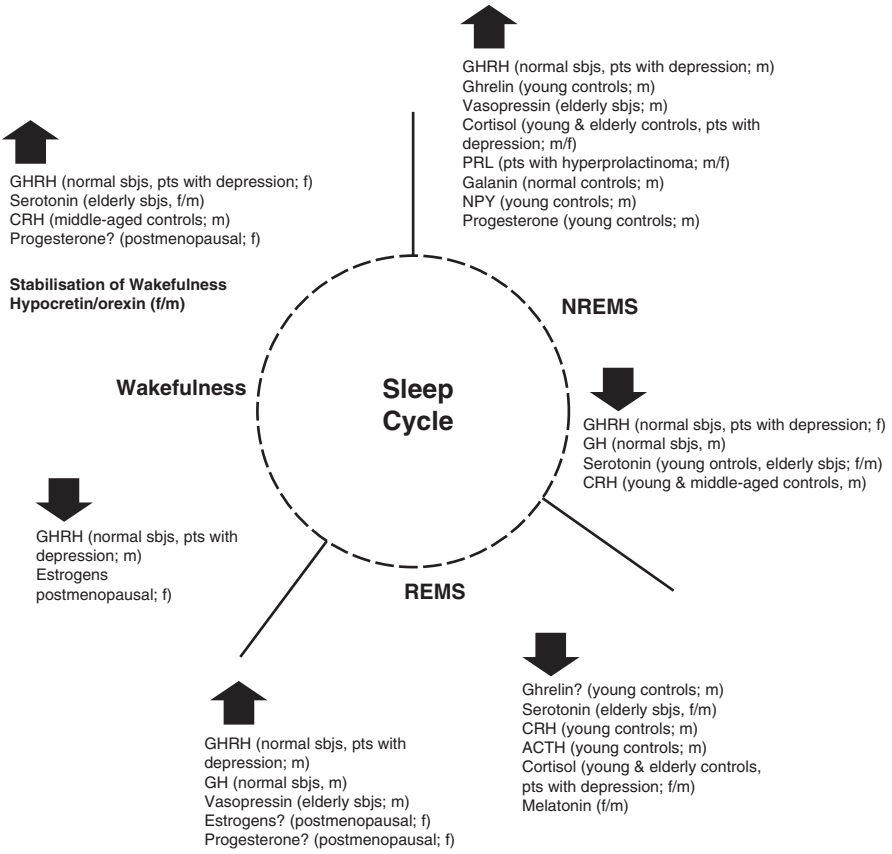

Fig. 1 The effect of hormones and hormonal agents on the sleep-wake cycle in humans. Pts: patients; sbjs: subjects; m: male; f: female; ↑: increase; ↓: decrease; ?: inconsistent effect. (Reprinted with permission from Kotronoulas et al. [6])

depressed. The integrative function of the hypothalamus becomes unbalanced. This modality of physiological regulation has been described as poiquilostatic, originating from the word "ποικιλο," which in Greek means diverse [7]. Apparently, it does not aim at physicochemical properties of the extracellular compartments that sustain cell survival.

1 Thermoregulation

The sleep-wake cycle is closely linked to the regulation of body temperature and metabolism [8]. In fact, the most opportune time of day for the occurrence of sleep is the rest period, when the circadian system causes a decrease in body temperature

and energy expenditure, and the probability of active interaction with the external environment is quite reduced. Although in the human adult, the decrease in energy expenditure during sleep is apparently moderate compared to silent waking, sleep may play a relevant role in energy conservation in animals with a less favorable surface-to-volume ratio (babies or small mammals), in which energy conservation is more persistent [8]. In general, the expenditure of body energy decreases during sleep.

The brain energy metabolism decreases widely during NREM sleep and increases during REM sleep to similar levels, or even slightly higher than those of waking [9]. Thermoregulatory responses can be experimentally induced by the delivery of external or internal thermal loads. These responses are present both in silent vigil and in NREM sleep but are depressed during REM sleep [7]. While the thermoregulatory differences between waking and NREM sleep depend only on the different levels of energy metabolism in the two states, a profound functional change occurs during REM sleep. This change alters the normal homeostatic regulatory modality from closed to open net [7]. In particular, during episodes of REM sleep that occur under a positive (hot) thermal charge, sweating is limited at the beginning of the sleep episode and subsequently depressed. On the other hand, under a negative thermal charge (cold), the tremor is suppressed and the vasoconstriction of the heat exchanger is reduced [10].

2 Respiratory System

The respiratory system is the result of a complex interaction between the central nervous system, motor neurons, and respiratory muscles, providing continuous homeostasis of arterial oxygen pressures, carbon dioxide, and pH levels during distinct physiological conditions and responding promptly to subtle metabolic variations. The ventilation control is mediated by two mechanisms: one is voluntary and related to cortical activity and the other is involuntary, being responsive to factors such as hypercapnia and hypoxemia [11].

The regulation of breathing differs significantly between wakefulness and sleep. With sleep onset, important changes occur in the various processes that regulate respiratory control, such as the cessation of voluntary breath control during the sleep onset. In addition, breathing is a function closely related to the sleep phase, in which great differences are observed between NREM and REM sleep [12].

2.1 NREM Sleep

When compared with waking, the frequency and amplitude of breathing are lower during NREM sleep, generating hypoventilation. These sleep-related changes are the result of a decreased tonic impulse of the respiratory network and increased

resistance of the upper airways. A quantitative analysis of neural activity during sleep showed that neurons with a higher proportion of tonic activity are predominantly affected by sleep [13].

2.2 REM Sleep

During the R sleep stage, the amplitude and respiratory frequency are marked by oscillations, so that ventilation acquires an irregular dynamic nature, accompanied by the occasional presence of central apnea [14]. Thus, ventilation during this sleep stage may be unchanged, increased, or decreased. During periods of hypoventilation, rapid eye movements are observed. As for the periods of hypoventilation, they are due primarily to the reduction of the activity of the thoracic muscles [15].

3 Cardiovascular System

Normal human sleep is accompanied by changes in blood pressure and heart rate [16]. These hemodynamic changes are mediated mainly by changes in the autonomic nervous system. During NREM sleep, sympathetic inhibition is associated with a decrease in blood pressure and heart rate. Already during REM sleep, there is an intermittent sympathetic activation with rapid fluctuations in blood pressure and heart rate [17]. Thus, in general, baseline cardiovascular activity is higher in wakefulness than during sleep and tends to decrease gradually from stage N1 to N3 of NREM sleep. Considering that NREM sleep is characterized by autonomic stability with parasympathetic predominance and sympathetic inhibition, there is a gradual decrease in sympathetic nerve activity, blood pressure, and heart rate progressing from stage N1 to N3 of NREM sleep. Blood pressure decreases as much as 30% [17, 18]. These changes are consistent with decreased metabolic demand during sleep. The drop in blood pressure is mediated by a reduction in cardiac output and a decrease in peripheral vascular resistance. During sleep, the arterial baroreflex has a reduced adjustment point that allows the reduction of blood pressure levels without activation of the sympathetic nervous system [19]. Transient excitation stimuli may give rise to high-amplitude K-complexes in the electroencephalogram during stage N2 of NREM sleep, which may be accompanied by transient explosions in sympathetic activity with brief increases in blood pressure [20].

REM sleep is associated with sympathetic activation. Although REM is a predominantly parasympathetic state, marked fluctuations in autonomic nervous system activity are typically seen. REM sleep can be divided into two distinct patterns: tonic and phasic. The tonic pattern is persistent throughout the sleep stage. On the other hand, the phase component is intermittent, superimposed,

and characterized by explosions of sympathetic activity, fast eye movements,

and brief irregular muscle contractions superimposed on muscular atony [17]. Blood pressure is high during REM compared to NREM sleep, particularly during phasic episodes. The increase of sympathetic activation during phasic REM leads to abrupt peaks in blood pressure [17, 18]. Heart rate variability increases during REM [21]. Heart rate during phase REM is faster compared to tonic REM sleep, consistent with sympathetic activation.

4 Endocrine System

The physiology of endocrine and sleep systems interacts in a complex and bidirectional way. In general, sleep and the circadian system modulate endocrine functions following two different patterns: (1) one is the influence of sleep or certain stages of sleep on hormone release; this is an ultradian process, as the frequency of change is greater than once every 24 hours; (2) another is the influence of circadian rhythm. More commonly, a combination of both types is found [22].

Most endocrine functions follow a more or less pronounced circadian rhythm. As sleep usually occurs at night, it becomes difficult to distinguish sleep influences from circadian influences. To elucidate the basis of the mechanisms, experimental protocols with night sleep restriction and daytime sleep periods were evaluated. A classic example of a predominantly circadian system is the hypothalamus-pituitary-adrenal axis (HPA) that determines cortisol release. A classic example of hormone release triggered by sleep is found in the case of growth hormone.

4.1 Hypothalamus-Pituitary-Adrenal Axis

Plasma levels of adrenocorticotropic hormone (ACTH) and cortisol are associated with circadian rhythm. Predisposing to the onset and maintenance of sleep, a decrease in cortisol is found in the late afternoon and evening hours with a minimum around 2–3 h, called cortisol nadir. In the short term, cortisol inhibition is reported to be derived from the onset of sleep. Around dawn, cortisol levels increase in order to prepare the body for the waking state with the peak around awakening. The increase in cortisol levels is linked to the predicted awakening time, as shown by plasma levels of ACTH. The real awakening is followed by an extra pulse of ACTH secretion. In the case of early awakening, time is preceded by real awakening, and the following ACTH pulse is most pronounced as a means of compensation [23]. Inhibition of HPA feedback is attenuated in the sleep state but becomes sensitive again in light sleep and wakefulness. Cortisol pulses occur as an unspecific reaction to excitation stimuli during sleep. However, the total release of cortisol is not reported to differ between sleep deprivation and fragmented and undisturbed sleep [24].

4.2 Growth Hormone

The observation that the growth hormone (GH) secretion is stimulated during sleep in normal adults was made more than 30 years ago [25]. The 24-hour plasma GH profile presents stable low levels interrupted abruptly by secretion outbreaks and the most reproducible pulse occurs soon after the onset of sleep [26]. In normal men, the GH pulse in early sleep is often the only daily episode of active secretion detectable in middle age and adulthood. In women with normal cycling, the daytime pulses of GH are more frequent, and the pulse associated with the onset of sleep, although present in most cases, usually does not take into account most of the release of 24 hours of GH [27].

The onset of sleep causes a pulse in the GH secretion, whether the sleep is advanced, delayed or interrupted, and restarted. There is a consistent relationship between the appearance of delta waves in the EEG and the high concentrations of GH, and its maximum release occurs minutes after the beginning of the slow-wave sleep [28].

4.3 Progesterone

Progesterone is an endogenous steroid hormone commonly produced by the adrenal cortex, as well as the gonads, which consists of the ovaries and testicles. Progesterone is also secreted by the ovarian corpus luteum during the first 10 weeks of pregnancy, followed by the placenta in the later stage of pregnancy. Progesterone is primarily known as the pregnancy hormone in women, and most of its function is related to maintaining pregnancy. It also plays a role in the menstrual cycle, causing hair growth and development as a result of increased vascularity and blood flow.

Evidence indicates that when progesterone is added to the hormone therapy regimen, there is no improvement in sleep [29]. However, there is a possibility that several types of progesterone may affect sleep differently. Montplaisir and collaborators [30] tested the sedative effects of progesterone by comparing hormone therapy with two different progestogens. They found that women treated with micronized progesterone had improved sleep efficiency. On the other hand, a study investigating the effects of estrogen-progestin treatment on pre-menopausal and post-menopausal women's sleep revealed that both groups receiving treatment had a significantly higher number of awakenings than the corresponding placebo group [31]. Also, progesterone is an important respiratory stimulant. Both progesterone [32] and estrogen [33] increase the contractility of the genioglossus, neutralizing the collapsibility of the upper airways during sleep. Progesterone prevents sleep disorders [34] and can therefore stabilize night breathing.

4.4 Testosterone

Testosterone is an androgen hormone that plays an important role in the development of male reproductive tissues, in addition to promoting the development of male secondary sexual characteristics. Much of the testosterone is produced by the testicles in men. Small amounts are also found in women, being produced by thecal cells of the ovaries, the placenta, and the reticular zone of the adrenal cortex. The release of testosterone by the testicles is episodic and occurs in response to the pulsatile stimulus of gonadotropin. In addition, there is a diurnal rhythm in its release, with a peak around 8 am, and minimum concentrations around 20 h [35]. Some studies show that the night rhythm of testosterone is related to REM and NREM sleep cycles. Schiavi and collaborators [36] demonstrated that in healthy elderly men there were positive associations between sleep efficiency, REM sleep latency, number of REM episodes, and plasma testosterone levels. Conversely, low sleep efficiency and reduction in the number of episodes of REM sleep were associated with attenuated testosterone levels. In addition, the increase in night testosterone in healthy young men during sleep was observed at the beginning of sleep, reaching a plateau after 90 minutes, approximately in the first episode of REM sleep [37].

4.5 Appetite Regulation

Sleep plays an important role in energy balance. The literature demonstrates that food scarcity or hunger results in sleep decrease [38] and conversely total sleep deprivation leads to severe hyperphagia [39].

Leptin, a hormone released by adipocytes, is associated with the state of energy for the regulatory centers in the hypothalamus. The circulating leptin concentrations show a rapid decline or increase in response to the acute caloric shortage or its excess, respectively [40]. These changes in leptin levels were associated with reciprocal changes in hunger. The 24-hour leptin profile shows a sharp nocturnal increase. This nocturnal rise is believed to suppress hunger during night fasting. Evidence also indicates that sleep deprivation may result in a decrease in the amplitude of diurnal leptin variation [41].

Ghrelin, a peptide produced predominantly by the stomach, is also involved in regulating energy balance and stimulates appetite. The diurnal profiles of plasma levels of ghrelin are regulated mainly by the food intake schedule, and the 24-hour profile of the levels of ghrelin shows a marked nocturnal increase, which is moderately attenuated when individuals are deprived of sleep [42]. The overnight increase represents in part the recovery of the ghrelin after the dinner meal. Despite the persistence of the fasting condition, the levels of ghrelin do not continue to increase throughout the sleep period and instead decrease during the latter part of the night, consisting of an inhibitory effect of sleep on the release of ghrelin.

5 Renal System

Renal blood flow decreases during sleep. The urinary volume also decreases due to the reduction in the renal glomerular filtration rate and the increase of renal tubular water reabsorption in normal individuals [43]. Anyway, urinary flow and osmolarity vary during the sleep cycle. During REM sleep, the flow becomes smaller, while osmolarity is increased with NREM sleep.

On the other hand, evidence suggests that sleep deprivation and night patterns may affect chronic kidney disease and cause a faster decline of renal function [44]. Still, there is a solid association between obstructive sleep apnea and chronic kidney disease, by the activation of the central nervous system or indirectly by the increase of inflammation, which can lead to glomerular endothelial injury [45].

6 Digestive System

Gastrointestinal system activity during sleep is controlled by the autonomic and enteric nervous systems. The basal secretion of gastric acid indicates a clear circadian rhythm [46]. A peak in acid secretion usually occurs between 22 h and 2 h. In the absence of meal stimulation, basal acid secretion in the waking state is minimal. The peristaltic amplitude and swallowing rate decrease with sleep, along with the prolongation of esophageal acid purification. The transient pressures of the lower esophageal sphincter and the upper esophageal sphincter also decrease during sleep. As a result, sleep is a very vulnerable period for reflux patients. On the other hand, sleep disorders are common in patients with peptic ulcer due to higher levels of gastric acid secretion after the onset of sleep [47].

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Part III
Physiotherapeutic Management of Sleep Disturbances

Insomnia: An Overview

Ana Carolina Aguilar and Cristina Frange

Insomnia is defined as a subjective perception of persistent difficulty with sleep initiation, duration, consolidation, or quality that occurs despite adequate opportunity and circumstances for sleep and results in some form of daytime impairment (International Classification of Sleep Disorders, ICSD-3). Diurnal repercussions may include drowsiness, fatigue, reduced cognitive performance, memory impairment, irritability, and mood disturbances. The ICSD-3 classifies insomnia into three categories: (i) chronic insomnia disorder, characterized by chronic sleep onset and/or sleep maintenance complaints with associated daytime impairment (Table 1); (ii) short-term insomnia disorder, characterized by sleep/wake difficulties that fail to meet the minimal frequency and duration criteria of chronic insomnia disorder and associated with clinically significant sleep dissatisfaction or waking impairment; and (iii) other insomnia disorders, assigned to those rare cases that fail to meet criteria for short-term insomnia disorder, but present sufficient symptoms of insomnia that need clinical consideration.

Insomnia is a multifactorial disease, with social, environmental, and psychological involvement factors. In addition, gender has a strong effect on the prevalence of insomnia, with women having insomnia more frequently than men at a ratio of 4:1. This difference becomes even greater after the age of 45 years, reaching a ratio of 7:1 [1].

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Table 1 Diagnostic criteria for chronic insomnia disorder according to ICSD-3

A. The patient reports, or the patient's parent or caregiver observes, one or more of the following: Difficulty initiating sleep Difficulty maintaining sleep Waking up earlier than the desired schedule Difficulty sleeping without parent or caregiver intervention
B. The patient reports, or the patient's parent or caregiver observes, one or more of the following related to the nighttime sleep difficulty: Fatigue Attention, concentration, or memory impairment Impaired social, family, occupational, or academic performance Mood disturbance/irritability Daytime sleepiness Behavioral problems (e.g., hyperactivity, impulsivity, aggression) Reduced motivation/energy/initiative Proneness for errors/accidents Concerns about or dissatisfaction with sleep
C. The reported sleep/wake complaints cannot be explained purely by an inadequate opportunity (i.e., enough time is allotted for sleep) or inadequate circumstances (i.e., the environment is safe, dark, quiet, and comfortable) for sleep
D. The sleep disturbance and associated daytime symptoms occur at least 3 times per week
E. The sleep disturbance and associated daytime symptoms have been present for at least 3 months
F. The sleep/wake difficulty is not better explained by another sleep disorder

The prevalence of insomnia varies between 10% and 30%, sometimes reaching 60% in some countries [2, 3]. Insomnia complaints were found in 45% of the population, while insomnia diagnosis was found in 32% of the Brazilian population [4]. It is important to emphasize that the complaint of dissatisfaction with sleep is not characterized as a diagnosis of insomnia. Insomnia can be a symptom, an isolated one, a secondary one due to a medication, an event (e.g., marriage), or a stressor factor (e.g., death). Therefore, insomnia complaints may not characterize a diagnosis of insomnia (Fig. 1).

Diagnosis of insomnia disorder is clinical, made by a physician, and requires clinical examination. The recommended procedure for the diagnostic management of insomnia disorder and its co-morbidities by the European Guideline for the Diagnosis and Treatment *of Insomnia* [5] incorporates medical history and examination (anamnesis, present somatic disorders, medication, alcohol, caffeine, nicotine, illegal drugs); physical examination; laboratory testing (e.g., blood count, thyroid, hepatic and renal parameters, c-reactive protein test, hemoglobin, ferritin, and vitamin B12); ECG, EEG, CT/MRT and circadian markers if necessary (melatonin, core body temperature); psychiatric/psychological history; former and present mental disorders; personality factors; work and partnership situation; interpersonal conflicts; and sleep history, including triggering factors; information from bed partner (periodic limb movements during sleep, pauses in breathing); work time/circadian factors (shift- and night-work, phase advance, delay); sleep-wake pattern, including daytime sleep (sleep diary for 10–14 days is strongly

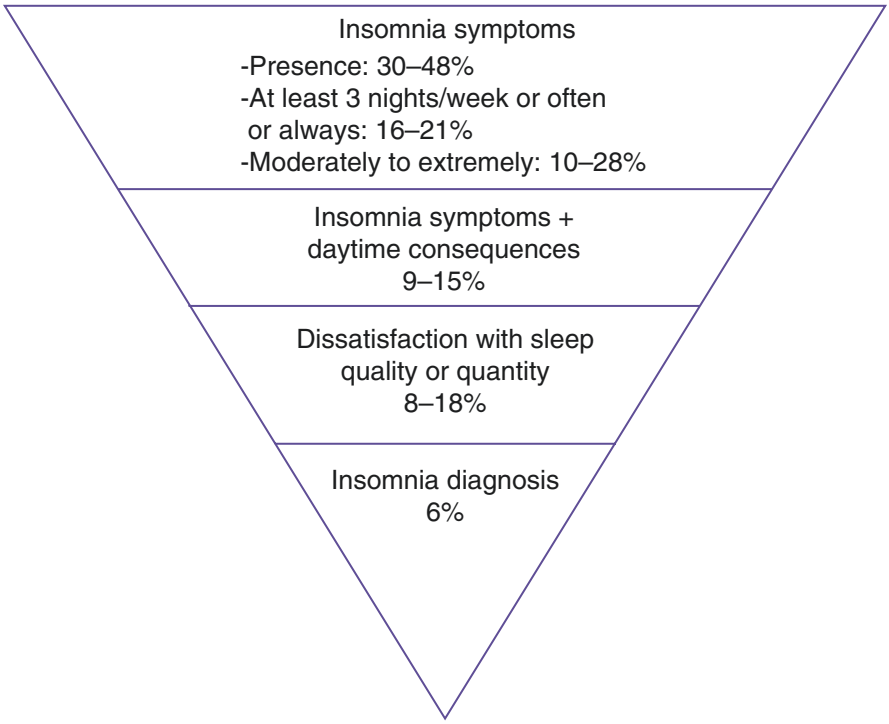

Fig. 1 Prevalence (average in the general population) of symptoms and diagnosis of insomnia. (Reprinted with permission from Ohayon [1])

recommended, which is a simple tool and very efficient that helps in the diagnosis of insomnia as it demonstrates the sleep routine of the patient); and actigraphy (if there is clinical suspicion of irregular sleep-wake schedules or circadian rhythm disorders, as it may also help with the follow-up of patients with insomnia, being useful to rule out circadian rhythm disorders, which may sometimes be confused with insomnia). Polysomnography is not usually indicated, except for ruling out other sleep disorders.

Despite polysomnography (PSG) not being indicated for insomnia diagnosis, many investigations focused on the macrostructure (the cycling between NREM and REM periods) and microstructure (power spectral analysis of the sleep EEG, a method that can be used to quantify the amount of frequency power in a specific frequency band, including arousals and specific elements) of sleep to better understand insomnia. PSG findings in insomnia patients demonstrate reduced sleep duration, long-lasting sleep-onset latencies, increased number of nocturnal awakenings and amount of time awake during the night, and reduced N3 NREM and R stages [6]. Other findings were characterized by an increased frequency of brief events, for instance, shifts in sleep stages between NREM and REM sleep, and among NREM stages (i.e., N1, N2, N3), brief periods of awakening, and microarousals (brief and transient changes in EEG frequency suggestive of an awake state), and not by

enormously long periods of wakefulness [7]. Other investigations failed to deliver objective changes in insomnia disorder or no clinically significant changes in PSG macrostructure. But, when analyzing the microstructure of sleep in, within both NREM and REM periods, a disorder of the switch between sleep and wakefulness can be found, as patients with insomnia have the most pronounced differences in the EEG fast frequency range (β power), compared with healthy sleepers [8] (Fig. 2).

Insomnia has been suggested to be a transitional state between "normal" sleep and "objectively verifiable" insomnia, leading to the use of terms such as "sleep misperception," "pseudoinsomnia," or "paradoxical insomnia." Polysomnographic investigations have shown that insomniacs often underestimate their total sleep time

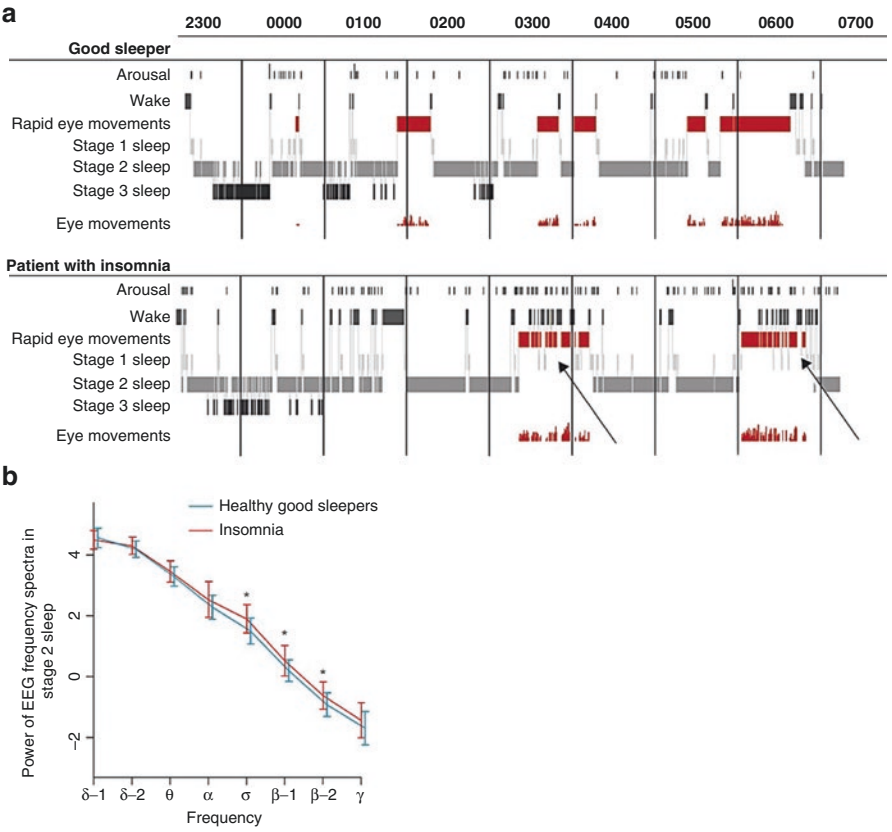

Fig. 2 Polysomnographic and power density differences between good and poor sleepers. (**a**) Comparison of the polysomnogram of a good sleeper and a patient with insomnia. With respect to the macrostructure of sleep, the sleep pattern of this patient with insomnia is mostly intact – the disturbance is mainly expressed through an increased frequency of stage shifts and increased brief waking periods and microarousals (arrows); (**b**) Asterisks show significant ($p < 0.05$) alterations in the sleep electroencephalogram of patients with insomnia as compared with healthy good sleepers, as shown by enhanced power in fast frequencies (derived from spectral analysis). (Reprinted with permission from Riemann et al. [9])

and sleep efficiency while overestimating the time it takes them to fall asleep [10]. Therefore, we may have a lack of correlation between objective findings of a PSG examination and subjective complaints of the patient, leading to a mismatch – a discrepancy between PSG outcomes and the patient's complaints and perception of sleep.

Insomnia is a risk factor for several diseases, such as arterial hypertension, myocardial infarction and chronic heart failure [11, 12], cardiovascular diseases [8, 13], type 2 diabetes [14], neurodegenerative disease, especially dementia [8], and also brain disorders [15]. Psychiatric disorders are among the most common comorbidities in insomnia, as it is present in most people; among them, the most common include substance use disorders and mood disorders. Clinical diseases and sleep disorders can also trigger or aggravate insomnia episodes, such as hyperthyroidism, fibromyalgia, sleep apnea, restless legs syndrome, mood disturbances such as anxiety and depression, and chronic pain [8, 16]. Furthermore, insomnia associated with short sleep duration (sleep <6 h) is associated with hypervigilance, increased physiological stimulation, and cardiometabolic and neurocognitive morbidities [8].

1 Pathophysiology

The pathophysiology of insomnia is not entirely clear; there seems little doubt that a self-sustaining cycle of misperception, apprehension about sleeplessness and its consequences, an exaggerated focus on sleep, and the concomitant physiological and cognitive processes accompanying these conditions are key components in the evolution and maintenance of many forms of chronic insomnia and, therefore, must be addressed.

The etiology and pathophysiology of insomnia involve genetic, environmental, behavioral, and physiological factors that culminate in cerebral hyperexcitation, causing this *"on"* and system to be unbalanced, leaving the patient in a state of hypervigilance. Evidence of hyperexcitation in insomnia includes high metabolic rate during sleep and wakefulness, elevation of cortisol and adrenocorticotropic hormone during the initial sleep period, heart rate variability, and high frequency of EEG activity during sleep. Functional imaging studies demonstrate minor differences between wakefulness and sleep in regional brain metabolism in individuals with insomnia disorder compared to people without insomnia [17].

From the perspective of behavioral science, the multidimensional model of chronic insomnia "3P" helps explain how acute insomnia becomes chronic, establishes the basis for evaluating insomnia in individual patients, and focuses on predisposing, precipitating (triggering), and perpetuating factors in the long-term evolution of insomnia [18]. Predisposing factors, which are generally not modifiable, include genetic and personality characteristics (for example, being worrisome, family history of unsatisfactory sleep), leading to physiological and cognitive hyperexcitation. Precipitating factors that trigger insomnia are typically stressful events, such as problems related to health, family, work or school, and anxiety [8].

Perpetuating factors are the poorly adaptive behaviors, thoughts, and coping strategies that allow insomnia to continue after the original triggers are solved [8], such as daytime naps, staying for a long time in bed without sleeping and ruminating, early bedtime, or long time in bed after waking up. The least quantifiable perpetuators include dysfunctional beliefs, expectations, and attributions about sleep, as well as an intense desire to solve the sleep problem [8]. Maladaptive strategies, such as increasing time in bed awake, result in the conditioning of the bed to waking. The same happens if one works or eats in bed or bedroom. Susceptible individuals are prone to focus excessively and in an exaggerated fashion on potential daytime consequences of insomnia. The result of this focus is progressive autonomic and emotional arousal that triggers a myriad of problems, which worsen the disturbance.

2 Treatment

The successful treatment of insomnia is dependent on the accurate identification of precipitating causes and perpetuating factors. In the presence of comorbidities, a clinical decision should resolve whether insomnia or the co-morbid condition is treated first, or whether both are treated at the same time.

The *European Guideline for the Diagnosis and Treatment of Insomnia* recommends cognitive behavioral therapy (CBT-I) as first-line treatment for chronic insomnia in adults of any age (strong recommendation, high-quality evidence [5] (see Chap. 31)).

Medication is also used, although the use of most sleep-inducing medications may cause some long-term harm and tolerance, and dependence is the most relevant [19–21]. Benzodiazepines (BZD), such as nitrazepam, flunitrazepam, and alprazolam, are the most prescribed class of medication for insomnia management [22], although several recent studies have associated chronic use of BZD with cognitive dysfunction [22–25]. Non-pharmacological treatments for insomnia will be discussed in the next chapter.

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Insomnia: Physiotherapeutic Approach

Carolina Vicaria Rodrigues D'Aurea, Giselle Soares Passos, and Cristina Frange

1 The Role of Physical Therapy in Insomnia Disorder

Physiotherapy can act on chronic insomnia as adjuvant treatment or, in some cases, being the treatment per se, depending on the type of insomnia, duration, clinical condition of the patient, and various contextual issues. A priori, the physiotherapist should consider how insomnia negatively affects the physical condition and overall health of the patient, but certainly how the physical condition interferes with insomnia, which can help to direct physiotherapy intervention. For example, a patient complaining of knee pain and telling the physiotherapist that he will need a surgical approach may not be able to sleep well from the moment of injury (or surgical indication). This may direct the physiotherapist to focus on pre-surgical interventions that can control pain, prepare local condition (knee), and improve the patient's sleep pattern *before* surgery.

Insomnia may result from an acute or chronic condition, and it will negatively impact the rehabilitation process. Insomnia may be a symptom of a disease, and depending on the diagnosis, the physiotherapeutic approach will be different. In the above example, insomnia in conjunction with the knee injury may generate kinesiophobia, pain, and fear from the surgery and the whole process, which could disrupt

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sleep and generate many thoughts as the patient goes to sleep. The patient may refer that he began with this knee pain a long time ago, and since then sleep was unrefreshing and fragmented and has worsened a lot after the surgery suggestion. He also may report concerns about the surgery, the rehabilitation process, functional difficulties such as walking and getting up/sitting, and getting back to work and social life. So, every night he stays in bed, thinking about the possibilities that may happen and fearing them. The next day, he feels more pain, tired, exhausted, anxious, and sleepy. Along the time, he starts to feel depressed. This clinical picture is often frequent and demands a need for investigation of the insomnia etiology (and in this case, refer the patient to a sleep specialist physician). The purpose here for physiotherapy is to indicate a therapeutic program to achieve the treatment objectives, not only for the pain and the knee itself (strength, flexibility, range of motion, etc.) but also for insomnia. These approaches will prepare the knee and the body as a whole for surgery and for the rehabilitation process and to dissociate the sleep-pain relationship that has been established in this patient (see Chap. 28 for more on sleep and pain relationship). Thus, the physiotherapist can treat insomnia, whether being a symptom or a disease, as an adjuvant or complementary treatment, by using many non-pharmacological resources.

The treatment of insomnia disorder is mainly cognitive and should include sleep hygiene, physical activities such as exercise, increasing the activities at work and at home (climbing stairs instead of the elevator, walking instead of driving, etc.), light therapy mindfulness, and manual therapies, such as acupuncture and soft tissue massage.

2 Cognitive Behavioral Therapy for Insomnia (CBT-I)

Current guidelines have indicated cognitive behavioral therapy for insomnia (CBT-I) as a first-line choice for the treatment of insomnia [1]. CBT-I is a structured program that aids patients to recognize and change thoughts and behaviors that cause or worsen sleep issues with habits that promote sleep, affecting the ability to sleep. CBT-I works with the precipitating, predisposing, and perpetuating factors of insomnia, intending to break the cycle of negative emotions, thoughts, and behaviors related to sleep (or the lack of). Pharmacological intervention should be adopted by a physician in case of failure or impossibility of CBT-I treatment [1, 2]. A detailed sleep diary for 10–14 days may help the patient to understand his/her sleep issue. CBT-I works with some techniques that will be defined by the physiotherapist according to the patient's need and can be seen in detail in Chap. 31.

To be considered effective, non-pharmacological therapies should reduce sleep onset latency and fragmented sleep, and the daytime repercussions such as sleepiness, unrefreshing feeling, and lack of concentration increase total sleep time [3]. However, very often, therapies may not demonstrate altered objective outcomes. The therapies can have positive impacts on patients' functional complaints, reducing symptoms of anxiety and depression and improving quality of life.

3 Sleep Hygiene

Sleep hygiene is the most widely used behavioral intervention in the treatment of insomnia [4, 5]. This method was developed to guide patients about healthy habits to promote sleep and prevent and treat insomnia (and many other sleep disturbances). Nevertheless, it has become a behavioral treatment for chronic insomnia. This technique can be combined with other resources, and the patient must understand why changes in his/her habits are needed (please refer to Chap. 31).

4 Physical Exercise

Epidemiological studies have described the influence of physical activity [6] and physical inactivity [7] in the natural history of insomnia. Some conditions such as low physical health, depressed mood, and low levels of physical activity were risk factors for the incidence of insomnia; physical activity was highlighted as a protective factor for the evolution of insomnia [6].

In recent decades, the regular practice of physical exercises has been studied as a treatment for insomnia [8]. The exercise characteristics such as type, intensity, duration, and time of the day practiced, as well as the mechanisms responsible for improvements in sleep, have been investigated in clinical studies. Studies investigating the acute effect of physical exercise on insomnia disorder have identified that acute moderate-intensity aerobic exercise is effective in improving sleep and reducing pre-sleep anxiety when performed in the late afternoon [9], and acute morning exercise can improve nocturnal sleep quality in individuals with difficulty initiating sleep, especially during the latter part of the night [10] (Table 1). For the chronic effect of exercise on insomnia disorder, aerobic exercises performed at moderate intensity [11–13], resistance exercise (i.e., muscle strength) performed at moderate intensity, and stretching [14] have been considered effective (Table 2).

Some mechanisms that can explain the effects of exercise on sleep are as follows:

- Thermogenic effect [15–18]: according to this theory, the increase in central temperature caused by exercise would facilitate the onset of sleep due to heat activation by hypothalamus-controlled dissipation mechanisms. Patients with insomnia presented a reduction of nocturnal temperature [19].
- Anxiety reduction: anxiety is one of the markers of insomnia; reducing it via exercise could improve sleep quality [20], and this effect has been observed in patients with insomnia [9].
- *Serotonin increase* (*5-hydroxytryptamine, 5-HT*): chronic insomnia may be the result of a serotonergic deficit [21]. Acute exercise (running) increased the synthesis of 5-HT [22].
- *Antidepressant effect*: there exists evidence on the chronic effects of physical exercise on depression in insomnia [11–13, 23], which correlated with improvement in sleep quality [11, 12].

Table 1 Effective physical exercises in the treatment of chronic insomnia

Type?	Aerobic exercise [11, 23] Resistance exercise (muscle strength)[14] Stretching [14] Regular physical activity (hiking, playing sports, dance classes, etc.) [13] The type of exercise can influence, as well as the environment in which it is performed. Think how different it is to practice swimming, hydrotherapy, or bodybuilding or to take an indoor bike class with a deafening sound and vibrant lights on
Intensity and duration?	Moderate to intense [11–14, 23] Duration of sessions: 50 minutes (3 times a week) [11, 13, 23]
Time?	Widely discussed in the literature and there are still controversies National Sleep Foundation recommends exercise before 2 p.m.. Although it is common to say that physical exercises performed at night impair sleep, there is evidence, both from epidemiological and clinical studies [56, 57], of no problems associated with the practice of exercise 4 hours prior to sleep onset in people with chronic insomnia; there is also reports that exercise increased cortisol concentrations [58], and exposure to intense light during the exercise (which could suppress melatonin levels and delay sleep) could be responsible for the impaired sleep To date, there is no significant evidence of sleep impairing when exercise is practiced before bedtime. However, a recent study provides some support for caution regarding late-night exercise for sedentary individuals with insomnia [59].
For how long?	1 session: improvement objective and subjective sleep in patients with chronic insomnia [9, 10] >4 months: improvements on subjective and objective sleep [11, 13, 14, 23] There is still no evidence of how long it takes to get improvements over time in sleep

- Immunological changes: training with moderate exercise can promote immunity [24]. Depressive symptoms, poor sleep quality, and systemic inflammation markers (e.g., interleukin (IL-6)) are frequently associated [25–28].

Remarkably, the level of evidence of physical exercise in the treatment of insomnia is considered of low quality, with a poor recommendation, according to the European Guideline for the Diagnosis and Treatment *of Insomnia* [1]. However, recently this topic has been the subject of several systematic reviews.

Moderate-intensity programmed exercise in middle-aged women improved sleep quality but had no significant effect on the severity of insomnia, both subjectively measured [29]. Physical exercise can improve the quality of sleep in patients with insomnia, when assessed subjectively, without triggering notable adverse effects [30]. Physical exercise improved the subjective quality of sleep for people with symptoms and insomnia disorder and improved objective measures of sleep (PSG) in participants with symptoms of insomnia [31]. In the most recent systematic review with meta-analysis, physical exercise improved subjective sleep measurements and decreased insomnia severity, with moderate power of effect []. However, the authors did not observe statistically significant differences in the objective variables of sleep

Table 2 Studies evaluating the effects of physical exercise on sleep in patients with chronic insomnia

Study	Number of sessions	Population	Intervention	Outcomes	Results
Passos et al. [9]	1 session	Women/men: MAE: 47,7–10/2; HAE: 42,2–9/3; MRE: 42.4–10/2; Control: 45.2–9/3.	MAE vs. HAE vs. MRE vs. control	PSG Sleep log STAI	Significant results only in the MAE group: PSG: reduction on SOL and TWT and increase in the TST and SE Sleep log: increase in the TST and reduction on SOL Reduction in pre-sleep anxiety
Morita et al. [10]	1 session	Men/women Age 55–65 years	MAE performed in the morning vs. evening in two groups: DIS and EMA	PSG Sleep diary	MAE decreased the number of stage shifts over the whole night. The arousal index and the number of stage shifts were decreased especially during the second half of the night in all groups. Furthermore, MAE decreased the number of wake stages during the second half of the night in the DIS group, but not in the EMA group
D'Aurea et al. [14]	4 months/3 times week	Average age: Women/men: MRE: 44.5–8/2; Stretching: 45.5–8/2; Control: 40.3–6/2.	MRE vs. stretching vs. no exercise (control)	PSG ACT PSQI ISI SF-36	Both resistance exercise and stretching decreased ISI and improved sleep quality (PSQI) and ACT measures (SOL, WASO, and SE) compared to the control group. Stretching also reduced tension-anxiety

(continued)

Table 2 (continued)

Study	Number of sessions	Population	Intervention	Outcomes	Results
Hartescu et al. [13]	6 months (a monitored program of ≥150 min of moderate- to vigorous-intensity physical activity per week)	Average age and women/men: Intervention: 60.10–15/6; Control: 59.50–15/5.	150 minutes of physical activity, moderate to vigorous, per week vs. no exercise (control)	ISI Epworth Sleepiness Scale EuroQoL5D-5 L	The physical activity group showed significantly reduced insomnia symptom severity, with an average reduction of four points on the Insomnia Severity Index and significantly reduced depression and anxiety scores
Reid et al. [12]	Chronic insomnia patients 16 weeks (4 times/week)	Average age and women/men: Intervention: 62–10/0; Control: 63.5–6/1.	Aerobic physical activity plus sleep hygiene vs. sleep hygiene only	PSQI Epworth Sleepiness Scale SF-36	The physical activity group improved in sleep quality on the global PSQI, SOL, sleep duration, daytime dysfunction, and SE (PSQI sub-scores compared to the control group). The physical activity group also had reductions in depressive symptoms, daytime sleepiness, and improvements in vitality compared to baseline scores
Passos et al. [23]	Chronic insomnia patients 4 months (3 times/week)	Homens/women Age 30–55 years	MAE, baseline vs. post-exercise	PSG PSQI BDI Cortisol Immune system	PSG: reduction on SOL, WASO, and REM latency and increase on TST, SE, and in the percentage of REM sleep. Latency of stages 2, 3, and 4 decreased significantly. Decrease in PSQI score, depression, cortisol, CD4, and CD8 and increased in apoA

(continued)

Table 2 (continued)

Study	Number of sessions	Population	Intervention	Outcomes	Results
Passos et al. [11]	Chronic insomnia patients 6 months (3 times/week)	Homens/ women Age 30–55 years	MAE, baseline vs. post-exercise	PSG Sleep diary POMS SF-36	Polysomnographic data shows a significant decrease in SOL and WASO and a significant increase in SE. Data from sleep diaries revealed significant improvement in SOL, sleep quality, and feeling rested in the morning. Some quality-of-life measures improved significantly and a significant decrease in the POMS measures of tension-anxiety, depression, and total mood disturbance

ACT actigraphy, *HAE* high-intensity aerobic exercise, *MAE* moderate-intensity aerobic exercise, *MRE* moderate-intensity resistance exercise, *DIS* difficulty in initiating sleep, *EMA* early morning awakening, *apoA* plasma apolipoprotein A, *RCT* randomized controlled trial, *SE* sleep efficiency, *ISI* Insomnia Severity Index, *BDI* Beck Depression Inventory, *POMS* profile of mood states, *PSG* polysomnography, *PSQI* Pittsburgh Sleep Quality Index, *REM* rapid eye movement, *SF-36* Short Form Health Survey-36, *SWS* slow-wave sleep, *WASO* wake time after sleep onset, *TST* total sleep time, *SOL* sleep onset latency, *TWT* total wake time

(PSG), such as total sleep time, sleep efficiency, sleep latency, and WASO. Unfortunately, this data obtained was considered exceptionally low quality of evidence, due to the heterogeneity of the investigations that composed the meta-analysis.

In general, the studies cited have low reliability, and there are several potential limitations, such as methodological limitations, small sample sizes, more women at old age, and a predominance of moderate-intensity aerobic exercise, among others. Moreover, the absence of data (and protocols) on the characteristics of physical exercises such as a place of practice, time of the day practiced, frequency, duration, type of supervision, and individual or group makes it impossible to infer whether these variables influenced the results of the meta-analysis [29–31].

5 Light Therapy

Several studies have identified the effectiveness of light therapy for patients with insomnia, mainly in those with difficulty starting sleep (initial insomnia) [32]. The treatment consists of luminous stimulation shortly after awakening, from a light box

with blue wavelength, positioned at eye level, at an approximate distance of 75 cm [32]. For the treatment of insomnia, the power of light is 10,000 lux [32], applied between 30 minutes and 2 hours [33]. Exposure to light in the early morning will facilitate sleep at the beginning of the evening [34]. Additionally, in patients with Parkinson's disease and insomnia disorder, a recent study showed that 1 hour of exposure to light, just before retiring/leaving the job market, significantly improved insomnia. Still, light therapy reduced symptoms of other sleep disorders such as REM sleep behavioral disorder by 1 month after the start of light therapy. Furthermore, improvements were maintained while light therapy was continued, for a period of 4–6 years, showing the importance of treating insomnia adjunct to Parkinson's disease [35], for example.

There is little evidence about phototherapeutic treatment in physiotherapy. According to the *European Guideline for the Diagnosis and Treatment of Insomnia*, published in 2017, the level of and evidence of the use of light therapy for insomnia is of low quality, and its recommendation is weak to be used as a single treatment. However, even in the face of these cautions, light therapy is a promising treatment for insomnia, used concomitantly with other treatments [1], still needing more studies in specific populations for a better understanding of its mechanisms and the possible creation of a consensus.

6 Massage

The search for manual therapies has been growing considerably, including massage. From constant skin stimuli on the body surface, touch, pressure, heat, vibration, and pain receptors are activated and transported to the somatic, autonomous, and central systems, triggering important neurochemical reactions [36]. The effects of massage on the circulatory, lymphatic, and muscular systems are already well established [37, 38]. Massage improves visceral functioning and restores body homeostasis.

Massage is pointed out as a pleasant intervention, as it promotes relaxation and sleep [39], as well by patients with insomnia to treat sleep complaints [40]. For instance, when investigating the severity of insomnia related to the postmenopausal period, the authors identified an improvement in the quality of sleep after the massage, as all participants fell asleep more quickly and reported better well-being upon awakening – probably due to the activation of the autonomous nervous system. Polysomnographic findings showed a decrease in REM sleep latency and an increase in the NREM stage N3 (slow-wave sleep) [37, 38].

In a multicenter investigation, massage was applied for the treatment of insomnia, and after subjective evaluations of symptoms, 96% of participants reported significant improvement of insomnia [41]. Despite some findings, massage alone is not recommended for the treatment of chronic insomnia due to an exceptionally low level of evidence [1]. However, due to few side effects and its high power of relaxation, massage can be used adjunctly to the treatment of insomnia.

7 Acupuncture

Acupuncture is an ancient technique of traditional Chinese medicine. Its effectiveness in the treatment of chronic insomnia has been described in several systematic reviews [42, 43]. For specific acupuncture points for insomnia, please see [42].

Some mechanisms have been suggested to explain the effects of acupuncture on sleep: acupuncture affects the central nervous system through structures in the spinal cord and the brain that regulate some neurotransmitters such as dopamine, norepinephrine, and acetylcholine [44]. Acupuncture can increase nocturnal melatonin secretion [45]. However, acupuncture alone is not recommended for the treatment of chronic insomnia due to the level of evidence [1].

8 Mindfulness

Many individuals with insomnia have sought alternative medicine and complement different approaches to try to expand the result of the various treatments already proposed. Data from the 2007 *National Health Interview Survey* (NHIS) indicate that 45% of adults with insomnia symptoms use some type of alternative medicine annually [46]. The physiotherapist can also act with the practice of mindfulness.

During mindfulness, the person intentionally seeks to "be attentive with his inner, thoughts and emotions," as well as the external perceptions that occur at present, without applying any form of judgment to them [47, 48]. The practitioner begins to observe the events that occur in his/her mind and let them go, without judgments, reflections, or desire to change the things that are happening around him/her.

The practice of mindfulness began in Eastern traditions, and the practice of meditation is considered a key point for its realization. This technique has been used in several clinical protocols, and its applicability in insomnia has been increasingly frequent, with encouraging results. Most sleep research has applied two types of interventions: mindfulness-based cognitive therapy (MBCT) and mindfulness-based stress reduction (MBSR) [47].

Some studies suggest that the practice of mindfulness can improve the quality and the amount of sleep in individuals with insomnia. The results are promising and point out that this method can significantly reduce the severity of insomnia, sleep latency, and pre-sleep hyperstimulation (presented in most patients with insomnia). Other benefits such as increased total sleep time, sleep efficiency, and sleep quality have already been reported by individuals with chronic insomnia after practicing mindfulness [48–51].

In addition, mindfulness is effective in secondary insomnia and in individuals who present other comorbidities such as cancer, depression, anxiety, and obesity [52–54]. The interesting fact is that mindfulness is a process of learning self-regularization of the body itself, of its emotions and needs, and, after learning, can be practiced whenever needed. For example, women in the postmenopausal period with insomnia demonstrated, after the practice of mindfulness, excellent results in

the quality of sleep and in reducing the severity of insomnia and ameliorating the quality of life, including better levels of attention and reduction in menopausal symptoms [47]. After 8 weeks of intervention, the severity of insomnia decreased by 15 points (in the Insomnia Severity Index) in the group that received mindfulness training. Note that a 6-*point* reduction is already considered a significant clinical change [55].

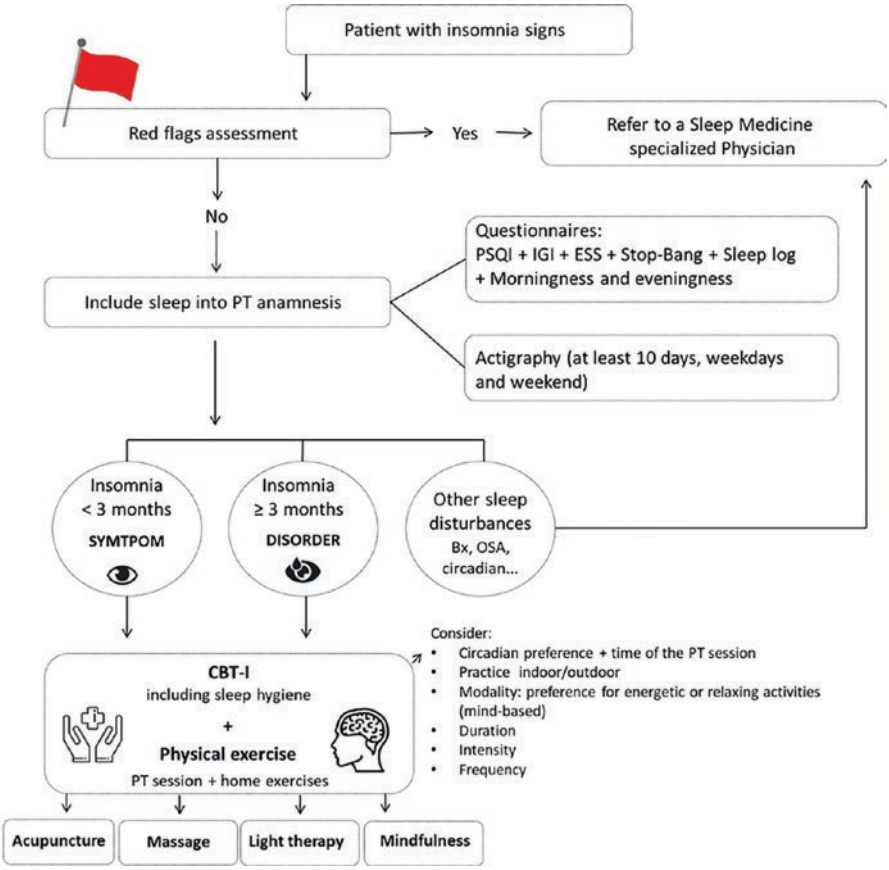

Fig. 1 Proposal for the physiotherapist for the management of both insomnia disorder and its symptoms. Red flags are specific characteristics derived from a patient's medical history and clinical exam which are usually linked with a high risk of having a serious disorder (such as inflammatory or neurological conditions, structural musculoskeletal damage or disorders, recurrent headaches, learning difficulties, fatigue, circulatory problems, suspected infections, tumors, or systemic diseases). *PSQI*, Pittsburgh Sleep Quality Index; *ISI*, Insomnia Severity Index; *ESS*, Epworth Sleepiness Scale; *Stop-Bang*, Stop-Bang questionnaire for the screening of sleep apnea; *CBT-I*, cognitive behavioral therapy for insomnia; *Bx*, sleep bruxism; *OSA*, obstructive sleep apnea. (Courtesy from Dr. Cristina Frange)

9 Final Considerations

Given the above results, physical therapists can take decision-making in the treatment of insomnia, as a single treatment, concomitant with other pharmacological treatment prescribed by the physician or not, based on the individual treatment choices and according to scientific evidence. In this sense, partnering with specialists in the field of sleep medicine and other areas can guarantee effectiveness in the treatment of insomnia, ultimately bringing benefits to the quality of life and, improving the prognosis of insomnia for patients.

The patient can seek a physical therapist to treat insomnia, or the physical therapist can observe the symptoms and refer to the specialist for diagnosis. Figure 1 shows a proposal for the physiotherapist for the management of both chronic insomnia disorder and its symptoms, highlighting the red flags. Red flags are indicators of possible serious pathology such as inflammatory or neurological conditions, structural musculoskeletal damage or disorders, circulatory problems, suspected infections, tumors, and systemic diseases, where serious medical disease may present as insomnia complaints such as other sleep disorders (e.g., excessive diurnal somnolence or obstructive sleep apnea), depression, anxiety, substance abuse, bipolar disorder, and menopausal symptoms.

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Restless Legs Syndrome (Willis-Ekbom Disease) and Periodic Limb Movements of Sleep: An Overview

Ana Carolina Dias Gomes and Fernando Morgadinho Santos Coelho

1 Restless Legs Syndrome/Willis-Ekbom Disease

Restless legs syndrome (RLS) or Willis-Ekbom disease (WED) is a common neurological disease characterized by unpleasant sensations that are relieved with movement and aggravated at night and by rest. The diagnostic criteria are based on the main clinical characteristics of the disease. Polysomnography (PSG) is not usually useful, but complementary exams are needed, especially in the assessment of differential diagnoses [1].

Thomas Willis first described RLS in 1685; however, only in 1945, Karl-Axel Ekbom described the main clinical features and coined the term RLS. For this reason, RLS is also recognized as WED. WED is currently the preferred name because although the lower limbs are most commonly affected, there is an involvement of other regions of the body. In this chapter and the next one, WED will be passed over to RLS for its easy recognition in the literature and current use [2].

The prevalence of RLS ranges from 5% to 10% worldwide. In a study in a Brazilian city, the prevalence of RLS was estimated at 6.4% [2, 3]. The prevalence of clinically significant RLS is 2–3% in Europe and North America. Pediatric prevalence rates are 2–4% in studies in the UK/USA and Turkey [1, 3].

The prevalence rates of RLS increase with age until the end of adulthood, stabilizing or decreasing slightly in the elderly. The prevalence of RLS is higher in older people and in women, but there is no difference between genders until the end of adolescence. Possible justifications for the higher prevalence in adult women

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include women's reports and perceptions differ from men; a hormonal difference; the reduction of iron stores in women; and effect of pregnancy [4].

The strong associations with anxiety, mood disorders, and reduced quality of life indices remain in people of older ages. The diagnostic criteria for restless legs syndrome in elderly people with cognitive impairment have been suggested, but not validated [5].

The diagnostic criteria and the clinical picture of RLS were grouped, characterizing a medical condition, whose diagnostic criteria cover these main clinical features. The diagnosis of RLS is clinical, and all of the items below must be present (Table 1).

RLS, according to the criteria of the *International Classification of Sleep Disorders* (ICSD-3) of 2014, is one of the diagnoses grouped in the chapter "Sleep Movement Disorders," where they are also located periodic limb movements (PLMS), sleep-related leg cramps, sleep-related bruxism, sleep-related rhythmic movement disorder, benign sleep myoclonus, propriospinal myoclonus in early sleep, sleep-related movement disorder due to a disorder medication or substance, and unspecified sleep-related movement disorder.

The diagnosis of RLS is not always obvious; patients often seek medical attention complaining of insomnia and do not report RLS symptoms spontaneously. A significant number of patients, 60% to 90%, have worsened sleep quality and complaints such as difficulty in initiating and maintaining sleep [1].

Another complaint that needs attention is those seen in disturbances of the sleep-wake cycle. Studies that evaluated symptoms based on circadian rhythm show that it is worse at night, regardless of the level of activity. Interestingly, patients who work at night and sleep during the day have their symptoms more tolerable.

Although the legs are the most affected, "restless legs" is an inappropriate name, since 21% to 57% of individuals describe some sensations in the upper limbs [1].

There are many ways to describe these sensations in different languages. References used may vary from one country to another, and, within the same country, regionalisms can influence the way the patient refers to them. It is important to note that the symptoms usually involve both legs, but they generally alternate between the legs and are rarely unilateral [6].

When symptoms are very severe, relief with activity may not be noticeable, as well as worsening at night. In cases of doubt, it is important to ask about symptoms

Table 1 Criteria for diagnosis of restless legs syndrome (*International Classification of Sleep Disorders* (ICSD-3))

A. Need to move the legs almost always accompanied by uncomfortable sensations, most commonly in the legs, that:
A1. Worsens at rest
A2. Improves with movement
A3. Worsens at the end of the day or early evening
B. The symptoms cause worry, distress, worsening sleep quality, or impairment in mental, physical, social, occupational, educational, behavioral, or other important areas
C. The symptoms cannot be explained by another medical or behavioral condition

in the past, as these characteristics have probably been present before. In the most challenging cases, the presence of a family history of RLS and response to dopaminergic drug therapy can help in the diagnosis [1].

PSG is not necessary for diagnosis and should not be ordered routinely; however, it can also help in a few cases. About 80% of patients with RLS have PLMS, whose diagnosis is essentially by PSG (PLMS can be seen in more than 90% of the exams of RLS patients if PSG is repeated). Other objective changes that may be present in PSG are the greater sleep latency and the higher rate of awakenings [7].

The outcome of RLS is different depending on the age of onset of symptoms. Two-thirds of patients who manifest symptoms before the age of 45 (early onset) have a slower progression of symptoms. Familial RLS has an onset of symptoms in the third and fourth decades on average. Adolescents tend to have more severe symptoms than younger children. When symptoms start at an older age, progression tends to be faster, and RLS tends to have many aggravating factors [1].

The most prevalent aggravating factors are iron deficiency, medications, pregnancy, chronic kidney failure, and prolonged immobility. Some drugs that can precipitate or worsen RLS and/or PLMS include sedative antihistamines, centrally active dopamine receptor antagonists, and antidepressants (Table 2). An exception is antidepressant bupropion, with its dopamine-promoting activity.

Complimentary exams are very important and should include at least complete blood count, complete iron profile, biochemistry, renal function, and thyroid function, in addition to the dosage of vitamins B12 and folate.

Pregnancy predisposes to the onset or worsening of RLS symptoms. The third trimester represents the worst period for pregnant women, and the resolution of symptoms, for most women, occurs after delivery. When faced with a pregnant woman with complaints of RLS, one should assess whether there is a family history of RLS or a diagnosis in the past, symptoms during pregnancy, and hemoglobin $\leq$11 g/dL [1].

In patients with chronic renal failure, the prevalence of RLS is two to five times higher than in the general population. Compared to patients with chronic renal failure without RLS, those with RLS have greater sleep disturbance and report worse quality of life, and many of them interrupt dialysis prematurely. Typically, the symptoms of RLS improve dramatically within a month after kidney transplantation, but they become severe again following the failure of the transplant [1].

OSA patients can increase symptoms of RLS due to sleep fragmentation, generating awakenings, and a higher probability of perception of the symptoms [6].

Table 2 Medications that precipitate or worsen restless legs syndrome

The action of medications that precipitate or worsen RLS	Medications that precipitate or worsen RLS
CNS-acting antihistamines	Dexchlorpheniramine
Dopamine receptor antagonists	Metoclopramide, haloperidol, etc.
Antidepressants (except bupropion)	Citalopram, amitriptyline, venlafaxine

RLS can begin in childhood, and it is essential that the peculiarities of evaluating younger patients are understood. Children can express their discomfort in their limbs very differently from adults: they say, for example, that their legs "need to move" or refer to the presence of insects, tremors, strange or even funny sensations, and tingling, among others. From the age of 6, the descriptors for the symptoms of RLS are more similar to those of adults [1].

It is important to exemplify situations of stillness that can worsen symptoms: sitting in the classroom, reading a book, doing homework, or riding a car, which are everyday situations. The same reasoning extends to the easing of discomfort in the limbs, which is usually achieved when moving, walking, rubbing, or kicking; it is important to try to pay attention to children's vocabulary. A child's drawing of RLS symptoms can be a good clue for diagnosis (Fig. 1). For younger children or those with developmental delay, a diagnosis of PLMS may be the initial diagnosis, with complete symptomatology of RLS evident over time [8].

The A3 diagnostic criterion, as seen in Table 1 (worse in the afternoon/evening), can also be clear only when comparing the same situation during the day and at night, for example, doing homework during the day or at night. However, even with these comparisons, many children do not report worsening at night, but meet all other diagnostic criteria and have supportive features for RLS, including positive family history [8].

As pediatric RLS is highly familiar, the presence of RLS in a first-degree relative helps to increase diagnostic certainty in childhood RLS. Likewise, the presence of PLMS can be very useful in supporting the diagnosis of RLS in children. Approximately 70% of children with RLS demonstrate PLMS ≥5/hour in a single night and almost 90%, when sampling multiple nights recordings. Pediatric RLS is comorbid to attention-deficit/hyperactivity disorder (ADHD) in about a quarter of cases, and, as in adults, higher rates of anxiety and depressive symptoms are found [8].

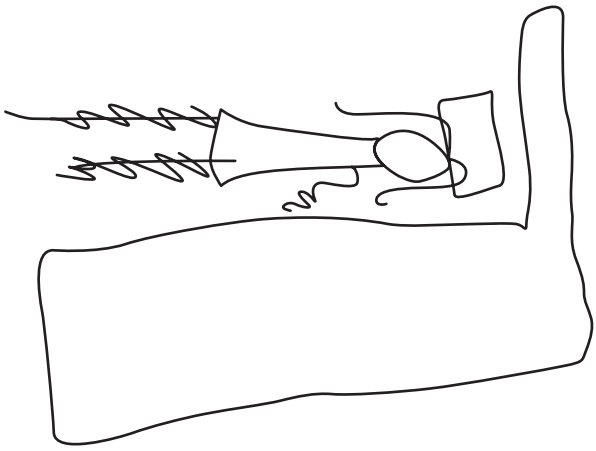

Fig. 1 Child's drawing of restless legs syndrome symptoms. (Image courtesy from Dr. Fernando Morgadinho Santos Coelho)

Table 3 Immobility testing procedure

1. At a time when the patient has more symptoms, usually in the afternoon or the first hour of the night, the patient remains in bed elevated at 45 degrees
2. The lower limbs must be resting on the bed and the eyes open; it is allowed to move the lower limbs without restriction to relieve the symptoms; the duration of the test is 1 hour
3. EMG activity is measured in the same way as in sleep, except for a maximum duration of 10 seconds
4. Every 5 minutes, the patient must report if he has discomfort
5. Discomfort on the 12 occasions has a sensitivity of 82% and specificity of 84%
6. The number of periodic limb movements is measured during the test (high specificity, but low sensitivity); values above 50/h are highly suggestive of RLS

EMG, electromyography; *RLS*, restless legs syndrome

The questionnaire of RLS severity is a very important tool and should be used routinely in these patients. Another instrument is the Restless Legs Syndrome-6 Scale (RLS-6), a smaller scale, involving six items classified on a scale from 0 to 10 (no symptoms at 0 to very severe at 10). The questions address the severity of RLS in the past week in four different circumstances: while falling asleep, at night, during the day sitting or lying down, and during the day on the move. The "RLS-6" appears to be a reliable and accurate instrument for assessing the severity of RLS in a specific and pragmatic way [9].

Immobility testing is not a routine test, but it can provide a standardized test condition for measuring symptoms of RLS, and it can be useful for confirming the diagnosis in difficult cases [10] (Table 3).

2 Periodic Limb Movements of Sleep

Periodic limb movements of sleep (PLMS) are characterized by limb movements that occur during NREM sleep, often without the patient's perception. The movements are characterized by involuntary dorsiflexion of the toes and ankles associated or not with flexion of the hip and knee. There is a difficulty in consolidating sleep and fragmentation by multiple awakenings. The diagnosis is confirmed by PSG, and the PLMS index is used to determine severity (Table 4, Fig. 2). Severity of PLMS is classified as PLM index (PLMi) in adults as normal, PLMi ≤5 n°/hour; mild, >5 n°/hour PLMi <25 n°/hour; moderate, >25 n°/hour PLMi <50 n°/hour; and severe, PLMi ≥50 n°/hour [1].

PLMS can be related to peripheral and central neurological diseases, just as it is prevalent in 50 to 90% of patients with RLS. The use of some medications may predispose to the appearance of PLMS such as lithium, antidepressants, and antipsychotics.

Activity monitors with high-frequency sampling and body position monitoring can be attached to the ankle or foot to provide an alternative measure of PLMS (see Chap. 37). Recordings assess the frequency and variability of PLMS overnight, usually three to five nights.

Table 4 Polysomnographic criteria for periodic limb movements of sleep

Frequency: minimum of four movements lasting between 0.5 and 10 seconds per movement
Interval: start of the first movement to the beginning of the second
Minimum of 4 seconds
Maximum of 90 seconds

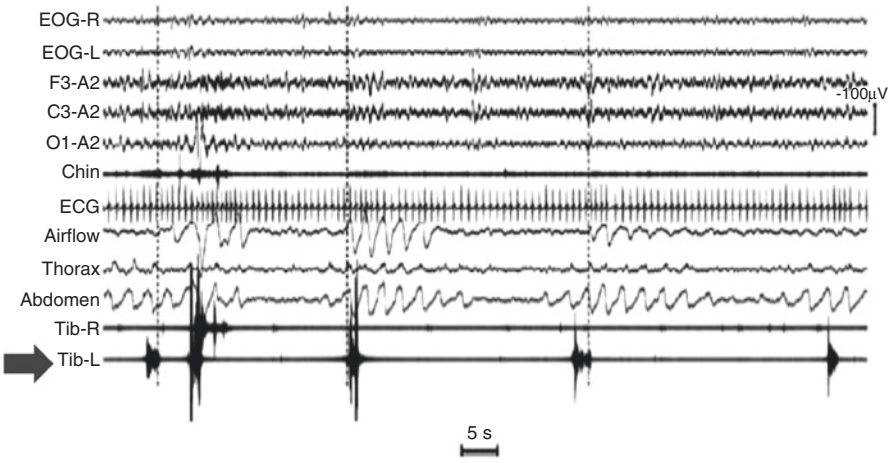

Fig. 2 A 30-second epoch of polysomnography elucidating a periodic limb movement (gray arrow indicates left tibialis anterior periodic movement). (Image courtesy from Dr. Fernando Morgadinho Santos Coelho)

When the PLMS disrupts sleep and is responsible for daytime symptoms without RLS, we name it periodic limb movements disorder (PLMD). Pharmacological treatment of PLMS is still controversial, except when associated with RLS or in patients with PLMD [1].

3 Differential Diagnosis

The differential diagnosis of RLS is not easy. About 40% of the general population who have RLS report some desire to move their lower limbs at rest. If the patient has the diagnostic criteria A2 (better with movement) and A3 (worse in the afternoon/night) as seen previously in Table 1, the specificity of diagnosis of RLS is about 70%. When we exclude leg cramps and positional discomfort, the specificity reaches 94%. Other confounders that should be part of the initial approach of a patient with suspected RLS are arthralgia/arthritis, myalgia, edema in the lower limbs, peripheral neuropathy, radiculopathy, and people who have the habit of moving their feet.

The main clues to exclude RLS are vigorous muscle contractions in the case of cramps, relief with a single postural dislocation when it comes to positional

discomfort, limitation of the joints in arthralgia/arthritis, pain on muscle palpation for myalgia, and radiated neuropathic pain for radiculopathy [1].

Other conditions that may confuse the examiner are akathisia induced by neuroleptics (a possible medication exposition must be detailed and, in the akathisia, need for movement involving the whole body), myelopathy, venous insufficiency, peripheral arterial disease, eczema, orthopedic problems, and anxiety-induced restlessness.

A patient with pain due to various causes may have a nocturnal presentation and may worsen at rest, but relief with movement may not be present, or a single movement could already bring some relief, and the person makes the movement in a planned way to obtain relief. However, be very careful when excluding the diagnosis of RLS when the complaint is pain; about 50% of RLS patients refer to the symptoms as painful. In addition, it is important to keep in mind that patients with RLS are not exempt from having cramps and arthritis, among others.

When the diagnosis of RLS is not yet certain, there are still supporting characteristics such as the presence of a family history of RLS, PLMS in PSG, disproportional drowsiness in relation to what is expected due to poor sleep quality, and assessing response to low-dose dopaminergic drug therapy. The exclusion of these differential diagnoses greatly increases the chance of a correct diagnosis of RLS, with sensitivity and specificity greater than 90% [11].

4 Pathophysiology of RLS and PLMS

RLS can be considered a continuous spectrum with two temporal extremes: one with a greater contribution of genetic factors and another with a bigger contribution of environmental factors or comorbidities. The pathophysiology of RLS includes genetic factors, neurotransmitter dysfunction, and iron deficiency [1].

Many studies have attempted to identify the genes involved with increased susceptibility to RLS. No monogenic causes have been found. Thirteen genes, represented by nucleotide polymorphisms, were identified on chromosomes 6p21.2 (BTBD9), 2p14 (MEIS1), 9p24.1-p23 (PTPRD), 15q23 (MAP2K5/SKOR1), and 16q12.1 (TOX3/BC034767). Of these, four were replicated: BTBD9, MEIS1, MAP2K5/LBXCOR, and PTPRD. It is estimated that BTBD9 confers a risk attributable to the population (PAR) of 50% for the RLS. Together, BTBD9, MEIS1, and MAP2K5/LBXCOR represent 70% of PAR for RLS in individuals of European descent. The association of these genes with familial RLS still requires further studies [12].

In addition, more recent studies have identified seven additional susceptibility loci, related to neurological development in the embryonic limbs, for RLS (12q12-q21, RLS2 in 14q13-q21, RLS3 in 9p24-p22, RLS4 in 2q33, RLS5 in 20p13, RLS6 in 19p13, and RLS7 in 16p12.1). However, these variants in the genomic loci represent only a small proportion of genetic susceptibility whose pathophysiological functions have not yet been specified [12].

Iron deficiency has been associated with RLS since its initial description by Ekbom. Iron is needed for dopamine generation, synaptic density, and myelin synthesis. There are autopsy data, MRI, brain sonography, and cerebrospinal fluid analysis supporting the link between RLS and low brain iron.

Low levels of iron have been found in brain tissue samples and in the evaluation of cerebrospinal fluid of patients with RLS. The areas of the brain where this can be seen mainly are the substance nigra, the putamen, and the caudate nucleus. Indeed, there is a correlation between the severity of RLS symptoms and brain iron. The disruption of iron transport across the blood-brain barrier could explain the low levels of iron in the brain.

Unfortunately, serum iron parameters are not good predictors of central iron levels. The current guidelines established by the International RLS Study Group recommend the prescription of oral iron replacement if serum ferritin levels are less than 75 mg/L. However, it is not possible to say that patients with serum ferritin greater than this value do not have a reduction in iron in the CNS [13].

The evidence for the involvement of the dopaminergic system is supported by the almost immediate improvement in the symptoms of the disease after the administration of dopaminergic agents. However, there is evidence suggesting hyperactivity of the dopaminergic system. The D1 receptor seems to have a leading role, which is in line with the increase in the symptoms of RLS over the years. A pre-synaptic hyperdopaminergic state also appears to have implications for PLMS and changes in glutamatergic neurotransmission, which in turn would be involved in hypervigilance and PLMS [14].

Studies about adenosine may help explain the link between these neurotransmitters and the overlap of RLS and PLMS. The deficiency of cerebral iron reduces the adenosine A1 receptors in the striatum and cortex. The lower stimulation of adenosine incites the dopaminergic and glutamatergic corticostriatal pathways. Directly, low adenosine would make hypersensitive receptors, generating PLMS. The depletion of A1 receptor in the cortex, basal forebrain, and hypothalamus could generate hypervigilance. Tests with dipyridamole, which increases extracellular adenosine, corroborate this hypothesis [12, 15].

5 Prognosis

A condition that reduces the quality or quantity of sleep is expected to generate excessive daytime sleepiness, but the assessment of sleepiness (e.g., Epworth Sleepiness Scale) in RLS generally shows results in the normal range. Sleep is affected in several ways in this disease; first, the sensory symptoms of RLS impair the return to sleep and, therefore, result in a prolonged awakening.

In addition, PLMS contributes to the primary morbidity of sleep disorder by RLS. About a third of PLMS are associated with cortical excitations, and most are associated with autonomic excitations. PLMS are associated with increases of 10–20% in heart rate and large increases in blood pressure (10–15 mmHg diastolic

and 25–30 mmHg systolic), contributing to the development of daytime hypertension in patients who had a periodic member movement index above 30. In the Sleep Heart Health Study, patients with a higher frequency or severity of RLS symptoms had a higher risk of coronary artery disease and cerebrovascular disease compared to control subjects [16].

Several studies have shown an increased prevalence of mood and anxiety disorders in individuals with RLS, such as depressive symptoms (OR 1.95 and 3.67), major depression (OR 2.6), major depressive disorder (OR 2.57 and 4.7), generalized anxiety disorder (OR 3.5), panic (OR 4.7, 12.9 and 18.9), and post-traumatic stress (OR 3.76). In addition, a positive correlation was found between the severity of RLS and the symptoms of depression/anxiety. Indeed, the treatment of RLS improves depressive symptoms [17].

Other conditions have increased rates in patients with RLS, such as attention-deficit/hyperactivity disorder (ADHD), narcolepsy, migraine, chronic obstructive pulmonary disease, Parkinson's disease, multiple sclerosis, peripheral neuropathy, obstructive sleep apnea, diabetes mellitus, fibromyalgia in both children and adults, rheumatoid arthritis, food night, obesity, thyroid disease, and heart disease. About a quarter of individuals with RLS have symptoms of ADHD, and 12% to 35% of those with ADHD meet the criteria for RLS [18].

Physical and mental health scores were consistently lower for individuals with RLS, using standard quality of life (QoL) assessment tools. Deficiencies in QoL are strongly associated with the severity of RLS and remain after controlling for age, sex, and comorbidity of the disease. In addition, patients with other comorbidities and RLS associated had a worse QoL than those who did not have RLS [19].]

6 Treatment

The treatment of RLS starts with an accurate diagnosis, the identification of reversible contributing factors, and the use of non-pharmacological and pharmacological therapies when indicated. Non-pharmacological treatment with increased physical activity; regular sleep times; withdrawal of precipitating factors such as medication, coffee, and alcohol; as well as iron and vitamin replacement solve the problem in many patients.

Daily treatment with any kind of medication should start only when symptoms have a significant impact on quality of life in terms of frequency and severity. An intermittent treatment can be considered in cases with short periods of worsening [18].

Many pharmacological agents can be effective in managing symptoms. Until recently, first-line treatment consisted of low doses of dopaminergic agonists; however, the use of dopaminergic agonists for a long period of time can worsen the symptoms. Therefore, international guidelines recommend that, whenever possible, the initial treatment should be done with α2δ ligands. If prescribed, dopaminergic agonists should be prescribed in the lowest effective dose and for the shortest

possible time. Iron therapy can be considered in patients with refractory RLS (Tables 5 and 6). New treatments based on pathophysiology may become reality; drugs with a focus on glutamatergic and adenosine pathways (dipyridamole) are examples and are being studied [18].

Table 5 Pharmacological treatment of restless legs syndrome

	Dose range (mg)	Initial dose <65 years (mg)	Initial dose >65 years (mg)
Dopaminergic agonists			
Levodopa	100–200		
Pramipexole	0.125–0.75	0.125	0.125
Rotigotine	1–3	1	1
Anticonvulsants			
Gabapentin	900–2400	300	100
Gabapentin enacarbil	600–1200	600	300
Pregabalin	150–450	75	50
Opioids			
Codeine	15–120		
Tramadol	50–150		
Oxycodone	10–40	5–10	5–10
Methadone	5–30	5–10	2.5

Table 6 A rational approach for pharmacological options for the treatment of restless legs syndrome

Characteristics of the patient	Rational choice
Daytime symptoms	Medication with a long half-life or two takes of a shorter half-life one
Sleep changes disproportionately to the symptoms of RLS	α2δ ligand
Comorbid insomnia	α2δ ligand
Risk of pregnancy	Consider iron supplementation
Renal dysfunction	Choose medications not excreted by the kidney or adjust the doses
Increased risk of falls	Dopamine agonist
RLS with painful symptoms	α2δ ligand
Chronic pain comorbid	α2δ ligand
History of compulsions	α2δ ligand
Past abuse of licit or illicit substances	Avoid opioids
Very severe symptoms of RLS	Dopamine agonist
Overweight/metabolic syndrome	Dopamine agonist
Availability/cost of medication	Dopamine agonist
Comorbid depression	Dopamine agonist
Comorbid anxiety	α2δ ligand
Risk of drug interactions	The select drug that does not have hepatic metabolism
Symptomatic PLMS	Dopamine agonist

7 Augmentation

The prescription of levodopa for the treatment of RLS was initially considered very promising, but it soon became clear that its effectiveness decreased over time. Subsequently, its use was still associated with a worsening of patients' symptoms after chronic use. It was named augmentation [1]. The main criteria for augmentation are symptom onset earlier (2–4 hours), shorter latency of symptoms at rest, dissemination of symptoms to other parts of the body, greater intensity of symptoms, and paradoxical response to treatment.

With the role of dopamine in the pathophysiology of RLS in mind, dopaminergic agonists could be interesting therapeutic options. Ropinirole and pramipexole, whose half-lives are longer than that of levodopa, were approved for the treatment of RLS about 15 years ago. In the randomized clinical trials, it was clear that they were effective in the short term. However, the worsening of symptoms observed with levodopa has also occurred, although the treatment time required for this to happen has been longer. One study estimated that 76% of all patients treated with dopaminergic agents showed evidence of partial increase with an annual incidence rate of approximately 8%. There is insufficient evidence that longer-acting drugs (cabergoline, rotigotine) have a lower rate of increase in incidence [18].

As well as the beginning of the treatment of RLS, whenever possible, it should start with the elimination of factors that can exacerbate the symptoms (iron level, antidepressants, and antihistamines). Iron replacement should be considered if serum ferritin levels are <50–75 μg/mL or if transferrin saturation is less than 20%, and treatment can be done with oral or intravenous iron depending on the clinical picture, as already mentioned. This can be done in combination with any of the other options [18].

In milder cases of augmentation, therapy with dopaminergic agonists can be continued by dividing or advancing the dose of the agonist, or rotigotine may be tried. Alternatively, treatment can be switched to an a2δ ligand, especially in more severe cases. These drugs are effective and have little risk of augmentation. However, in cases where dopaminergic drugs are prescribed, the daily dose should be as low as possible and should not exceed that recommended for the treatment of RLS [20].

For patients with almost 24 hours of symptoms, an opioid may be considered. According to the latest consensus, it is suggested that prolonged-release oxycodone or methadone should be considered if the other approaches fail. There are, however, precautions inherent in the prescription of opioids and the physician must be aware: family or personal history of alcohol or drug abuse and psychiatric comorbidities, severe constipation, and prolonged QT interval, in addition to the risk of recreational use. When patients are chosen appropriately, low-dose opioid therapy is effective and safe, even when used for long-term therapy [20].

8 Final Words

RLS is a prevalent disease with several differential diagnoses, whose consequences for the individual's QoL is well documented. Therefore, it is imperative the knowledge about this condition and regular screen for all patients with sleep complaints. Once diagnosed, an assessment of confounders and associated conditions should be detailed. The iron depletion should be promptly corrected. The α2δ ligands should be prioritized as an initial treatment in most patients. If the physician does not feel able to manage the treatment for any reason, the patient should be referred to a sleep medicine specialist.

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Restless Legs Syndrome (Willis-Ekbom Disease) and Periodic Limb Movements of Sleep: Physiotherapeutic Approach

Simone Barreto dos Santos and Cristina Frange

To date, the treatment of the symptoms of restless legs syndrome (RLS) and periodic limb movement of sleep (PLMS) is pharmacological. Existing data does, in some cases, support some physiotherapeutic interventions in both, as an adjunctive treatment, without interruption of medication. Therefore, clinical judgment must be used in any physiotherapeutic intervention in these diseases. It is worth remembering that the diagnosis of the disease is clinical and can only be performed by a physician.

Non-pharmacological treatment of RLS is part of the overall treatment and includes intermittent pneumatic compression, infrared light, acupuncture, electrical stimulation, yoga, whole-body vibration, manual therapies, and kinesiotherapy and physical exercise. This latter is also the adjunct physiotherapy treatment for PLMS. Yet, some investigations regarding PLMS alone include accommodative strategies, sleep hygiene, stimulus control, muscle relaxation therapy, sleep restriction therapy, cognitive therapy for sleep, bright light therapy, and compression devices. Few and sparse evidence of investigations showed the effect of exercise on PLMS isolated and co-occurring with RLS.

According to the latest American Academy of Sleep Medicine (AASM) practice parameters (from 2012) with an evidence-based systematic review and meta-analyses [1], there was insufficient evidence to evaluate the use of non-pharmacological

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therapies for RLS and PLMS. Since then, several investigations have been conducted to examine the non-pharmacological treatment for RLS and PLMS.

The Brazilian consensus on sleep physical therapy, published in 2013, stated that exercises, mostly aerobic ones, are an adjunct treatment for RLS and PLMS. For RLS, physiotherapists must promote education about the disease and advice the patients with orientations with the recommended non-drug therapy: to perform physical exercises, to change the periods of inactivity to daytime, to follow a good sleep hygiene program (as sleep deprivation may increase the symptoms substantially), and to avoid nicotine, caffeine, alcohol, and drugs. The usage of some medications (i.e., antidepressants, antihistaminic, anti-nausea, and antipsychotics) should be discussed with the physician, as they also can increase the symptoms. Similarly, attention should be given to iron deficiency populations (i.e., pregnant), peripheral neuropathy, spinal cord, and amputee's rehabilitation [2].

The Brazilian consensus on guidelines for diagnosis and treatment for RLS, published in 2015, stated that there was evidence to support the use of physical exercise, pneumatic compression, and infrared light for RLS, as they were able to reduce the severity of the symptoms. Therefore, acupuncture and enhanced external counterpulsation[1] were considered ineffective for RLS [3].

Two recent systematic reviews bring new evidence on the theme. The first one found that primary RLS severity was improved by complementary and alternative options such as exercise training, pneumatic compression devices, and acupuncture among others. As for secondary RLS (i.e., uremic), intradialytic exercise training showed to be highly efficient in the reduction of RLS symptom severity [1]. In the second systematic review, non-pharmacological interventions including exercise, compression devices, counter-strain manipulation, infrared therapy, acupuncture, cryotherapy, and yoga showed to be complementary to pharmacological managing in individuals with RLS [4]. Vibratory pads, yoga, pneumatic compression devices, acupuncture, and local cryotherapy significantly increased the sleep quality of the participants of those studies but did not change the RLS symptoms severity score [4]. Short-lasting effects were identified with whole-body cryotherapy, repetitive transcranial stimulation, and transcutaneous stimulation. However, despite the relatively few studies included in this last review, most of them had some limitations that reduced their reliability.

A scoping review published in 2020 demonstrated limited evidence for most non-pharmacological treatment options, with scarce studies evaluating each modality. Yet, there is a reliable trend in the findings showing positive results in RLS symptom severity, and most of the non-pharmacologic options did not have any adverse effect [5]. More studies are necessary to investigate the efficacy of yoga, massage, traction straight leg raise, and whole-body vibration. No adverse effects were identified for moderate-intensity exercise, yoga, massage, and pneumatic compression devices [5]. Taken together, these results indicate that there exists insufficient evidence for confidence in resting only in non-pharmacological therapies for RLS and PLMS. Moreover, further exploration with high-quality

[1] The enhanced external counterpulsation treatment compresses the blood vessels in the lower limbs to increase blood flow to the heart. This happens via cuffs attached to air hoses that connect to valves that inflate and deflate the cuffs in accordance to heart beats. This treatment is used in the treatment of patients with angina.

randomized controlled trials is needed, comparing non-pharmacological therapy plus pharmacological treatment with the same pharmacological treatment – to support clinical practice for the treatment plan.

The severity of RLS (and the physiotherapeutic effectiveness) can be assessed using the International RLS Study Group Scale (IRLSSGS), which is a validated questionnaire designed to assess symptom severity, frequency, and impact on daily life [6], before, during, and after treatment (please see more in Chapter "Subjective assessment of Sleep" of this book).

Here we present some therapies and their evidence regarding RLS and PLMS, to build knowledge, and to fundament further investigations on the topic, urgently needed.

1 Intermittent Pneumatic Compression

Pneumatic compression therapy is performed with a device that inflates pressure in bandages placed on the legs. The pressure used in previous studies was 40cmH_2O, for 5 seconds every 1 minute. The patients used the device at home for 1 hour daily and were instructed to activate the device a few moments before they related the onset of the symptoms [7]. The use of the pneumatic compression device for 4 weeks reduced the RLS severity scale score by 12 points, which characterizes an important clinical improvement. It is of value to mention that the patients had been using the medicines for the disease for at least 2 months and the non-pharmacological treatment as adjuvant to the medication. The improvement in symptoms may be explained by the hypothesis that patients with RLS present with venous insufficiency. Tissue hypoxia and ischemia can generate neuronal dysfunction. Compression would stimulate the release of endothelial mediators that modulate the symptoms of the disease, improving local perfusion and lymphatic venous drainage with consequent relief of ischemic symptoms [7].

2 Infrared Light: Light therapy

Infrared light has a wavelength range of about 750–1000 nm. Treatment with near-infrared light with a wavelength between 880 and 890 nm presented increased cutaneous pressure sensation in patients with peripheral neuropathy and increased wound healing and for these reasons started being investigated for RLS. The mechanism of infrared light is its capacity to generate nitric oxide in the endothelium [8] and release it from the red blood cells [9]. Thus, nitric oxide, a neurotransmitter itself, can initiate and maintain vasodilation [10]. In addition, light (i.e., phototherapy) produces changes in the permeability of the membrane, leading to enhanced synthesis of endorphins, increased nerve cell potential, and therefore pain relief [11]. Taken together, infrared light can influence blood flow, neurotransmission, and pain – all factors related to RLS. Infrared light devices were investigated with different frequencies and their impact on RLS symptoms associated with pharmacological treatment in a study showing positive effects [12]. In this study, 25 patients

were randomly allocated to near-infrared light devices (either an Anodyne® or HealthLight™, both using a dosage of 650 nm and different frequencies, 292 Hz and 4698 Hz, respectively) treatment for 12 treatments with near-infrared light, 30-minutes, 3 times a week, for 4 weeks, and both frequencies improved significantly the symptoms of RLS, with no significant difference between the two devices [12]. This investigation provided support for the use of infrared light as a noninvasive and non-pharmacological treatment of RLS.

3 Acupuncture

Acupuncture presented insufficient evidence in a systematic review to determine its efficacy for RLS [13]. A Cochrane database systematic review from 2008 brought no evidence for the use of acupuncture solely for RLS [14]. In an objective investigation, participants with RLS used the actigraphy device in the ankles during the evening and night to detect movements before and after treatment. This group was in no pharmacological treatment, neither at the moment of the investigation nor previously, and underwent 6 weeks of acupuncture (i.e., 30 minutes, three times a week) in standard (local) points of traditional Chinese medicine and sham points (randomized and distal points). The authors found improvement in the IRLSRS in the standard group with the use of acupuncture [15]. In the view of traditional Chinese medicine, RLS is considered "(…) a deficiency of 'Yin' and 'Xue' (blood) of the legs, because 'Yin' and 'Xue' are in effect at night and function to relax the mind and body. According to TCM, the activity and function of legs are controlled by liver function, and, thus, the deficiency of 'Yin' and 'Xue' of the liver at night is the main cause of RLS Shenshu (BL23, bilateral), Mingmen (DU4), and Chenshan (BL57, unilateral) have effects on the uncomfortable waist and leg symptoms, Shenshu (BL23, bilateral) and Mingmen (DU4) can also improve 'Shen Qi' (energy and immunity) and increase the 'Yin' of the waist and legs, and Xuehai (Sp10, unilateral) increases 'Xue' (blood) of the body, which means it can tranquilize the legs. Taichun (LR3, bilateral), Zusanli (St36, unilateral), Sanyinjiao (Sp6, bilateral), and Taixi (Ki3, bilateral) increase both 'Yin' and 'Xue' (blood) of the body. If these acupoints are treated properly, the legs should be quiet at night" [15]. The mechanisms of acupuncture in the view of traditional Chinese medicine are not the focus of this book, yet the mechanisms leading to improvement of RLS severity remain to be elucidated. In addition, the dry needling therapy must also be an object of further investigations.

4 Electrical Stimulation

Transcutaneous electrical neural stimulation (TENS) is being investigated for RLS. When the TENS were applied to bilateral legs on a handheld device (3 Hz), the RLS symptom severity decreased in both groups, active group and sham group, revealing a placebo effect of the treatment [16]. Its effect for treating RLS

symptoms is used to reduce spinal cord excitability in patients with RLS [17], with short-lasting effect [18]. Recently, some investigations on noninvasive transcutaneous spinal direct-current stimulation emerged, indicating positive effects on the RLS symptoms [19] and providing a rationale for its use [20–22].

5 Whole-Body Vibration

Vibration therapy is an exercise realized through the body vibration platform. The patients are positioned standing on the platform, with semi-flexed knees and feet apart. Whole-body vibration (WBV) applied in healthy individuals resulted in nitric oxide generation, which increased blood flow. The effectiveness of this intervention was investigated in patients with RLS. The patients underwent ten 30-s bouts of WBV at a frequency and amplitude of 26 Hz and 2 mm per bout, and had blood collected for nitric oxide analysis and skin blood flow (flux), as determined by laser Doppler imaging, before and after the sessions, and also compared to a control group. RLS group presented an increase in skin blood flow immediately after the session's bout compared to baseline, in 5-minute post-treatment flux, and also when compared to the control group. These results indicated that the WBV increased the flux in the RLS group. No differences were found in nitric oxide concentration between baseline and after treatment and when compared to controls [23]. Unfortunately, the intervention was performed in the early afternoon and not at evening/night – when symptoms aggravate, as there seems to be circadian rhythmicity of the disease. In addition, the researchers observed an increased skin blood flow in the feet related to controls, and a weakened spatial cooling ability when the environmental temperature was raised [23]. In this sense, patients with RLS have a kind of sympathetic dysfunction as it controls skin microvascular circulation. Furthermore, the length of capillary/perimeter of fiber in the anterior tibialis (indicating a significant remodeling in capillary geometry) has been found to be higher in patients with RLS than in controls [24], as this is one of the hypotheses, as microvessel arrangement are changed, indicating an attempt to counteract local hypoxia in the tissue [24]. Some years later, this same research group investigated the effect of the WBV (i.e., ten 30-s bouts at a frequency and amplitude of 26 Hz and 2 mm) in RLS symptom severity for 2 weeks and found a 5-point decrease in IRLSSG Scale indicating that vibration had a positive effect on symptoms associated with RLS, although it did not normalize skin blood flow in patients with RLS compared to controls [25].

6 Yoga

An Iyengar yoga program was designed for women with RLS: two 90-minute classes per week, and at least 30 minutes of home practice on non-class days, for an overall period of 8 weeks. The yoga postures practice routines were illustrated in a manual

and given to the participants. The postures were modified, and props (e.g., blankets, chairs, blocks, and straps) were used as needed to allow participants to perform the sequences easily and safely. The Iyengar yoga reduced the IRLSSGS from 21.1 to 10.8 [26]. Other investigations on yoga indicated improvement of sleep quality in RLS participants [27].

7 Manual Therapies

Two small investigations focused on Mulligan traction straight leg raise. Mulligan's concept involves several different mobilizing techniques to treat the spine and limbs affected by the damaged spine. The traction straight leg raise technique (Fig. 1) has been previously used to improve straight leg raise hip flexion range of motion in normal subjects as well as those with lower back pain [29]. It comprises posterior leg stretching and increasing the hip range of motion, to influence the mobility of the nerves in the lower extremity. Both small investigations found the effectiveness of the technique alone on the self-reported improvement of the severity of the RLS symptoms. The first investigation focused on nurses having RLS, as their duty included long hours of standing [30]. The second investigation focused on a series of traction straight leg raise treatments in adults, both sexes, with a prior diagnosis of RLS. For this sample, symptoms were reduced by a mean of 63% with self-reported [28]. The mechanism for such improvements might involve alterations of the typical stretch reflex at the posterior leg and improve nerve mobility in the lower extremity [29]. Increased hip range of motion achieved during the technique might offer neural mobilization to the posterior lower extremity, with no stress or tension to these structures. In addition, the traction of the limb may trigger reflex pathways in the central nervous system, affecting lumbar and lower extremity mechanoreceptors. Neural

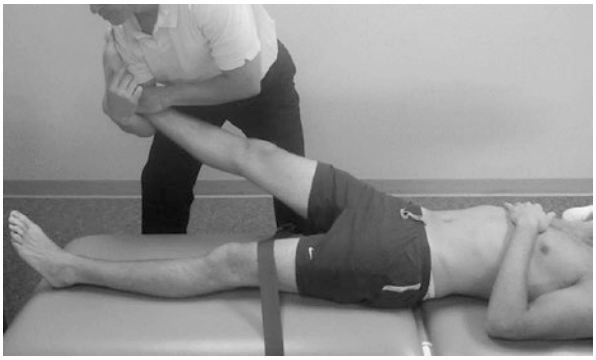

Fig. 1 Mulligan traction straight leg raises technique. (Reprinted with permission from Dinkins et al. [28])

mobilization is a neurodynamic intervention through which the nervous system is not slack and provides changes in sensation. Further inhibition may be achieved from various descending supraspinal pathways causing alterations to the stretch reflex of the hamstrings and lumbar paravertebral. This may account for the improvement of participants in these investigations, as both increased hip range of motion and perceived stretch response by patients. This is encouraging for the development of programs to address the symptoms of idiopathic RLS with physical therapy techniques.

8 Physical Exercise and Kinesiotherapy

Physical exercise has long been one of the few non-pharmacological treatment options for RLS and PLMS. A randomized controlled trial showed that exercises significantly decreased RLS symptom severity [31]. The exercises performed were lower-body resistance exercises and treadmill walking for aerobic exercise, performed three times a week for 12 weeks with the maintenance of pharmacological treatment. The RLS symptoms reduced 8 points in the severity of the disease, being clinically significant and relevant [31].

Table 1 shows scientific evidence of adjuvant treatment through exercises for RLS. The performance of physical activity indicates that the chronic adaptations induced by the exercises promoted the improvement of the symptoms more than the acute relief conferred by the movement of the legs. Another hypothesis for improvement is the effect that exercise exerts on the β-endorphin system, which are opioids that promote the sensation of well-being, in addition to the improvement of cerebral blood flow [13].

To evaluate the effects of both acute and chronic physical exercise on sleep patterns in patients with PLMS, a group of scientists allocated their sample, composed of sedentary individuals diagnosed with PLMD into two groups: acute exercise ($n = 22$), which performed intense acute exercise at maximum effort test and underwent polysomnography (PSG) on the same night, and chronic exercise (n = 11), in which the same participants performed 72 sessions of 50 minutes of aerobic physical exercise. The exercise was performed in a cycle ergometer; stretching was made before and after the session, three times a week for 6 months. Both groups underwent a PSG at baseline and after 1 (acute), 36, and 72 (chronic) sessions. The authors found that acute intensive exercise was able to increase total sleep time (TST), sleep efficiency (SE), and stage R, and to decrease WASO (wake after sleep onset or sleep fragmentation) and, importantly, decreased PLM index PLMi, from 31 n°/h at baseline to 24.2 n°/h - after just one session of exercise [35]. Just to remember, the PLMi is set as mild (5–24 n°/h), moderate (25–49 n°/h), and severe (≥50 n°/h), according to the PSG exam. Regarding chronic exercise, statistically significant differences emerged in the comparison with baseline: TST increased after 72° session; SE increased after 36° and 72° session; SL increased after 36° session; REM sleep latency decreased after 36° session; stage N2 increased after

Table 1 Exercise protocols for restless legs syndrome and periodic limb movement disorder

Study	Sample	Protocol	Outcomes
de Mello et al. (2002) [32]	12 patients with complete spinal cord injury between T7 and T12	Chronic aerobic exercise	↓PLMi
de Mello et al. (2004) [33]	13 patients with complete spinal cord injury between T7 and T12	Chronic aerobic exercise	↓PLMi
Aukerman et al. (2006) [31]	41 patients with RLS	Chronic aerobic + resistance exercise	Improvement in RLS symptoms
Sakkas et al. (2008) [34]	14 patients on hemodialysis	Chronic aerobic exercise	Improvement in quality of life
Esteves et al. (2009) [35]	22 patients with PLMS	Acute/chronic aerobic exercise	Acute: ↑TST, ↑SE, ↑ Stage R, ↓WASO, ↓PLMi Chronic: ↑TST, ↑SE, ↑ SL, ↓REM SL, ↓PLMi
Giannaki et al. (2010) [36]	18 patients on hemodialysis with RLS and PLMS	Acute aerobic + resistance exercise	↓PLMi
Esteves et al. (2011) [37]	11 patients with RLS	Chronic aerobic exercise	↓SL ↓SE ↑Stage R ↓PLMi
Cavagnoli et al. (2013) [38]	16 patients with PLMS	Acute aerobic exercise	↑Stage N1 ↓PLMi
Giannaki et al. (2013) [39]	24 patients with CKD	Aerobic exercises	Improved RLS symptoms and depression scales
Giannaki et al. (2013) [40]	32 patients with dialytic CKD + RLS	Aerobic exercises at dialysis	Improvement of RLS symptoms
Mortazavi et al. (2013) [41]	26 patients with CKD + RLS	Aerobic exercises	Improvement of RLS symptoms
Giannaki et al. (2015) [42]	14 dialytic patients with RLS	Aerobic exercises during dialysis	Improvement of RLS symptoms
Aliasgharpour et al. (2016) [43]	33 patients with dialytic CKD	Stretching during dialysis	Relief of RLS symptoms

RLS restless legs syndrome, *PLMS* periodic limb movement of sleep, *CKD* chronic kidney disease, ↑ increased, ↓ decreased, *TST* total sleep time, *SE* sleep efficiency, *Stage R* REM sleep stage, *WASO* wake after sleep onset, *REM SL* REM sleep latency, *PLMi* periodic limb movement index (n°/h)

36° session; stage R increased after both sessions; and, most importantly, PLMi decreased after the 72° session, from 31 n°/h at baseline (moderate) to 14.8 n°/h after chronic exercise (mild) (Fig. 2), indicating the importance of exercise for PLMS.

These data showed that both acute and chronic exercise decreased PLMi and single sessions of intense exercise as well as longer-term regular workouts reduced leg muscle contractions and improved sleep in a small group of people with PLMS

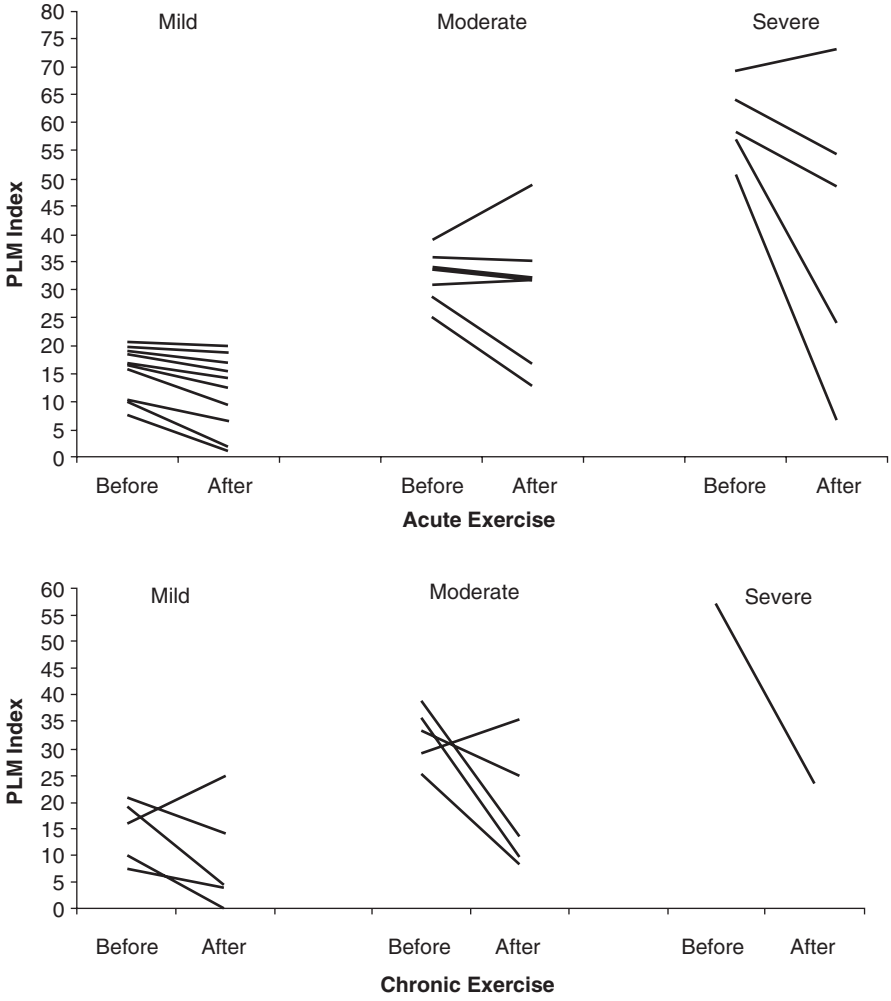

Fig. 2 Above: Changes in the individual PLM index (n°/h) before and after intense acute (1 session) physical exercise using PLMS classification. Below: Changes in the individual PLM index (n°/h) before and after 72 sessions of chronic physical exercise, using PLMS classification (mild, moderate, and severe). (Reprinted with permission from Esteves et al. [35])

[35]. Searching for the mechanisms of which this might happen, the researches investigated the release of ß-endorphin after exercise sessions and found an inverse relationship: more ß-endorphin release and lower PLM indices. Thus, ß-endorphin acted as "a proxy measure", being sufficient to reduce PLMi and to enhance sleep quality. The changes of ß-endorphin were not correlated with the intensity of exercise [35]. Therefore, it is suggested that for individuals with PLMS, physical exercise may be a plausible alternative (or better, complementary alternative) to pharmacological treatment.

There is plenty of evidence on the relationship between the intensity of physical exercise and the release of ß-endorphin, including its mechanisms [44, 45], but not in patients with PLMS. The release of ß-endorphin, which is based on amount and intensity of exercise, affects the dopaminergic system. Conversely, some investigations demonstrated that only chronic physical exercise can lead to these changes [35] and not a single session of physical exercise [38].

Having the dopaminergic system affected, and not knowing completely the role of the opioid and dopaminergic system in the pathophysiology of PLMS, a group of scientists investigated the changes in the dopaminergic system by acute exercise in patients with PLMS. The treatment with pharmacological therapy (such as opioids and dopamine) resulted in an adequate improvement of PLMS severity, so why not?

For acute physical exercise (maximal exercise test), the hypothesis was that a change in dopaminergic dysfunction (known to be present) that occurred in PLMS might happen due to exercise [38]. PLMS symptoms might result from a unbalance of dopaminergic and opioidergic systems in the regions involved in motor actions and/or pain perception, and that is why dopaminergic and opioid compounds are effective in treating RLS/PLMS [46]. Therefore, taking into account that dopamine is a neurotransmitter involved in motor function (and cognitive and emotive responses) [47, 48], dopamine is captured in the synaptic cleft by many different neural receptors, including the dopamine transporter. The dopamine transporter is a molecule located in the presynaptic neuron that modulates the uptake of dopamine using an electrical mechanism coupled to Na^+ and Cl^- [49]. The dopamine transporter regulates the levels of available dopamine in the synaptic cleft [50]. Seventy percent of the dopamine removed from striatal synaptic clefts is mediated by dopamine transporter, which also regulates the levels of available dopamine in the synaptic cleft [50], and its concentrations reflect the homeostatic tone of the dopaminergic system [50, 51]. The researches investigated the dopamine transporter density via SPECT (single-photon emission computed tomography) in patients with PLMS, and found that, despite the reduced symptoms of PLMS after exercise, no changes in dopamine transporter availability occurred. This result showed that physical exercise did not modulate dopamine transporter density - other mechanism might be involved. Curiously, the authors found slightly lower dopamine transporter density in the left putamen region of the PLMS patients compared with healthy participants [38].

Until now, we do not know the exact mechanism of which exercise mediates a decrease, both in symptoms and in objectively measured PLMi. Some well-conducted investigations by a Brazilian group demonstrated that acute exercise statistically significantly reduced PLMi during sleep, measured by PSG, in a sample of athletes with spinal cord injuries [52]. In addition, the effects of aerobic exercise for 45 days in this population were not different from those produced by pharmacological therapy with L-DOPA [33]. Despite the small sample size, both treatments resulted in significant reductions in the PLMi from 35.1 to 19.9 for L-DOPA and from 35.1 to 18.5 for the exercise program [33]. Such studies need reproduction in other PLMS populations. Other investigation was performed to assess the effectiveness of aerobic training in PLMi in individuals with complete spinal cord injury. Using an arm crank ergometer, the physical training program was performed

for 44 days, and reduced the PLMi when comparing baseline, 35.1 nº/h, with fifth, 12.7 nº/h, and sixth evaluation, 18.5 nº/h demonstrating objectively (PSG) improvement of PLMS [32].

The message is quite simple, yet it deserves more investigations: any physical intervention is more effective than no treatment or treatment with placebo in abolishing or reducing the occurrence of PLMS and improving the quality of life. There is emerging evidence for providing such suggestions as a more active and comprehensive intervention for exercise program/therapy as part of a treatment for PLMS in physical therapy settings.

9 Final Words

Currently, there is insufficient evidence to evaluate the use of non-pharmacological intervention for RLS and PLMS alone. The interventions presented here appear to be beneficial in improving mainly RLS severity, PLMi and PLMS complaints, and sleep in some individuals. Nevertheless, it is unclear to what extent benefits are because of individual/group interventions, publication bias, or even placebo responses.

Pharmacological treatment is the first line of therapeutic choice for relieving the symptoms of RLS, especially in moderate and severe cases, and non-pharmacological treatment should be considered as an adjunct to pharmacology. The physiotherapist should encourage the patient to maintain the use of his medications, even with the improvement of symptoms with the proposed intervention.

As PTs, many of our daily patients/clients are at risk of having RLS and/or PLMS, such as pregnancy, sleep apnea/snoring, narcolepsy, diabetes mellitus, anemia, iron deficiency, spinal cord injury the ones in use of dopaminergic medications, benzodiazepine or barbiturate withdrawal, drug dependency, and antipsychotic medication. So far, RLS and PLMS have already been handled by programs including aerobic exercises (treadmill bicycles or treadmill) which vary in duration, number of sessions, intensity, and follow-up with favorable outcomes.

Despite no consensus or guidelines on PT management of RLS and/or PLMS, our suggestion, even though more investigations are urgently needed, is that individualized physiotherapy should be considered as a complementary treatment for both diseases, as it has no negative side effects and can contribute to better health overall.

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Circadian Rhythm Sleep-Wake Disorders: An Overview

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Circadian rhythm refers to the biological rhythm that lasts about 24 hours (circa *diem* means "about a day"). The concept of circadian rhythm includes a period that varies from 20 to 28 hours. In humans, the *tau* or circadian rhythm is about 24.2 hours. There are cyclic variations in behavior and physiology, and the sleep-wake cycle is an example of a biological rhythm that is considered circadian. The sleep-wake cycle is the alternation between wakefulness and sleep. There are several other biological rhythms with circadian patterns such as appetite, body temperature, hormone levels, blood pressure, alertness, daily performance, reaction times, etc. The synchronization of the internal rhythms to the external environment is the *circadian phase*.

The regularity and periodicity of biological rhythms are one of the determinants of good organic function and human health. Several circadian rhythms oscillate over 24 hours, and the phase relationship established between these rhythms is important for general well-being. This process is called internal temporal order [1].

The desynchronization (also called circadian rupture, internal desynchronization, or rupture of the internal temporal order) between the internal circadian regulation system and the desired/needed sleep-waking times can result in one of the sleep-wake circadian rhythm disorders and is an important factor to be considered for other sleep disorders [1, 2].

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1 Physiology of Circadian Rhythm

The intrinsic internal temporal control system modulates several physiological systems, such as body temperature, hormones (e.g., cortisol, melatonin), and digestion. The suprachiasmatic nucleus (SCN) located in the hypothalamus acts as an internal regulator that generates circadian rhythm. Circadian rhythmicity is created endogenously by genetically encoded molecular clocks, whose components cooperate to generate cyclic changes in their activity, with a periodicity of about a day. The SCN is the major circadian pacemaker in humans and helps to maintain alertness by producing alerting signals during the day and maintaining sleep during the night by a reduced signal. If there were no environmental cues, the circadian rhythm would manifest itself for more than 24 hours. However, the earth's axis of rotation generates an important exogenous environmental cue – the dark-light cycle resulted from the alternation between day and night. External cues of luminosity stimulate photoreceptors located in the retina (melanopsin-containing retinal ganglion cells are the major circadian photoreceptors), which communicate the presence of light to the SCN, to the optic nerve, via the retinohypothalamic tract. In turn, this neural pathway synapses with the suprachiasmatic nuclei and generates cues that synchronize endogenous rhythms [2]. In response to the degree of luminosity, the SCN synapses with the pineal gland, thus regulating the release of melatonin. Light (sunlight) is the major *zeitgeber* (German for "time givers") and entrains the SCN into the physical environment. Therefore, light is an important environmental cue that acts to influence the circadian timing system. Environmental factors that can modify biological rhythms are called synchronizing agents or *zeitgebers*. Therefore, exposure to different 24-hour light-dark cycles can shift the circadian rhythm phase. There are peripheral (local) oscillators that are operative in the cells of most organs and tissues such as the thyroid gland, skeletal muscles, pancreas, skin fibroblasts, and others [3, 4]. In addition, the peripheral oscillators serve as input pathways for the SCN. The circadian system in humans is a hierarchical multi-oscillatory network, composed of master pacemaker(s) in the brain and oscillators in peripheral organs [5].

The circadian system has an imperative role in the regulation of the sleep-wake cycle since it influences the duration, continuity, and sleep structure. The mechanisms by which the circadian system interacts with sleep and waking states remain elusive. One of the hypotheses raised refers to the activation of nerve impulses by the circadian system promoting wakefulness during the day and helping to compensate for the progressive increase of sleepiness of the homeostatic sleep system, which accumulates along with prolonged wakefulness and promotes the onset of sleep. After the first half of the sleep episode, this sleep impulse decreases rapidly. This regulatory process takes place under normal homeostatic conditions. A properly aligned circadian system increases the propensity to sleep at night, particularly in the second half of the night, helping to maintain sleep consolidation until the usual time of awakening [6]. Thus, there is an internal order among the rhythms. The core body temperature Variation shows a lower phase during nighttime sleep, and between 3:00 and 4:00 of the night, the melatonin concentration level is at its peak. Subsequently,

the core body temperature rises, and the plasma concentration of melatonin begins to fall and finally reaches its lowest rates, which occurs simultaneously to the light (day) phase of the light-dark cycle. In an organism, when the phase shift of the circadian rhythms is altered by any reason, there is a desynchronization, constituting a circadian rhythm sleep-wake disorder (CRSWD).

Therefore, the advent of electric light and technology allowed prolonged exposure to light during the night, anyplace, anywhere, which may desynchronize circadian rhythms due to SCN sensitivity to light [7]. The effect of phase shift from dark to light in the circadian system depends on when light exposure occurs. Exposure to light during the last hours of the typical sleep phase and the early hours of the morning shifts the circadian rhythm to earlier (advanced phase), as physiologically happens with older ones. On the other hand, exposure to light at night and in the first half of the usual sleep phase shifts the circadian rhythm to later (delayed phase), as physiologically happens with adolescents.

The SCN acts on circadian oscillators in peripheral tissues by neural signals from the autonomic nervous system, as well as the secretion of neurohormones. The hypothalamic-pituitary-adrenal axis is important for the hormonal regulation of the circadian system. For example, corticotropin-releasing hormone enters the hypothalamus-pituitary system and stimulates the secretion of adrenocorticotropic hormone (ACTH) by the anterior pituitary gland. ACTH then regulates cortisol production in the adrenal cortex, a hormone with a robust circadian oscillation and important synchronization effects on many peripheral oscillators. Therefore, cortisol peaks when waking up in the morning, while at night its concentration decreases (Fig. 1).

The rhythmic variation of different hormones, as well as of cognitive functions, strength, muscular performance, and dexterity, which occur in 24 hours constitute a predictable time for circadian oscillation of human abilities [9]. In other words, there is variation in alertness, attention, and physical performance according to hormonal and neural variations in a predictable way. In a study with healthy people in which the average sleep period was from 22:30 to 6:30, for example, the peak level of circadian rhythm occurred approximately at the following times: insulin at 16:00 h; triglycerides and cholesterol at 18:00; gastric acid secretion at 22:00; cortisol at 06:00; catecholamines at 07:00; and hemoglobin at 11:00 [10]. In addition, metabolic processes in peripheral oscillators are also modified by nutritional status, and peripheral oscillators relay feedback metabolic information to the hypothalamus. Nowadays, uninterrupted access to food can distort the feeding/fasting cycles that have characterized much of our history and therefore disrupt the circadian system [2]. When the organism is synchronized, the active period is concomitant with the caloric intake during the day (wake). In contrast, inactivity and anabolism occur during the resting phase (sleep). As a result of synchronization, the circadian system ensures a maximum physical performance during the active phase, with predictable circadian changes in blood pressure, heart rate and contractile efficiency of skeletal and cardiac muscles, and substrate oxidation to prepare the body for every day (light, day) activity.

The International Classification of Sleep Disorders (ICSD-3) [11] lists general criteria for CRSWD. The following must be present:

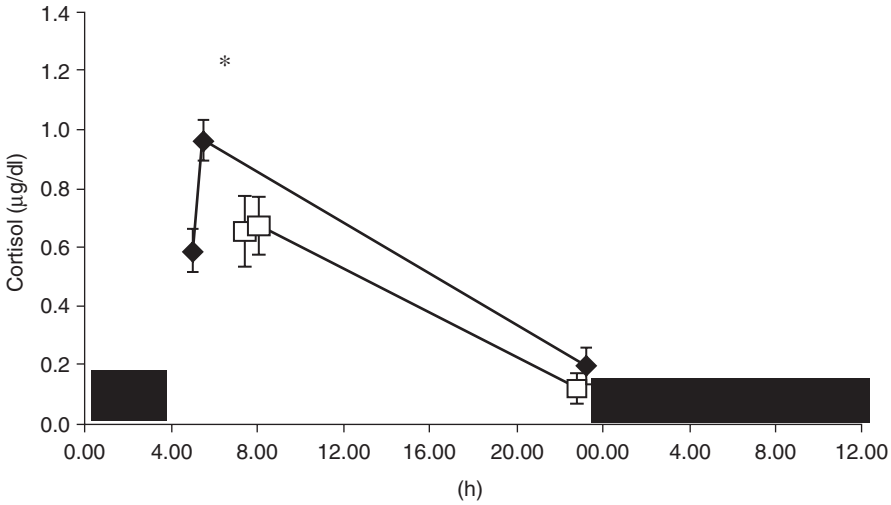

Fig. 1 Correlation between salivary cortisol concentrations (µg/dl) and the time of collection of cortisol (hours) in day shift drivers. The continuous line represents a working day, and the dotted line represents a day off. The dark period indicates sleep time in workers with regular hours. (Reprinted with permission from Ulhôa et al. [8])

1. A chronic or recurrent pattern of sleep-wake rhythm disruption primarily due to alteration of the endogenous circadian timing system or misalignment between the endogenous circadian rhythm and the sleep-wake schedule desired or required by an individual's physical environment or social/work schedules.
2. The circadian rhythm disruption leads to insomnia symptoms, excessive sleepiness, or both.
3. The sleep-wake disturbances cause clinically significant distress or impairment in mental, physical, social, occupational, educational, or other important areas of functioning.
4. Sleep diary and actigraphy monitoring for at least 7 days (preferably 14 days) demonstrating disruption of the circadian sleep-wake cycle.

2 Circadian Disturbances Imposed by Intrinsic or Extrinsic Causes

There is evidence that intrinsic and extrinsic factors may be related to circadian rhythm sleep-wake disorders (Table 1). Air travel that transverses time zones or shift work, which requires individuals to be awake at times when they should be asleep, leads to desynchronization of biological rhythms, as many diseases related to circadian rupture (Fig. 2).

Table 1 Circadian disorders are imposed by intrinsic and extrinsic causes

	Type of disorder	Examples	Main features
Intrinsic causes	Delayed sleep-wake phase disorder	Neurodevelopmental features in adolescents	Extension of the intrinsic circadian period The individual has evening-type preference/habits
	Advanced sleep-wake phase disorder	Neurodevelopmental features in the older	The individual has morning habits
	Irregular sleep-wake rhythm disorder	Neurodegenerative process (e.g., dementia)	They show irregular interruption of the circadian system
	Non-24-hour sleep-wake rhythm disorder	Blindness	Free-running
Extrinsic causes	Jet lag disorder	Changes in time zones due to air travel	Change from the usual exposure to light generating desynchronization of circadian rhythms and timing at local time
	Shift work disorder ("social jet lag")	Waking and alertness are needed at a time when sleep should be present	Excessive daytime sleepiness Curtailed sleep duration

2.1 Circadian Disorders Imposed by Intrinsic Causes

Intrinsic circadian disorders are caused by variations of the circadian time-keeping system, its entrainment mechanisms, or a misalignment of the endogenous circadian rhythm. It is believed that delayed sleep-wake phase disorder and advanced sleep-wake phase disorder are related to misalignment of the circadian timing system intrinsic to the desired sleeping hours. Rhythm desynchronization or impairment of the circadian modulation of the sleep-wake cycle often results in impairment of physical, mental, neurocognitive, and social functioning, leading to the occurrence of insomnia and excessive daytime sleepiness [13].

Misalignment in delayed sleep phase disorder (DSWPD) is not well established and probably has a multifactorial cause. Individuals with this disorder typically score as evening-type. DSWPD is characterized by typical sleep-wake timing that is delayed, usually more than 2 hours, relative to conventional or socially acceptable timing (Fig. 3a). Affected individuals complain of difficulty falling asleep at a socially acceptable time, as required to obtain sufficient sleep duration on a school or work night. When sleep onset happens, it is supposedly of normal duration. These individuals also have trouble arising at a socially "adequate" wake time, as required to prepare for school or work. When allowed to follow the preferred schedule, the patient's timing of sleep is delayed. DSWPD is

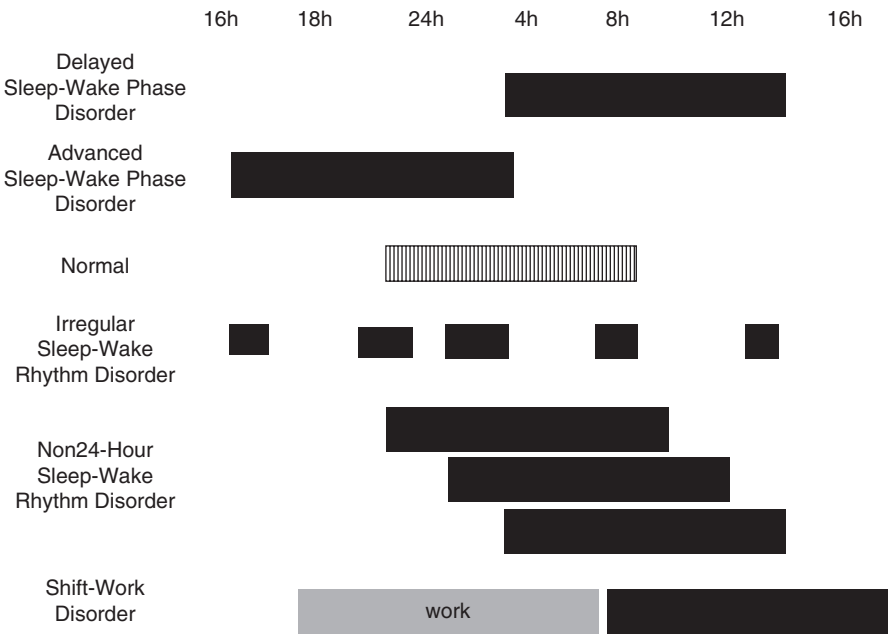

Fig. 2 Schematic representation of the major circadian rhythm sleep-wake disorders including intrinsic and extrinsic causes. Black bars represent sleep periods of circadian disorders; striped bars represent conventional sleep time. (Modified (with permission) from Lu and Zee [12])

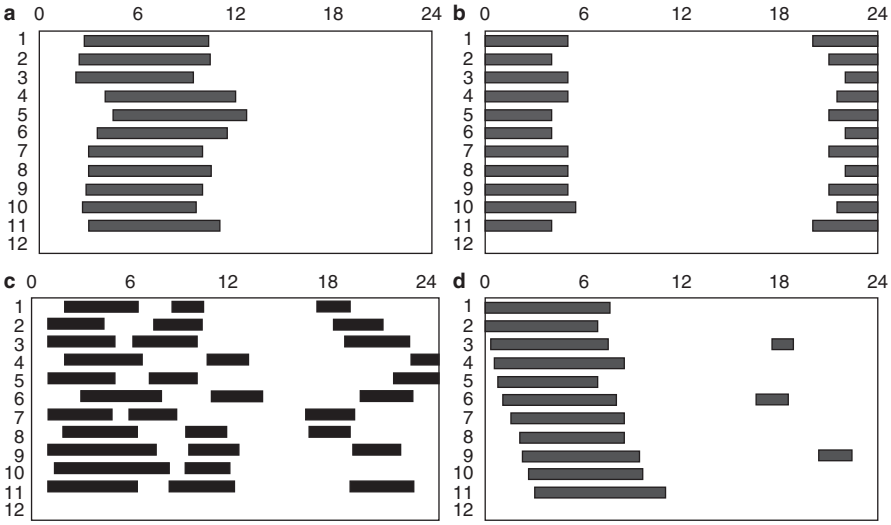

Fig. 3 Example of actograms of clinical manifestations of circadian disorders imposed by intrinsic causes. Each line corresponds to 1 day (12 days in this actograms). Above each graph the 24 hours of a day. The black bars correspond to sleep. (**a**) Individual with delayed sleep-wake phase disorder; (**b**) individual with advanced sleep-wake phase disorder; (**c**) individual with irregular sleep-wake cycle disorder; (**d**) individual with Non-24-hour sleep-wake rhythm disorder or free-running. (Image courtesy from Dr. Claudia Moreno)

encountered in any age group; nonetheless, it is particularly prevalent among adolescents and young adults. Adolescents have a neurodevelopmental feature that promotes changes in sleep-wake rhythm and an extension of the intrinsic circadian period during this age range. Another cause presented in DSWPD is changing in light exposure and altered sensitivity of the circadian system to light [14]. Having this circadian knowledge, school activities should be planned to take into account the biological rhythms for each age range. For instance, pre-adolescents (between 10 and 12 years) usually study in the morning, having classes starting around 7 h/7:30 h. In this age group, the habits have changes to an evening-type, preferring falling asleep and waking up later (night owls) [1]. As a result, school performance in the early morning hours is often compromised. It is important to note that this disorder is part of the neural development in preteens and adolescents and tends to soften with the maturation of the central nervous system in adulthood. Standardized chronotype questionnaires are useful tools to assess circadian preference (morning-, evening-, or intermediate-type) (Chap. 35 of this book).

The advanced sleep-wake phase disorder (ASWPD) happens when there is an advance (early timing) in the phase of the major sleep episode in relation to the desired or required sleep time and wake-up time (Fig. 3b). This must be demonstrated by a chronic or recurrent complaint of difficulty staying awake until the required or desired conventional bedtime, together with an inability to remain asleep until the required or desired time for awakening. Advanced age appears to be a risk factor for ASWPD, in part due to the advancing physiological phase that occurs with aging, combined with the weakening of circadian rhythms and age-related environmental signs. Such phase disorder can be genetically determined in some individuals.

The irregular sleep-wake rhythm disorder (ISWRD) represents a failure of the circadian system to maintain a stable alignment within 24 hours; consequently, the sleep-wake pattern is temporally disorganized (Fig. 3c). In ISWRD patients present with a chronic or recurrent pattern of irregular sleep and wake episodes throughout the 24-hour period, characterized by symptoms of insomnia during the scheduled sleep period (usually at night), excessive sleepiness (napping) during the day, or both. In ISWRD sleep and wake episodes are fragmented, with the longest sleep bout being typically less than 4 hours, but sleep duration across the 24 hours may be normal for age. The risk for ISWRD is increased in neurodegenerative disorders (e.g., Alzheimer's disease, Parkinson's disease, and Huntington disease) and children with developmental disorders. Poor sleep hygiene and lack of exposure to external synchronizing agents (i.e., light, activity, and social cues) may be predisposing as well as precipitating factors involved in the development of ISWRD, particularly in institutionalized older individuals.

Non-24-hour sleep-wake rhythm disorder (Non24 SWD) is characterized by a period lasting 1–2 hours longer than 24 hours, progressively delayed sleep period. Patients with Non24 SWD are not adjusted (entrained) to the 24-hour cycle (Fig. 3d). The disease is also called *free-running* or *non-entrained disorder*. As the biological clock (SCN) continues to operate in *free-running*, appropriate

alignment periods may occur eventually, but this resolution is temporary. Symptoms of insomnia or excessive daytime sleepiness can occur because the intrinsic circadian pacemaker is not entrained to a 24-hour light/dark cycle. This disorder can occur in people in which the circadian system loses its ability to synchronize to environmental cues. Blind individuals have an obvious failure to entrain circadian rhythms due to the lack of photic input to the circadian pacemaker. Also, there is an increased incidence of Non24 SWD in psychiatric disorders, and occasionally, the disorder is associated with dementia or developmental intellectual disability.

2.2 Circadian Disorders Imposed by Extrinsic Causes

Jet lag and shift work disorders are considered of extrinsic origin. The advent of air travel crossing time zones has led to a disorder called jet lag, since crossing different time zones is associated with the need to sleep and to be awake at times that are misaligned with the circadian system. This change in the time zone modifies the habitual exposure to light, generating a desynchronization of circadian rhythms or a circadian rupture. The severity of the misalignment depends on how many time zones have been crossed and the direction of travel. Because the natural circadian cycle is slightly longer than 24 hours, the journey to the west usually causes fewer interruptions, as it is easier to delay than to advance the circadian cycle. In this case, individuals have difficulty falling asleep at local time in the new zone or keeping awake when necessary. Daytime sleepiness may occur due to sleep deprivation as well as circadian misalignment. These disturbances persist until the circadian system is synchronized to the new destination time zone.

A term used nowadays is "social jet lag," referring to shift work disorder, that is, the desynchronization of circadian rhythms originating from the disorder between the preference of sleep schedules and social obligations (work, school, childcare, domestic and family responsibilities, etc.) [15].

The shift-work disorder manifests by complaints of insomnia or excessive sleepiness that occur in association with work hours that happen during the usual sleep episode – at least in part. There are numerous categories of shift-work agendas, including evening shifts, night shifts, early morning shifts, rotating shifts, split shifts, on-call overnight duty, and long-duration work shifts that include work hours at night. As a result, people accumulate sleep deficit and increase the risk of accidents, mistakes, and other adverse health outcomes in addition to presenting sleep disorders, such as gastrointestinal (stomachache, diarrhea, etc.), cardiovascular (coronary heart disease, hypertension, etc.), and psychosocial disorders (affective and sexual difficulties). The worker cannot rest properly after the shift and cannot participate in social activities [16–19].

Despite the consequences of shift work on workers' health, night work is part of modern society due to the need for services available 24 hours a day. However, night

shift work contradicts a biological determination of the human being to perform their waking activities during the day and sleep at night. In this context, shift work can be one of the causes of circadian desynchronization and, therefore, is considered a stressor, causing stress, and can stimulate the HPA axis, thus leading to obesity [20, 21].

The sleep of night or shift workers has a shorter duration compared to day workers. The inversion of the sleep phase (daytime sleep) also generates a higher number of complaints related to sleep and health, since it interferes with sleep structure and results in chronic sleep restriction [22].

For example, truck drivers who worked irregular hours, including during the night, reported worse health conditions and showed higher cortisol concentrations with daily drivers, including the day off, suggesting a more prolonged response to stress [8].

3 Diagnosis and Follow-Up

Several strategies are used to evaluate and monitor the patient with sleep-wake cycle disorder of the circadian rhythm. Some self-reported measures, including sleep diaries/sleep logs, and objective measures such as actigraphy (see Chaps. 35, 36, and 37) have additional benefits to establish a diagnosis. Polysomnography is not normally indicated, except when a sleep disorder is suspected [13, 23] (i.e., obstructive sleep apnea syndrome or narcolepsy).

Regarding melatonin, it can be dosed to determine the circadian phase of an individual. Schedules can be designed with the physician to regulate the release of melatonin and thus help within sleep onset. Melatonin is usually released about 90–120 minutes before the usual bedtime, as long as there is no strong light. Intense light suppresses melatonin production [7]. The dim-light melatonin onset (DLMO) protocol [24] involves intermittent blood or saliva collection every 30–60 minutes, around 6 hours before and 1 hour after bedtime. The time at which melatonin levels rise above the limit provides a valid and reliable indicator of the position of the circadian phase [25]. The DLMO protocol is commonly used in research. It may eventually be used more routinely in clinical practice to help confirm diagnoses in challenging cases and to help identify the ideal time for interventions that aim to change the circadian phase (e.g., exposure to intense light, administration of exogenous melatonin, the practice of physical activity).

4 Final Words

It is very important to recognize the different types of CSWD so that management is as appropriate as possible and patient-centered. In this way, the person will be fully benefited, with improved sleep, health, and quality of life. It is also imperative

to remember that some people have preferences (circadian preference) to carry out their activities in the morning (morning-types), while others prefer the afternoon and evening (evening-types). Therefore, these circadian preferences do not characterize circadian rhythm disorders and are related to routine, habits, and heritable genes.

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Physical Therapy in Circadian Rhythm Disorders: Chrono-rehabilitation?

Cristina Frange

Every circadian sleep-wake disorder requires a specific treatment strategy. For the success of the treatment, the circadian rhythm should be synchronized with the desired/needed sleep-wake cycle. Physiotherapists together with other health practitioners (physicians, psychologists, nutritionist, etc.) treat the patients in order to synchronize the rhythm.

According to the American Academy of Sleep Medicine Clinical Practice Guideline for the Treatment of Intrinsic Circadian Rhythm Sleep-Wake Disorders (CRSWD) [1], and depending on the disorder, useful approaches may include careful adjustments of sleep-wake times, sleep hygiene strategies, behavioral and pharmacological therapies (e.g., administration of melatonin or melatonin receptor agonists), exercise, and bright light therapy.

The physiotherapeutic treatment of CRSWD starts with the clinical picture of the patient: the anamnesis. Questionnaires such as the Munich Chronotype Questionnaire or the Morningness-Eveningness Questionnaire (described in chapter "Subjective Assessment of Sleep") combined with actigraphy and sleep diary for more than 10 days (to have weekdays and weekends sleep-wake cycle) can help to set up the diagnosis (done by a physician), and to follow with the treatment regimen. In case any circadian misalignment is suspected, the physiotherapist (PT) must send the patient to the sleep medicine specialized physician.

Circadian disorders are often presented within sleep disorders. A patient seeking treatment for sleep disorders, or even a patient found to have a sleep disorder,

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need to be evaluated regarding his/her routine: at what time he/she goes to bed, what time sleeps, how many times and why he/she wakes up in the night (nocturia? noise? worries? etc.), and at what times he/she wakes up and gets off the bed. Also, daytime repercussions such as waking up refreshed, restored, with lots of energy, or wanting to sleep more and feeling restless, tired and sleepy. In addition, behaviors related to bedtime such as the use of electronic devices (e.g., tv, computer or smartphone) after sleep, light, alarm clock, room temperature, snoring partner, etc., should be taken into consideration to have the most complete "clinical picture" of the patient's routine and behaviors regarding sleep. Having said that, sleep hygiene should be taught, explaining the rationale for each one of the "rules" and implementing it into clinical practice, as the behavior strategies might be used (e.g., stimulus control, sleep restriction therapy, relaxation therapy, cognitive therapy, paradoxical intention) (more on Chapter "Optimizing Behavior Strategies for Sleep".

As diurnal animals, human activity, exercise, and feeding primarily occur during daylight hours, in contrast to sleep, rest, and fasting throughout the night – and we must respect these rhythms, even in the presence of light, technology, and the "avatar" that we became of ourselves in the contemporary life, constantly exposed to light (and specifically to blue bright light). Of course, some preferences, whether determined genetically or by the environment such as chronotype, circadian preferences, and being a shorter, intermediate, or longer sleeper should be taken into account.

1 Morning Larks and Night Owls

Genetically, we can talk about chronotype. The chronotype is associated with an individual's endogenous circadian clock rhythm and determines the circadian preference to realize their activities. The elucidation of molecular clock gene polymorphisms as a genetic basis of chronotype has become a consideration for sports performance, for example. A length polymorphism in the human Per3 gene (along with the gene's endogenous circadian expression) has been associated with altered morning-evening preferences in the general population, the longer allele being linked to morning type, and the shorter allele with evening type [2]. Analysis of elite athletes from both genders, from a variety of sports reveals an overrepresentation of morning types in sports generally taking place in the morning, such as marathon running, cycling, or triathlon [3, 4]. These findings suggest that those with strong morning preferences may be more drawn to sporting activities that take place during the early morning. Alternatively, those with chronotypes that radically oppose the performance schedules of that sport may simply not progress to the very elite level, resulting in a selection bias. Thus, exercise capacity and chronotype may exhibit reciprocal feedback. It's hard to change chronotype; some even say it cannot be changed, but we can learn how to have

the best of our genetic predisposed preference, adjusting it in some types of routines, not extreme ones. For example, a morning-type person will always present difficulty to work during the night (e.g., shift work), and PTs can help to ameliorate the difficulties, but no technique/method that PTs make will transition this person to an evening-type.

2 At What Time to Rehab?

Circadian preferences are another fact to be considered, linked to chronotypes. Circadian preferences are the propensity for an individual to sleep at a particular time during 24 hours (classified as morning, evening, or intermediate types). Morning-type people are individuals who prefer to get up early and carry out their activities in the morning; evening-type people are those who prefer to wake up late and carry out their activities during the afternoon or evening, and intermediate ones are those who choose intermediate times between the two extremes and can easily adapt to either one.

Can circadian preferences influence rehabilitation or physiotherapy sessions? Until now, we do not have a consensus on this. Even though clinically (and empirically) I believe that yes, they do have an impact on rehabilitation, no systematic reviews with meta-analysis have been made so far. In a recent investigation, our group examined circadian preferences and sleep quality of stroke rehabilitation. The participants were divided into morning-type, indifferent, and evening-type preferences, according to their responses to the Morningness-Eveningness Questionnaire. All the participants underwent rehabilitation of the upper extremity by the same protocol, performed during the morning (the time that many of the rehabilitation centers work in Brazil). We noticed that evening-type patients demonstrated less improvement in motor skill performance, compared to morning and intermediate types [5], as in other investigations [6, 7]. The influence of circadian preference may help within rehabilitation or may represent a stressor at requesting cognition, strength, memory, and motor learning at non-preferred times, having less cognitive reserve to compensate for additional demands in times of stress. These can lead to fatigue and other physiological, psychological, and environmental factors that affect learning, especially motor abilities.

The time of the day of rehabilitation/physiotherapy session matters, according to the patient's circadian preferences and chronotype. Again, we do not have any evidence to state that the time of rehabilitation should be this or that way. Therefore, some investigations with specific populations are arising. If there is a time of the day (*when*) that we can optimize the session, it means that *what* we do in this session may act as a *zeitgeber*: a rhythmically occurring natural phenomenon that acts as a cue in the regulation of the body's circadian rhythms (German word for time giver). These *zeitgebers* include social contacts, the timing of ingestion of food, the knowledge of time itself, the scheduling of normal rest and activity habits, and, possibly, the participation in regular physical activity and exercise.

3 Chrono-exercise

Could scheduled exercise be used to fix a "broken clock"? Exercise is a non-photic oscillator, and thus independent of the retina and, therefore, of the suprachiasmatic nucleus. Exercise has a myriad of health benefits and would trigger a metabolic rhythm and physiological responses capable of re-establishing the rhythm, demonstrating its circadian properties. Exercise produces a multitude of physiological responses in humans, including hormonal changes and increased body temperature, which can help to entrain to a new routine.

Numerous studies have investigated the effects of exercise on the circadian rhythms of young, healthy humans. Some studies used "re-entrainment" designs, in which participants underwent a shift of the sleep/dark period (e.g., mimicking night shift work), and exercise was used as a stimulus to accelerate entrainment to the new sleep/wake cycle. Results of these studies indicated that exercise was capable of accelerating the entrainment to the new sleep/dark schedule: performed during the day, exercise accelerated phase advances [8]; and when performed during the night, exercise accelerated phase delays [9]. Exercise type, intensity, frequency, and the daily timing of physical activity impact its efficacy. Some investigations did not involve a shift in the sleep/dark schedule, and in these nocturnal exercise was associated with circadian phase delays [8, 10, 11]. Regarding older individuals, a single 3 h bout of low-intensity nocturnal exercise has been demonstrated to be capable of delaying the circadian melatonin, suggesting that the phase-shifting effects of exercise are preserved in healthy older adults [12].

In experimental models, some studies show that even in the absence of the central oscillator (suprachiasmatic nucleus (SCN) surgically removed), the animals express phase and rhythm adjustment due to regularity (rhythm) of the offered exercise after feeding at the same time every day [13].

To minimize the phase-resetting effects of light, a group of investigators set up exercise in a very dim light condition. For that, young and fit males completed a 15-day randomized clinical trial in which the circadian phase was measured in a constant routine before and after exposure to a week of nightly bouts of exercise or a non-exercise control condition. The authors found that exercise facilitated the shift of the timing of the circadian clock to a 9-h delay of the sleep-wake cycle [14]. But what are the proposed mechanisms by which exercise can help to change circadian rhythms? There is evidence on experimental studies involving the intergeniculate leaflet, which is anatomically important in the transfer of non-photic information to the SCN via specific neuropeptides [15]; and the serotonergic system may also be involved in non-photic input to the suprachiasmatic nuclei [16].

Yet, there is supporting evidence that exercise might be a human *zeitgeber* [17] and that exercise can act as a behavioral countermeasure to facilitate circadian adaptation. Regarding the phase-shifting effects of exercise, there is plenty of evidence, which supports its use in clinical practice. Exercise, depending on the time of day or internal time of stimulus application, has been shown to phase-shift the melatonin and thyroid-stimulating hormone and increase body temperature [8, 14, 18, 19], and

the activity itself that may produce effects on the circadian clock was performed at the same time. Recently, the involvement of the vestibular system in the regulation of circadian rhythmicity in experimental studies has emerged. Vestibular inputs seem to be involved in daily rhythm regulation by influencing the CNS independently of direct proprioceptive and muscular inputs. The vestibular system could normally act as an actimeter, providing information about motion during the wake period [20].

Taken together exercise has circadian rhythm phase-shifting properties, both immediate as observed in assessments of classic circadian hormone and body temperature rhythms and more long term as observed by studies on the timing of peak performance [17]. In this view, the timing of exercise ("chrono-exercise") is important for both entrainment signals and energy expenditure.

Until some years ago, we believed that exercise by itself could not fix a broken clock. The influence of light is imperative, especially for melatonin rhythm, which means its presence but also its absence. Thus, the environmental light-dark cycle is the key entrainment signal of human circadian rhythms and must be taken into account. In order to optimize exercise as circadian entrainment, light cues could also be part of a physical therapy session, depending on your PT objectives: to exercise outdoors or indoors? What type of exercise and what environment is proposed to exercise? Bright light or dim light? Room or natural temperature?

Multiple *zeitgebers* such as light, noise, meals, or social contacts may act synergistically or antagonistically, that is, they interact in terms of their "push" or "pull" on circadian rhythm phase. Perhaps, exercise could be combined with other *zeitgebers* such as light to maximize their health benefits and target the physical therapy aim. For example, a patient with delayed sleep phase syndrome and being an evening-type, needs help to get a job that starts at 8 h and finishes at 18 h. This patient has difficulties in being awake during the morning, being sleepy and having difficulties with concentration and memory. The goal for this patient would be to advance his/her biological rhythm, and for that, exercise should be performed during the day, preferably outdoors or in exposure to blue light. With time, 1 or 2 months, the exercise time can be advanced a little bit again. There is no "protocol" ready to synchronize this patient, but taking into account exercise, sleep routine, light, and food, and also the patient's circadian preferences, PTs can help to entrain this patient indifferently to his natural preferences, but always remebering that he/she has a preference for afternoon and evening (performing better at this times).

Therefore, it is important to mention that the American Academy of Sleep Medicine Clinical Practice Guideline for the Treatment of *Intrinsic* CRSWD does not recommend timed physical activity and exercise solely [1].

4 And the Light Became Therapy

Bright light therapy is an approach of exposing to artificial light, greater than 2500 lux, for a limited duration of time, practically to mimic sunlight and its "circadian" effects, hypothesizing that bright light suppresses plasma melatonin level [21],

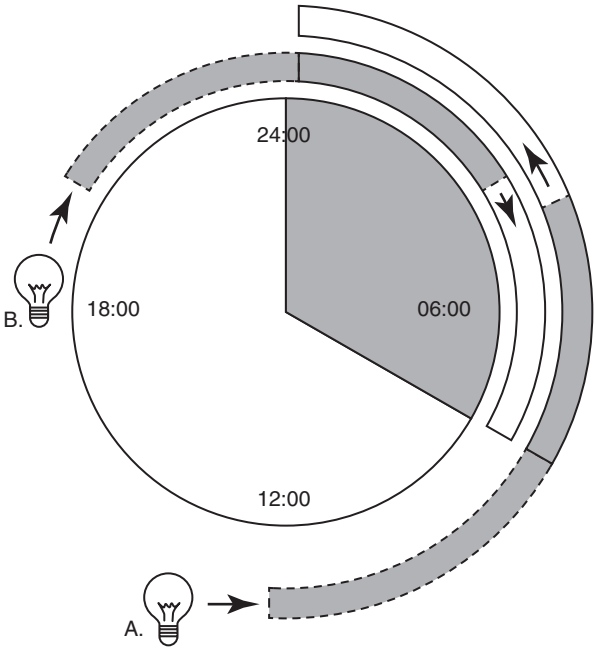

Fig. 1 Schematic representation of light therapy for CRSWD. Bottom, (**a**) morning light therapy will phase advance delayed sleep phase. Left, (**b**) evening light therapy will phase delay advanced sleep phase. Gray pie represents conventional sleep time, and gray bars represent disordered sleep times being phase-shifted. (Reprinted with permission from Lu and Zee [28])

restores the circadian amplitude in sleep-wakefulness [21], and improves restless behavior, enhancing neuronal activity in the suprachiasmatic nuclei [22].

Bright light is a promising non-pharmacological intervention that has been applied therapeutically as a treatment for sleep disorders and for compensating circadian misalignments [23–25]. Some authors suggest the application of bright light at predetermined times to improve sleep, but especially to promote synchronization between biological rhythms (Fig. 1) and working hours in the case of workers undergoing fixed night shifts of work, as well as adapting the content of meals and encouraging the practice of physical activity of these workers [26, 27]. A meta-analysis showed that in general, light therapy is effective in treating sleep problems [24]. Having a routine is a must and will help to reset the internal clocks.

Bright light therapy is offered for the patient by portable units generating about 10,000 lux, and exposure time is about 30–45 min/day [29], and the recommendation is to keep the face directed at the light source, but not to continuously stare into the light. The patient can be eating, reading, or working on a computer while receiving light therapy. Cool color temperatures (blue wavelengths) inhibit melatonin secretion and stimulate the production of cortisol (i.e., alertness and activity hormone), while warm color temperatures stimulate the secretion of melatonin [30]. Hence, treatment must be individualized.

Therefore, there is an urgent need for standardized protocols to allow a comparison between investigations and, further, the writing of a consensus and guideline. Although there is no consensus about the ideal treatment characteristics (duration, frequency, dose, intensity) [31], there is an agreement about the timing of treatment according to the phase response curve to light [29, 32]. This bright light

administered in the morning after the lowest point of core body temperature (nadir, around 4 h) shifts the biological clock rhythm to an earlier point in time, having a phase advancing effect, whereas exposure to bright light in the evening (before the nadir of the core body temperature) shifts it to a later time, having a phase delaying effect. Roughly speaking, light in the evening normally causes phase delay, and light in the morning, phase advance. That happens because nocturnal melatonin secretion is suppressed by bright light [21] and therefore can interfere with neuroendocrine hormone production and release timing.

The effectiveness of bright light therapy is supported for the treatment of a variety of diseases: seasonal affective disorder and major depression; sleep disorders [23, 24, 33]; sleep problems related to Alzheimer's disease and dementia [25, 34]; premenstrual dysphoric syndrome [35]; bulimia nervosa [36]; and antepartum and postpartum [37, 38].

5 Circadian Disruption

It has been hypothesized that chronic circadian disruption may be a contributing factor for the increased susceptibility to diseases of the musculoskeletal system [39], including degenerative intervertebral disease and low back pain [40]. Chronic circadian rhythm disruption, as experienced by shift workers, for example, has been associated with an increased risk of various disorders and diseases, including insomnia, obesity, diabetes, hypertension, cardiovascular disease, and cancer [41–43]. The role of the circadian clock within the musculoskeletal system has only recently been studied. In animal studies, evidence shows that disruption of the circadian rhythm acts as a risk factor for the development of osteoarthritis in the mouse knee joint [44], demonstrating a possible link between environmental chronic circadian dysfunction, such as that experienced by night shift workers and frequent travelers moving across time zones, and the development of osteoarthritis over time. Those authors found that phase-shifting activated catabolic signaling and suppressed chondroprotective pathways in the knee joints of the studied animals [44]. Also, mutations in clock genes demonstrated regulation of bone volume [45], suppression of long bone growth [45], and increased vulnerability to rheumatoid arthritis [46], suggesting that the molecular clock is important for proper function within the skeletal system.

CRSWD can result from alterations in the endogenous circadian clock, such as delayed sleep phase, advanced sleep phase, free-running type, and irregular sleep-wake cycle, or from alterations in the physical environment with the endogenous clock, such as shift work disorder and jet lag, as described in the previous chapter of this book. The clinical characteristics and treatment of CRSWD are presented in Table 1.

Even though there is robust evidence that alteration in the circadian timing system is a common etiology of CRSWD, as well as a result of misalignment between endogenous rhythms and the external environment, the specific mechanisms

Table 1 Overview of Clinical Characteristics and Non-pharmacological Treatment of CRSWD

CRSWD	Clinical presentation	Preferred sleep/ wake times	Treatment
Delayed sleep phase	Difficulty falling asleep at night; difficulty waking up in the morning	Bedtime: 02–06 h; wake time: 10–13 h	Bright light therapy: 2000–2500 lux for 2–3 h starting from 06 h Dark goggles from 16 h to dusk (optional)
Advanced sleep phase	Early evening sleepiness; difficulty maintaining sleep in the morning	Bedtime: 6–9 pm; wake time: 2–5 am	Bright light therapy: 2500 lux for 4 h starting from 20 h or 4000 lux for 2–3 h starting from 20–21 h
Free-running type	Alternating periods of insomnia and excessive sleepiness or both, with short asymptomatic periods	Bedtime: delayed each day; wake time: delayed each day	Sleep hygiene
Irregular sleep-wake rhythm	Insomnia or excessive sleepiness	Irregular pattern of sleep and wake times	Increase in social interaction Physical activities Light exposure during the day Bright light therapy: 2500–3000 lux for 2 h in the morning is effective
Shift work disorder	Difficulty falling asleep or maintaining sleep; sleepiness at work	–	Bright light therapy: 5000–10,000 lux beginning early during the night shift and terminating 2 h before the end of shift (continuous or intermittent) Avoidance of morning bright light with dark goggles Wake-promoting agents: caffeine
Jet lag	Sleep initiation and maintenance insomnia; daytime sleepiness; decreased performance	–	Timed light exposure at destination: on eastward flights, minimize morning light and maximize afternoon light; on westward flights, stay awake while there is light outside

Reprinted with permission from Lu and Zee [28]. We have excluded from the original table the melatonin treatment as it only can be prescribed by a physician and was not the scope of this chapter

responsible for most of these disorders are yet unknown. As both behavioral and environmental influences may interfere within CRSWD, physiotherapeutic interventions need to address circadian physiology, along with these influences.

6 Final Words

Circadian rhythmicity of many common diseases and their rehabilitation requires to be explored to establish *chronopreventive* and *chronotherapeutic* strategies, and here we must think about PT practices incorporating these new ideas.

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Sleep Bruxism: An Overview

Cibele Dal Fabbro and Gilles J. Lavigne

Physiotherapists and dentists collaborate for years in the management of orofacial pain (OFP) and temporomandibular joint disorder (TMD) that is frequently associated with muscle and/or joint pain, joint noise, jaw movement limitation, or jaw lock. They are also among the interprofessional team contributing to improving the sleep of patients with or without orofacial pain/TMD [1].

It is about 4–8% of the general population that complains of TMD with dominance in female adolescent of middle age; a large variability is reported probably due to the type of question, duration/frequency of pain assessments, etc. [2, 3] At a lower occurrence, TMD may be associated with degenerative joint disease (DJD) including osteoarthritis in patients with TMD and juvenile idiopathic arthritis (JIA) or rheumatoid arthritis (RA) in some cases [4]. Again, a large variability in the occurrence of DJD was reported in a recent systematic review, as large as 18–77% for the TMD and 40–93% for JIA and RA [5]. It is obvious that in the presence of TMD and DJD, physicians and orofacial pain dentists have to make a clear diagnosis before the dentist and physiotherapist perform the treatment. What is usually used include medication, oral appliance therapy, manual therapy, and in some instances psychotherapy. The role of the physical therapists in managing OFP and TMD is relatively well established although some debate on its efficacy remains present [6–8].

Furthermore, according to a recent systematic review of six studies, TMD is a condition associated with poorer sleep quality [9]. Association of TMD pain to sleep disorders/poor quality plus other pain, such as headache, back pain, irritable

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bowel syndrome, and fibromyalgia, illustrates the complexity in diagnosis and treatment planning of such a condition that requires interdisciplinary collaboration [10–14]. The common clinical belief suggesting that the frequency of sleep bruxism motor activity, a condition further described below, and TMD can be associated or be in a causal relationship is largely debated and not supported by solid evidence at this time [15–18]. Muscle pain dominance over joint one may have different manifestations during sleep [19], a phenotype to be confirmed. A recent consensus study report of the *National Academies of Sciences, Engineering, and Medicine* from the USA published a solid text on many issues related to TMD; it is exploring future directions to improve our understanding and management of such a challenging clinical manifestation (http://nap.edu/25652).

The objective of this chapter is to focus on a sister condition, probably not as well known by a physical therapist, sleep bruxism (SB). It is noteworthy that SB can occur by coincidence or can contribute to exacerbating OFP and TMD, a debated topic well beyond the focus of the present review [15, 17, 18, 20, 21].

It is important to clarify that sleep bruxism (SB) and TMD are not the same entities. Some individuals may have SB without TMD, and some may have OFP and/or TMD for other reasons, such as awake parafunctional habits, acute trauma, and systemic conditions. Also, the physiopathology and mechanisms are most likely different as explained in this chapter.

1 What Is Sleep Bruxism?

Sleep bruxism (SB) is defined, based on an international group of experts, "*as repetitive masticatory muscle activity characterized by clenching or grinding of the teeth and/or by bracing or thrusting of the mandible and specified as either sleep bruxism or awake bruxism*" [22, 23]. SB can be considered a behavioral condition when it is repeated for a non-purposes reason too frequently and/or a motor condition to sleep disorders when its frequency reaches harmful or disrupting level or when SB is associated with comorbidities. Its prevalence is in the range of 5–16% in adults up to 40% in children, again depending on the type of question, methodology used, and duration covered [24–26]. Much higher prevalence is reported for younger age individuals, and it seems the condition runs in families. A study with questionnaire and polysomnography of an adult general population in Sao Paulo City, Brazil, has shown the SB prevalence of 12.4% for reports of SB complaints at least once a week, 5.4% for polysomnography, and 7.3% for both [27].

In the clinic, it is recognized by the following criteria suggested by the ICSD-3 (International Classification of Sleep Disorders), where criteria A and B should meet [28]:

A. Tooth grinding sound awareness has been reported by sleep partner or parents.
B. The presence of one or more of the following clinical signs:

   (i) Tooth wear or damage to a dental restoration

(ii) Complaints of morning jaw muscle pain or fatigue and/or temporal headache and/or jaw locking

SB can also be concomitant to headache, orofacial pain, and temporomandibular disorders and can occur with comorbidities such as obstructive sleep apnea (OSA), gastroesophageal reflux disorder (GERD), insomnia, headache, orofacial pain, periodic limb movement (PLM), REM sleep behavior disorder, and sleep epilepsy [27, 29, 30].

SB can be graded as follows (this is based on the 2018 International consensus) [23]:

(i) **possible** if the individual is aware of tooth grinding or jaw clenching within the sleep period, self-reports
(ii) **probable** if the following is or is not associated with tooth wear, clinical examination
(iii) **definitive (more confirmatory)**, if recording of masseter and/or temporalis muscles activity show a rise in electromyography (EMG) [23]

The EMG recordings are done in the sleep laboratory, polysomnography (PSG), for extensive descriptive research, or in the presence of critical comorbidities or in-home with an ambulatory system using multichannel on only one EMG. The last is mainly a screening or follow-up tool not yet considered for diagnosis. The EMG biomarker is named masticatory muscle activity (MMA), and its frequency can be counted in hours of sleep. Although such index is used in research, their clinical correspondence to clinical severity and manifestations remains to be demonstrated to the therapeutic outcome and presence of sleep comorbidities [29, 31]. Other markers may emerge for such purposes as jaw movement sensors or biomarkers listed in the following section [32, 33].

2 Putative Risk Factors and Mechanism Associated with the Genesis of SB

Even though this is an ongoing area of research with divergent opinions and evidence, few hypotheses have emerged such as emotions, autonomic cardiac and sleep stability, and genetic and other biomarkers with putative mediator roles. So far, none of these could provide a dominant *one-siz-fits-all* explanation. A complex interlaced series of influences probably need to be identified with the use of machine learning analyses and algorithms adapted for age, gender, comorbidities, and cultural differences in the context of personalized medicine.

The role of wake or diurnal emotions as a driver to impede sleep instability is one axis of interest by many investigators. In summary stress and anxiety, although they have different constructs and that their role is debated by some, were shown to be among risk factors [17, 34–36]. Several factors such as mood, concomitant pain, occupational stress (musician), female gender, less sleep duration, and acute vs.

persistent or chronic influences of risk factors must be considered in the analyses [37–39]. In the context of personalized medicine, individual reaction and adaptation are expected. The specificity of emotion, stress, and/or anxiety as a dominant trigger of rising in jaw muscle activity characterizing remains an open research domain for SB [35, 36, 40]. A recent study in TMD individuals reported that "workload and drive to perform" was associated to rise in temporalis muscle activity; such can be a predisposing factor but not a causal one and probably not specific to SB alone [41]. Children and adolescents seem to be more reactive to stress and display a higher rate of reported SB tooth grinding; children of parents under social and emotional pressure seem also at a higher risk to present tooth grinding [42]. Boys with SB tooth grinding with lip-biting habits and poor sleep quality were observed to present more severe SB [43]. Most of these findings are derived from self-reports or parents' reports grading SB as "possible" according to the proposal of the SB international consensus described above [23]. At that moment, caution in the extrapolation of such association is recommended, since parents are not always reliable in reporting awareness of SB for their children's; the concordance of parent reports with studies using EMG is rather weak, and the numbers reported for such prevalence may be influenced by geographical/cultural differences [36, 44–46].

The evidence related to SB and genetic candidates is somehow intricate to interpret. Some studies reported possible association of serotonin and dopamine in adults and others for the muscle fiber gene-related alpha-actinin-3 in children, this with specific but different polymorphism and variant, while some studies did not [47–50]. Genetics of SB is an area of research that will need more attention and probably larger sample size studies, done in a collaborative mode with saliva and/or blood collection with confirmation of definitive SB using standardized methodologies [51, 52]. Furthermore, differentiation of awake from sleep or concomitant type of bruxism was a challenging issue in published studies till now; the sample size of the subgroup was getting small and prevents any firm conclusion since the genetic studies are avid of large sample to prevent false discovery rate [53]. The search for gene candidates for SB and maybe MAD, based on phenotype and endotype, are to come, but this will probably not explain all clinical manifestations. Indeed, as for most conditions, the environment also plays an important role [54].

The role of autonomic cardiac activation in SB individuals has been known for over half a century, but more recently a series of studies have shown that SB-related onset of MMA is associated with a sudden shift in sympathetic dominance over the parasympathetic one resulting in rising in heart rate and blood pressure [55–58]. Such very time-locked activity to SB-MMA events is further supported by a proof-of-concept experimental study using a medication. Clonidine, an alpha agonist, contributes to reducing the surge of sympathetic activity associated with the onset of MMA, this about sleep arousal; such findings have been confirmed by a clinical randomized trial [59, 60]. The effect of clonidine was in part mediated through its action on the cyclic propensity of arousal during sleep, a recurring phenomenon named cyclic alternating pattern, which contributes as a permissive window for MMA onset [61]. Furthermore, a slight reduction in oxygen level was observed in

about 25% of otherwise healthy SB individuals, a finding reproduced in older SB patients with concomitant OSA [62, 63].

The role of blood, urine, salivary biomarkers such as hormonal and inflammatory (17-hydroxycorticosteroids, C-reactive protein, and fibrinogen), and also oxidative factors remains to be confirmed, although some preliminary evidence supported that more comprehensive analyses should be performed taking again into account age and comorbidities such as stress, cardiovascular risk (e.g., hypertension), and the possible contribution of sleep breathing disorders [64–67].

3 How to Manage Sleep Bruxism

Although the role of physical therapy is discussed in chapter "Sleep bruxism: physiotherapeutic approach", in this section we elected to overview SB management from a dental and medical perspective. When dentists propose a treatment for SB, first they must establish a differential diagnosis excluding the presence of other health and/or sleep conditions such as sleep apnea, insomnia, gastroesophageal reflux disorders, and rare ones such as sleep epilepsy and REM behavior disorders. Collaboration with a sleep physician is essential [29]. Plus, the clinician needs to assess the role of other conditions such as anxiety, stress, intense lifestyle, smoking, or drug use among exacerbating risk factors.

Management of SB in otherwise healthy individuals is rather straightforward with an oral appliance to act as a tooth protector. But in the presence of comorbidities such as sleep apnea or insomnia, different oral appliance designs or medications are indicated as described below. A recent systematic analysis concluded the following for managing bruxism: "*Although many of the described variables cannot be influenced by prophylactic or therapeutic means, we recommend the following patient-centered approach ('SMS therapy'): self-observation, muscle relaxation, stabilization (Michigan) splint*" [34]. Then the role of physical therapist within a multi-professional team needs to be precise as described below (Table 1) and this more importantly in the presence of sleep comorbidities [1, 68].

Table 1 Route to manage sleep bruxism

After a medical (apnea) and dental (bruxism, orofacial pain) diagnosis, the management should include:
(i) By dentists, oral appliances such as occlusal splint in individuals without sleep breathing condition, otherwise mandibular advancement appliance are recommended
(ii) By a physical therapist, manual therapy, muscle-stretching exercises and education for home exercise, sleep position, sleep hygiene
(iii) By a psychologist, advanced sleep hygiene advice under cognitive behavioral therapies
(iv) By physician medication, if insomnia and prescription of CPAP, sleep positioning devices, oral appliance and/or medication if sleep apnea and proton pump inhibitor if GERD

4 Oral Device

4.1 Occlusal Appliance or Splint

An occlusal splint (OS) is among the most accepted therapy for SB to prevent its harmful effect on the dentition [69, 70]. They are made in translucent synthetic material adapted to the upper or lower dental arch. For SB they act as a tooth protector against forceful jaw movements that contribute to destroying tooth structure or dental restoration. That situation can be exacerbated in subjects with dry mouth due to the absence of lubrication, GERD, oral breathing, and poor tooth enamel density [71]. In the presence of risk of snoring or sleep-disordered breathing, it is advised to avoid upper-maxillary splints since they may contribute to exacerbate the disrupted breathing [72, 73]. There is also over-the-counter or mail-ordered OS; these are at a low cost; however, caution is recommended in their use for many reasons such as the hiding of dental caries and/or periodontal infection, tissue damage, occlusal changes, tooth displacement, choking hazards, and, as cited above, exacerbation of breathing disorders [74].

5 Mandibular Advancement Device

The mandibular advancement devices (MAD or MAA, last A for appliance) have been used extensively to manage snoring and OSA as a complementary tool to positive airway pressure (PAP) devices [29, 75, 76]. MAD is a recognized therapy for individuals with mild to moderate OSA and for the ones with severe OSA who cannot tolerate the PAP mask [77]. Success to MAD is associated with some specific phenotype such as "*lower age, female, lower body mass index, smaller neck circumference, lower apnea-hypopnea index, a retracted maxilla and mandible, a narrower airway, and a shorter soft palate*" as recently reported in a systematic review/meta-analysis [78]. It is also associated with higher adherence to treatment due to better comfort and ease of use. The oral health of patients should be under control, with no caries, and no periodontal-gum disease. There were some concerns about side effects such as tooth displacement and skeletal changes, a fact to be recognized, and a warning was given to patients but not as critical for most of them, and for exacerbation of TMD, but most recent evidence tends to diminish the impact on TMD [79–81].

The use of MAD for SB was first done to assess if a change in airway patency can contribute to reducing MMA in otherwise healthy subjects, a mechanism that was not yet confirmed in the absence of OSA [76]. A recent analysis in OSA patients showed it contributes to reducing MAD associated to sleep respiratory arousal [82]. The MAD is then mainly recommended for SB patients in whom snoring is concomitant or sleep-disordered breathing risk suspected; sleep physician collaboration makes all sense in such situation [29]. Two studies showed

beneficial use for SB, reduction of MMA, with MAD use for 30 days and up to 3 months [83, 84].

6 Medication

No definitive medication is indicated to manage SB; most lack solid and long-term evidence, and they have side effects restricting their use [65, 85]. Moreover, none are specifically approved by governmental agencies as a treatment for SB (e.g., FDA in the USA). Botulinum toxin seems to reduce the strength of jaw muscle contraction but not the onset of MMA events [86–89]. Clonazepam was suggested as an alternative, but recent reports diminish the likelihood of supporting its efficacy; furthermore, it is a medication with an addictive risk requiring caution in its prescription [59].

As listed above, clonidine may be an alternative in the presence of documented sleep and arousal instability, and again the risk of hypotension requires vigilance when it is prescribed [60]. Dentists should not prescribe such cardioactive medication, since it is belong to physician expertise, who should start with the lowest dose as available and monitor their patients for risk of hypotension and falls.

So far, although it is used by patients, to our knowledge no evidence supports the use of cannabis (CBD or THC derivatives) for SB. Gabapentin was described to be beneficial in a comparative occlusal splint trial; since that publication, no further evidence has emerged to our knowledge [90]. Few psychotropic medications have some SB exacerbation risk (odds ratio from 2.1 to 3.6 for antidepressants such as duloxetine, paroxetine, and venlafaxine and 14.7 for the psychostimulant methylphenidate); the low level of evidence requires caution on such association, and future studies with MMA recording on the long term will be welcome [91, 92].

7 Stimulation

Biofeedback has been used for decades as a method to alter SB oral behavior. A recent systematic review/meta-analysis grades the level of evidence and does support that contingent electrical stimulation (CES), acting like aversive conditioning, and contributes to reducing SB when used over a few nights [93]. Again, long-term benefit needs to be demonstrated. In absence of evidence, a consensus suggested the duration of CES be used by one commercial device [94]. An important clinical aspect related to acceptance of CES is that no pain nor sleep arousal was induced as a secondary effect [95]. Independent trials are awaited to provide replication of current evidence on the benefit of CES on SB.

Another emerging approach is transcranial magnetic stimulation (TMS); so far little evidence is available to support its use for SB [96, 97].

8 Final Words

In the era of precision medicine, (i) "differential" diagnosis skills with a comprehensive assessment of risk factors, (ii) multidisciplinary/"inter-sector" health management strategies, and (iii) contribution of patients as a partner are essential to achieve clinical success.

The role of physical therapists in the interprofessional management of sleep and pain disorders is essential. However, for SB the lack of evidence supporting the value of physiotherapy suggests caution in differentiating between SB and DTM (or OFP) during the diagnosis and also in choosing the best management therapies.

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Sleep Bruxism: Physiotherapeutic Approach

Cinthia Santos Miotto and Amélia Pasqual Marques

There is not much evidence on the role of physical therapy on sleep bruxism (SB) management. Some research has been done showing the results of physiotherapy on the pain control of individuals with temporomandibular disorders (TMD) related possibly to SB [1].

A systematic review published in 2018, which included 24 randomized and non-randomized and controlled and noncontrolled clinical trials and interventions, focused on physical therapy as a treatment for SB or awake bruxism and concluded that there is very low-quality evidence that diverse methods used in physical therapy improve muscle pain and activity, mouth opening, oral health, anxiety, stress, depression, temporomandibular disorder, and head posture in individuals with bruxism. This finding is mainly a result of the poor methodological quality of most of the studies [2].

Although muscle-stretching exercises are a recommended part of several international guidelines for musculoskeletal disorders and may be effective in the management of the jaw muscle activity that gives rise to bruxism, it was shown in a randomized controlled trial using masticatory muscle activity from polysomnography as an outcome measure. Masticatory muscle stretching was not effective in reducing the frequency of SB events in the absence of pain and/or TMD [1–3].

However, most studies of muscle-stretching exercises have mainly focused on their influence on performance (e.g., range of motion, coordination, and muscle strength) of the limb or trunk muscles of healthy individuals or individuals with sports-related injuries. Very few have investigated the stretching of the human

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masticatory muscles and non-muscle-stretching exercises in the management of SB. So far there is no prescribed treatment for SB, and conservative and reversible approaches have been used. Among them are physical therapy modalities that focus on reducing the adverse effects of SB on the stomatognathic system and guiding individuals with SB on the importance of awareness of this habit to decrease its frequency and severity [1–3].

The etiology of bruxism is controversial, which makes it difficult to identify a direct cause-effect relationship for its triggering. However, it can be considered a multifactorial disorder, with different factors involved: morphological, psychosocial, and pathophysiological [1–3]. Among the factors related to SB, several investigations highlight that psychosocial factors such as mood disorders and stress play a role in the occurrence, perpetuation, frequency, and severity of SB – especially those based on clinical diagnosis. Although studies based on chin electromyography and/or polysomnography at the sleep laboratory are insufficient to declare that such associations exist in SB, stress and anxiety are related to almost 70% of cases [1–3].

Therefore, it is important to focus on the negative association of the quality of sleep and SB, which can be noticed by the report of the patient having difficulties in sleeping, excessive daytime sleepiness, and insufficient and non-refreshing sleep. They may also complain of insomnia and sleep fragmentation. Sleep duration of fewer than 8 hours, changes in subjective quality, and poor sleep efficiency were associated with SB and suggest impairment of sleep quality, repercussion in daily life activities, and exacerbation of psychosocial factors (e.g., stress, anxiety, and depression), which can consequently contribute to the intensification of SB [1–3].

Among the diagnostic methods for bruxism, polysomnography (PSG) with or without audiovisual recording, performed in the sleep laboratory, and electromyography (EMG) conventional and portable are two of the best ways to establish uniformly and accurately the presence of SB. Clinical diagnosis is a simple, easy-to-apply, affordable, low-cost method and widely used in clinical practice and in studies on bruxism [1–3].

Consequently, anamnesis and clinical examination are used to check for signs, such as the presence of abnormal tooth wear, and specific questionnaires confirm the presence of vigil bruxism (teeth squeezing perceived by the individual himself) and/or sleep (teeth squeaking sound, usually noticed by family members or roommates) in the last six months [1–3].

1 Resources

Despite no consensus or guidelines, some evidence of the physiotherapeutic approach includes resources such as electrotherapeutic transcutaneous electrical nerve stimulation (TENS), microcurrent electrical nerve stimulation (MENS), and biofeedback (BFB) by electromyography (EMG) with visual, sound, and electrical stimuli; postural awareness by movement or Feldenkrais method; muscle relaxation, such as relaxation training and muscle awareness; cognitive behavioral

therapy (CBT), such as progressive muscle relaxation and imagination; therapeutic mandibular exercises, muscle stretching, and with facial exerciser; and acupuncture and manual therapy, such as massage therapy [2, 4–21] (Table 1).

Similar to MENS and BFB by visual EMG, TENS improves the pain of the masticatory muscles and generates local relaxation of these muscles respectively [4, 7,

Table1 Evidence on physiotherapeutic treatment for sleep bruxism

	Author	Study	Physiotherapeutic treatment	Parameters (number, duration, and attendance)
Electrical stimulation	Treacy [7]	Blinded RCT	MART/TENS	MART *vs.* TENS *vs.* TENS placebo: 20–30 min session, 20 sessions, 2×/week
	Alvarez-Arenal et al. [4]	Blinded RCT	TENS	TENS: 15 sessions of 45–60 min every 2 days *vs.* Occlusal plaque: 45 days, 24 h/day
	Rajpurohit et al. [11]	Ct	TENS/MENS	TENS *vs.* MENS: 20 min session, 7 sessions
	Jadidi et al. [14]	Blinded cross over RCT	Electrical stimulation	Contingent electrical stimulation: Grindcare® device: 10 weeks
	Jadidi et al. [15]	Pilot study: double-blinded RCT	Electrical stimulation	Contingent electrical stimulation: 5 nights
	Raphael et al. [5]	Ct	Electrical stimulation	Contingent electrical stimulation *vs.* Grindcare®: 6 weeks
	Nishigawa et al. [12]	Pilot study	Electric labial stimulation	Electrical lip stimulation: 5 nights, 1st night: no stimulus, 2nd to 5th night: stimulus every 1 h in the middle of the sleep period
Cognitive behavioral therapy	Restrepo et al. [8]	RCT	CBT	CBT, competency reaction and directed muscle relaxation: 6 months
	Ommerborn et al. [9]	Blinded RCT	CBT	CBT, problem solving + progressive muscle relaxation + night biofeedback + leisure and fun training: 1 h 50 min session,12 sessions *vs.* Occlusal plaque: 12 weeks
Acupuncture	De La Torre et al. [18]	Ct	Acupuncture	acupuncture: 1 session
	Dallanora et al. [10]	Ct	Acupuncture	acupuncture: 1 session

(continued)

Table 1 (continued)

	Author	Study	Physiotherapeutic treatment	Parameters (number, duration, and attendance)
Exercise/ manual therapy	Quintero et al. [6]	Blinded RCT	Feldenkrais method	Feldenkrais method: 3 h session, 10 sessions *vs.* no intervention
	Amorim et al. [2]	RCT	Massage/Muscle stretching exercises/ Progressive muscle relaxation/ Imagination	Massage + muscle stretching exercises *vs.*progressive muscle relaxation + imagination: 40 min session, 12 sessions *vs.* Dental treatment: 2 h session, 2 sessions
	Makino et al. [21]	Ct	therapeutics exercises + CBT	therapeutics exercises + psychological intervention *vs.* therapeutics exercises: 4 sessions 10 min therapeutics exercises + therapeutics exercises at home 1×/day *vs.* control
	Jardini et al. [19]	Ct	Pro-fono® facial exerciser	Pro-fono® facial exerciser (maximum 15 min/day at home): 1–3 series of 15–20 repetitions of isotonic contraction exercises of closing the device by compression force of the cheeks, followed by relaxation and 1–3 sets of 15 s of exercises in an isometric contraction of the device closure, keeping it stuck by the compression force of the cheeks
Biofeedback	Watanabe et al. [16]	RCT	BFD by EMG	BFD by EMG *vs.* control: 4 consecutive days for 5 h, day 1–4: EMG recording, and days 2–3: BFB
	Conti., et al [17]	Pilot study: blinded RCT	BFD by contingent electrical stimulation	BFD by contingent electrical stimulation, Grindcare® device *vs.* inactive: 10 nights
	Wieselmann-Penkner. [13]	Pilot study: RCT	BFD by EMG/ TENS	BFD by EMG *vs.*TENS: 20 min session, 3 sessions, 1×/ week
	Needham et al. [20]	Pilot study	BFD by EMG	BFD by EMG (Grindcare® device): 5 weeks

RCT randomized controlled trial, *Ct* clinical trial, *TENS* transcutaneous electrical nerve stimulation, *MART* muscular awareness relaxation Training, *MENS* microcurrent electrical nerve stimulation, *CBT* Cognitive behavioral therapy, *EMG* electromyography, *BFD* Biofeedback, *h* hour, *min* minutes

11, 13]. BFB by EMG suggests a promising method for sleep and wakefulness bruxism, pain, and oral health quality [5, 9, 12–17, 20].

There is an improvement in the anteriorization of the head of children with bruxism by postural awareness by movement. This technique when compared to TENS showed greater effectiveness in reducing pain and increasing mandibular opening, thus improving anxiety, pain, and mandibular opening in children with bruxism [6–8]. For awake bruxism, the mandibular exercises combined with CBT have demonstrated to be effective for neck pain and mandibular movement when compared to isolated exercises or CBT [21]. The use of a facial exerciser has improved the pain symptoms for the buccinator muscle and masseter muscle activity [19]. Furthermore, acupuncture was shown to be effective in decreasing masticatory and neck muscle pain and activity [10, 18]. The study in individuals with SB indicate that massage therapy associated with dental treatment decreases orofacial pain and that CBT, based on problem-solving training, progressive muscle relaxation (PMR), BFB by sound EMG and leisure and fun training, decreases SB activity, its associated symptoms, and increased stress coping strategies [9, 22]. BFB by portable EMG seems to be more effective than dental treatment in individuals with mild SB [17].

Therefore, there is a growing interest in the application of the biopsychosocial model proposed by the International Classification of Functioning, Disability, and Health (ICF) in chronic musculoskeletal conditions, such as pain and bruxism by health professionals, such as physiotherapists. Physical therapists recognize the importance of addressing physical and/or cognitive-behavioral aspects in their interventions, also associating them with other treatments [1–3] and other professions.

2 Final Words

SB has been considered the most harmful nonfunctional activity to the stomatognathic system with high prevalence, multifactorial nature, and numerous consequences not restricted to dental problems and the stomatognathic system, such as poor quality of sleep and the sleep-pain association (see chapter "Sleep and Chronic Pain Interlaced Influences: Guidance to physiotherapy practice"). There is a need for health services focused on interdisciplinary, conservative, differentiated, and strategic therapeutic approaches, as physiotherapeutic interventions focusing on the biopsychosocial model associated with other treatments, with the purpose of preventing and/or controlling SB and its clinical manifestations.

Despite the scarceness of studies on physiotherapeutic interventions for SB, differentiated therapeutic approaches focusing on the biopsychosocial model allow a broad view of individuals with pain and SB, without dissociation between the mind and the body and with the integration of biological and psychosocial factors. These treatments must aim at the improvement of pain, the range of motion of mandibular opening, mood symptoms such as anxiety and depression, stress, oral health quality,

and sleep – which justifies the use of physiotherapy interventions concomitant with other treatments for the management of SB.

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Obstructive Sleep Apnea: An Overview

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Obstructive sleep apnea (OSA) is a sleep-related respiratory disorder characterized by intermittent episodes of upper airway collapse during sleep. The events are predominantly obstructive, with partial (hypopnea) or complete (apnea) occlusion of the upper airway (Fig. 1), resulting in reduced oxyhemoglobin saturation and sleep fragmentation [1].

The pathophysiology of OSA is multifactorial and includes reduction of the upper airways, resulting from both anatomical narrowing of the pharynx and functional alterations such as obesity (infiltration of fat in the neck region), maxillofacial injury or structural alterations [3, 4], increased pharyngeal collapsibility due to reduced neuromuscular compensation (decrease of the pharynx dilatory musculature response), lack of protective reflex of the pharynx during sleep [5], reduction of the awakening threshold, increase of the ventilatory response, decreased pulmonary volume and caudal traction of the pharynx, and fluid displacement to the neck

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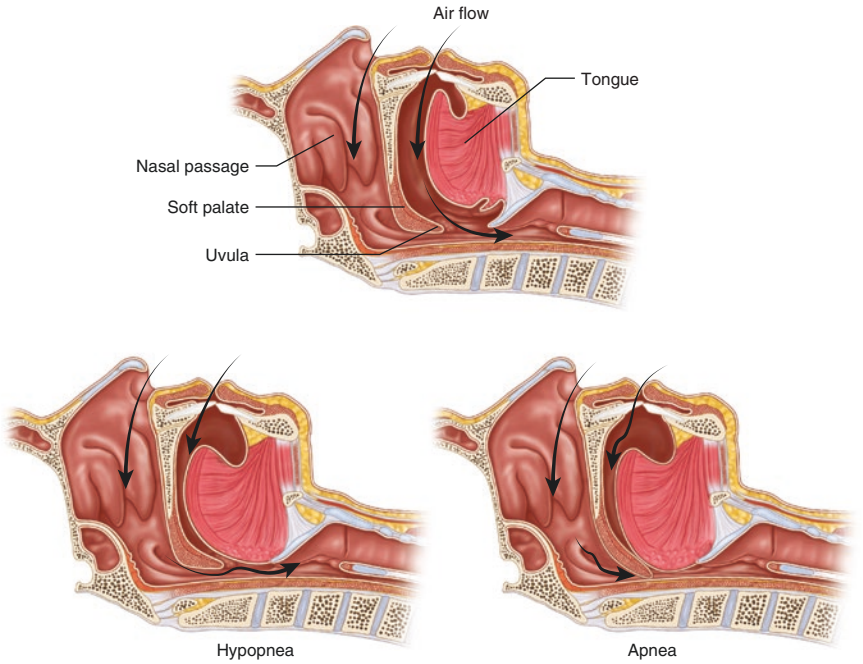

Fig. 1 Partial and complete upper airway obstruction, resulting in hypopnea and apnea, respectively. (Reprinted with permission from Somers et al. [2])

during the night [6–9]. Decreased upper airway size and increased resistance may result in snoring, a vibration of the soft palate, uvula, and/or pharyngeal walls.

OSA also has an individual variability regarding the clinical presentation of patients. The main risk factors are the male sex, age progression, obesity, craniofacial structure, and postmenopausal stage, and in the latter two factors the genetic and ethnic constitution may have a determining role.

OSA is considered an important public health problem, affecting about 5–15% of the general population, increasing linearly with age up to at least 60–65 years [10, 11]. The prevalence of OSA is alarmingly high and varies widely between studies, from 0.5 to 32.8%. This disparity is due to methodological differences and limitations with different samples (e.g., different ethnicities), inconsistencies in the techniques used to monitor sleep and breathing, and variability of diagnostic criteria for OSA. An epidemiological investigation conducted in the city of São Paulo found a prevalence of 32.8% of OSA in individuals between 20 and 80 years by polysomnography [12]. Epidemiological studies have shown an increase in prevalence ranging between 14% and 55% in the last two decades, affecting mainly middle-aged men [13].

In the current International Classification of Sleep Disorders (ICSD-3)[14], the diagnosis of OSA is defined by the presence of items A and B or C:

A. Presence of one or more of the following items:

   1. Complaint of drowsiness, non-repairing sleep, fatigue, or insomnia symptoms
   2. Awaken with breathing suspension, panting, or asphyxiation
   3. Bed partner or another observer report usual snoring, interruptions of breathing, or both during the patient's sleep
   4. Diagnosis of hypertension, mood disorder, cognitive dysfunction, coronary artery disease, stroke, congestive heart failure, atrial fibrillation, or type 2 diabetes mellitus

B. Portable polysomnography or polygraph with:

   1. Five or more predominant obstructive events (Fig. 2): apnea, hypopnea, or RERA (respiratory effort-related arousal) per hour of sleep during polysomnography or per hour in monitoring

C. Portable polysomnography or polygraph with:

   1. Fifteen or more predominant obstructive events (apnea, hypopnea, or RERA) per hour of sleep during polysomnography or per hour at monitoring

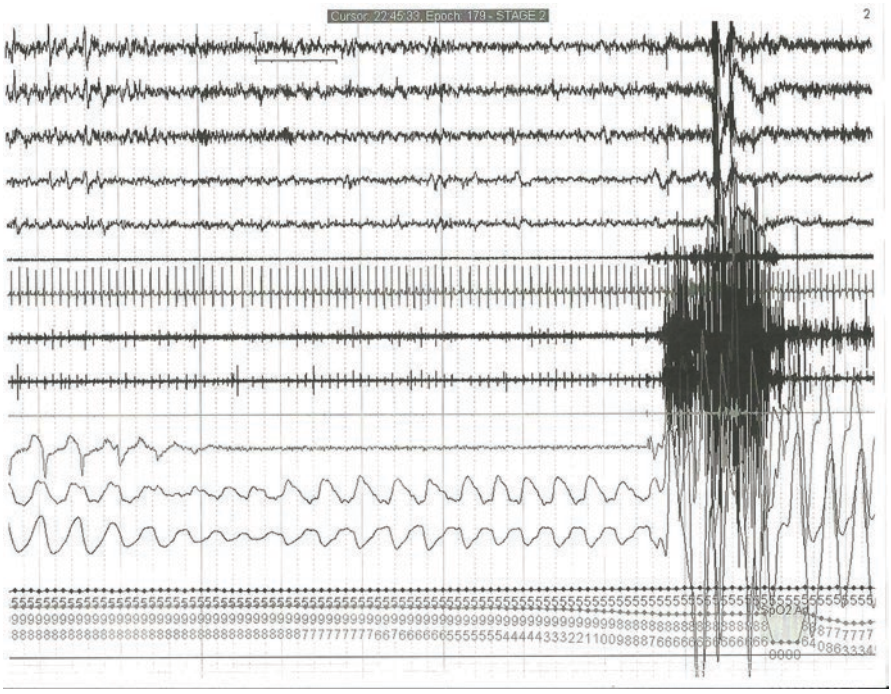

Fig. 2 Representation of an OSA event in a 30 seconds epoch seen in this window from a polysomnographic examination. (Image courtesy from Dr. Fernando Morgadinho Santos Coelho.)

1 General Treatments

Several treatments are available for OSA, but the choice should be based on severity, including symptoms, complications, and polysomnographic findings. In moderate to severe OSA, positive airway pressure (PAP) is the gold standard treatment. Other therapeutic modalities such as behavioral measures, positional therapy, and oral devices are available and involve an interdisciplinary approach. Surgical treatment in well-selected patients may be indicated.

Clinical and behavioral measures should be offered to all patients with OSA even in those treated with other therapies, such as PAP. Obesity is one of the main risk factors for OSA, so weight loss should be strongly recommended, and a nutritionist may be suggested. Studies with dietary intervention for weight loss along with prescription by a physical therapist for an active lifestyle are welcome in patients with OSA. In patients with mild OSA, the prescription of very low calorie together with lifestyle counseling showed an average weight reduction of 10.7 Kg, and for apnea-hypopnea index (AHI) of 4 events per hour, demonstrating that the greater the weight loss, the greater the decrease of AHI [15]. Another investigation assessed whether PAP influenced weight loss in patients with moderate and severe OSA [16]. For that, three types of intervention were instituted for 24 weeks: (i) use of PAP, (ii) management of weight loss, and (iii) combined intervention of PAP plus weight loss. The isolated PAP group did not present weight loss but presented a reduction of insulin resistance. The other two groups showed a significant weight reduction (~5 kg) in addition to decreased triglycerides and insulin resistance in the group with PAP plus weight loss [16]. This study showed that PAP can enhance metabolic improvement of weight loss.

In patients who do not respond to dietary intervention, bariatric surgery may be indicated. Weight loss through bariatric surgery showed a decrease in OSA in 83.6%–88.5% of patients, with an average reduction of the AHI of 34 n°/h, being the most effective gastric bypass [17]. However, even with considerable weight loss, many patients persist with residual OSA [18] and changes in OSA severity, decreasing it. Bariatric surgery may be an adjuvant in the treatment of OSA, except for the risks of perioperative complications due to OSA and recognition of the possibility of residual OSA.

Behavior measures should also be taken together along with OSA treatment. Alcohol, for example, aggravates OSA by having a dose-response effect [19]. Untreated OSA patients should avoid ingestion of alcohol because it leads to increased duration and frequency of apnea aggravating desaturation during sleep. In addition, other effects of alcohol include reducing sleep latency onset and the REM sleep stage.

Some medications may also aggravate OSA, such as benzodiazepines, benzodiazepine agonist receptors, opioids, and barbiturates, and should be avoided especially in those not under treatment. In cases where such medications are necessary, it is important that the monitoring is performed with adjustment in the prescribed treatment (e.g., increased PAP pressure, adequate mandibular advancement in the

case of the oral appliance, etc.). Attention should also be given to medications that increase weight and may aggravate OSA such as some antidepressants and antipsychotics.

2 Myofunctional Therapy

It is an alternative therapy indicated in the presence of orofacial myofunctional disorders associated with mild to moderate OSA associated or not with the use of PAP or intraoral device. Studies have demonstrated, in addition to the improvement of the orofacial myofunctional condition, the quality of life with reduction of the AHI and increased saturation of oxyhemoglobin [20]. When concomitant to CPAP theraphy, can improve CPAP adherence, reducing the require pressure. In many countries, myofunctional therapy is provided by speech therapists.

3 Oral Appliance

An oral appliance, or oral device, is like an orthodontic retainer, a noninvasive treatment, and the patient uses it only at sleep, to support the jaw in a forward position, therefore increasing the upper airway space. Research shows that oral appliance therapy is an effective treatment option for snoring and OSA. They are nocturnal oral devices that stabilize the upper airways and increase their diameters, inducing a decrease in the collapsibility of the pharynx. There are many types, such as maxillary expansion; mandibular advancement devices, which induce the advancement and distraction of the lower jaw; and tongue retaining devices that primarily keep the tongue from falling to the back of the upper airway (Fig. 3). They are made by dentists specializing in dental sleep medicine.

Therefore, the practical parameters of the American Academy of Sleep Medicine together with the American Academy of Sleep Dentistry stipulate that oral devices are not indicated for all OSA patients [23] and are indicated for primary snoring, upper airway resistance syndrome (please refer to chapter "Upper Airway Resistance Syndrome: An Overview"), mild OSA, moderate OSA, and severe OSA that are intolerant to PAP therapy. For example, patients with mild OSA showed no difference in the improvement of AHI between oral devices and PAP therapy [24]. However, in those with moderate or severe OSA, PAP was better in reducing AHI and hypoxemia compared to oral devices [24]. A moderate degree of evidence of the effect of the oral devices of the custom adjustable mandibular advancement type was observed in reducing the AHI, increasing oxygen saturation, decreasing nocturnal awakenings, and improving daytime sleepiness and quality of life compared to the condition before the use of the oral device. Therapeutic adherence to oral devices is generally higher, and its discontinuity is lower compared to PAP [25]. The most common adverse effects are dry mouth,

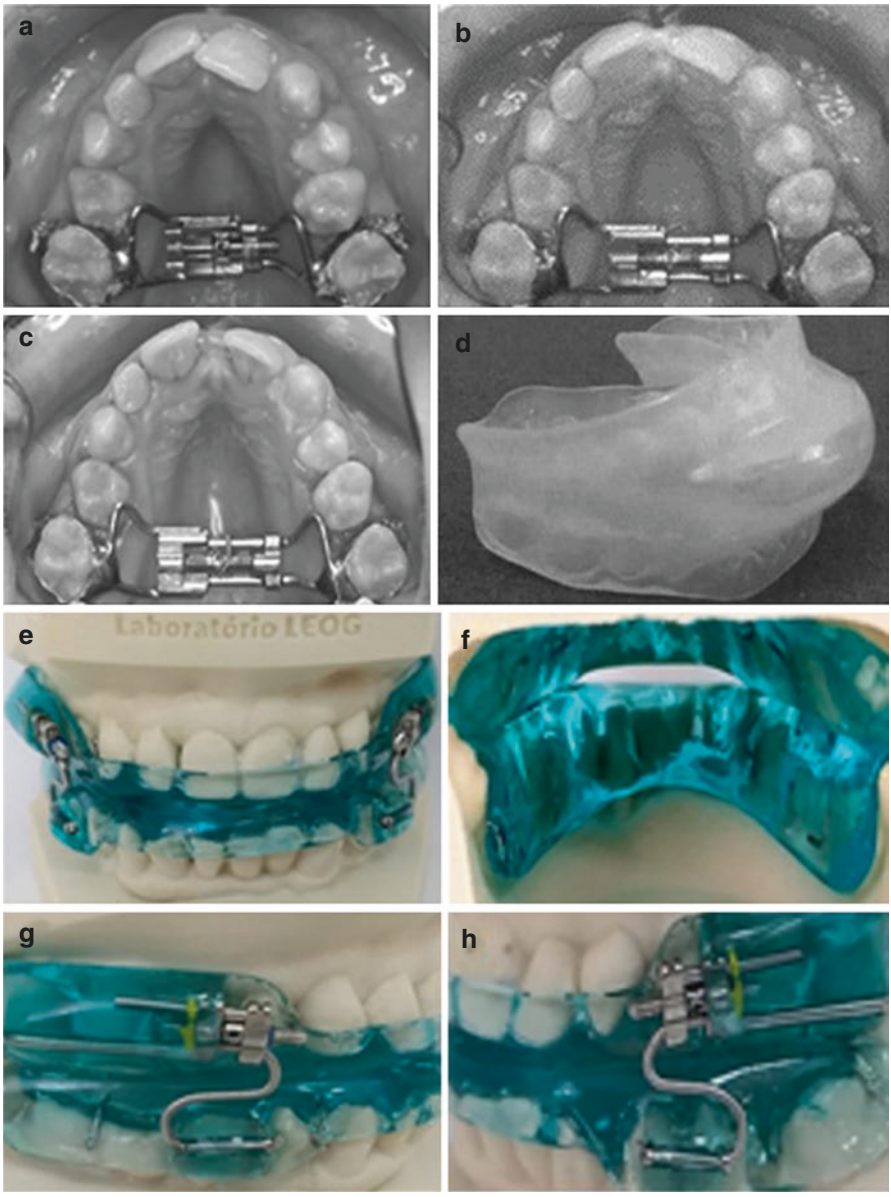

Fig. 3 Oral appliance devices: (**a**–**c**) Occlusal sequence of treatment with rapid maxillary expansion from crowding in the upper central incisors (**a**) to a wide space (**c**); (**e**, **f**) adjustable mandibular repositioning device, front view (**e**), from inside (**f**), right (**g**), and left (**h** sides; and **d**) tongue retaining device, designed to keep the tongue in an anterior position during sleep. This device secures the tongue by means of negative pressure in a soft plastic bulb. A flange, which fits between the lips and teeth, holds the device and tongue anteriorly in the oral cavity. (Reprinted with permission from: (**a**–**c**) Pirelli et al. [21]; (**d**) Higurashi et al. [22]; (**e**–**h**) (Image courtesy from Dr. Eliana Lottenberg Vago (original figure)))

excessive salivation, mandibular discomfort, increased sensitivity to teeth, dental mobility, and occlusal changes. Among the contraindications, we have periodontal disease, acute temporomandibular dysfunction, uncontrolled generalized convulsions, and limited mandibular advancement. Detection of oral device response predictors (positional apnea, BMI, younger patient), as well as accurate determination of the optimal degree of mandibular advancement, may improve the effectiveness of this treatment. It is important to perform follow-up PSG to assess the effectiveness of the oral devices because subjective reports of improvement may not be safe.

4 Surgical Treatment of OSA

The surgical treatment may be indicated with curative purpose, seeking to control the disease, and it may also be indicated as a supporting role, to facilitate adherence to the PAP or oral devices. Recently, studies on different OSA phenotypes started identifying different clusters to try to customize the treatment of OSA and also to understand why surgical treatment has distinct responses in "apparently similar" patients [26]. These different possibilities of responses from the surgical treatment must be presented to the patient at the time of the surgical indication, to suit their expectations within the treatment.

Different surgical modalities and techniques can be performed in the different levels of upper airways, both in the soft parts of the pharynx and in the facial skeleton, such as pharyngoplasty, maxillomandibular advancement and hypoglossal nerve stimulation.

The risks of surgical treatment should be considered, considering the patient's age, the severity of OSA, and the presence of comorbidities such as obesity, diabetes, hypertension, and cardiopathies. The risks of complications are higher in patients with OSA, and care should be taken with pre-anesthetic and anesthetic drugs, orotracheal intubation, extubating in the immediate postoperative period, upper airway edema, and medications prescribed in the postoperative period.

4.1 Nasal Surgeries

The most frequent procedures performed in the nose in the treatment of OSA are septoplasty and partial inferior turbinectomy. They aim to clear the nose to improve nasal breathing. Several studies have shown that nasal surgery, when performed in isolation, has little impact on the improvement of AHI, but there is evidence of improvement in the subjective quality of sleep and may help in the adaptation of PAP [27]. These procedures are often performed in association with other surgical procedures, especially pharyngeal surgeries.

4.2 Pharynx Surgeries

There are several surgical techniques performed in the pharynx, which clear the airway and decrease its collapsibility. Older techniques, such as uvulopalatopharyngoplasty [28], which were widely performed in the 1980s and 1990s, without any criteria for patient selection, have demonstrated over the years controversial results and high incidence of side effects and sequelae [29]. In recent decades, with the best knowledge of the pathophysiology of OSA and seeking to decrease the rates of adverse effects, new surgical techniques have emerged, which act more on the pharynx lateral walls, sparing the midline, such as lateral pharyngoplasty and expander pharyngoplasty, among others [30]. Recently, criteria for a better selection of patient candidates for surgical treatment have been valued, seeking better success rates. Friedman staging [31], which uses modified Mallampati, palatine tonsil size, and body mass index to classify patients, has been used in the selection of patients for the indication of pharyngeal surgeries.

Minimally invasive palatal procedures are different surgical modalities (soft palate radiofrequency, palatal implants, and sclerotherapy), which can be performed on an outpatient basis with local anesthesia and have as objectives the increase of the tonus and the stiffening of the soft palate leading to the improvement of the snoring. They are indicated in patients with primary snoring or mild OSA and, generally, in individuals with normotrophic or amygdalectomized palatine tonsils, with contraindication for use of oral device and history of intolerable PAP therapy [32]. The results are variable; usually, there is an improvement of snoring in the short term; however, the success rate decreases in the medium and long term.

In the hypopharynx, procedures performed at the base of the tongue are indicated in cases of suspected collapse in this region with increased volume of the base of the tongue, mainly increased lingual tonsil. When indicated, these procedures are often performed in association with other surgical procedures (multilevel surgeries).

4.3 Hypoglossal Nerve Stimulation

The genioglossus muscle, innervated by the hypoglossal nerve, is one of the main dilating pharynx muscles and is directly involved in the pathophysiology of OSA, contributing to prevent the pharynx from collapsing during sleep. In recent years, a new treatment modality has been proposed, in which a hypoglossal nerve stimulator is implanted unilaterally and is able to synchronize stimuli with respiratory effort, preventing the collapse of the pharynx that leads to respiratory events during sleep [33]. The results seem promising; however, it is a high-cost treatment, and more long-term studies are needed to better evaluate its results.

4.4 Skeletal Surgery

Several skeletal procedures are performed for the treatment of OSA, such as suspension of the hyoid bone, advancement of the genioglossus muscle, and maxillomandibular advancement. The first two are usually performed in association with other procedures in multilevel surgeries. Maxillomandibular advancement is a treatment that presents excellent results in the treatment of OSA [34] and is generally indicated for patients with accentuated OSA who were unable to adapt the CPAP or in patients with other grades of OSA who present significant skeletal abnormalities.

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Obstructive Sleep Apnea: Physiotherapeutic Approach

Moara Gomes da Rocha Cruz and Rafaela Garcia Santos de Andrade

1 Understanding the General Concept

There are many treatments available for obstructive sleep apnea (OSA) that consider the severity of the disease. Treatment involves simple measures such as weight loss in those overweight or obese individuals, avoiding alcohol or sedatives [1], and sleeping in the lateral position for patients with positional OSA.

The positional therapy (tennis ball technique or vibrating chest belts (Fig. 1)) has great results with an important reduction in the supine sleep time and consequently in the apnea-hypopnea index (AHI) [2]. Mandibular advancement devices are widely used in OSA treatment, with greater benefits in mild and moderate sleep apnea [3]. In some apnea patients, surgical techniques are also available and have good results when appropriately indicated [4]. More recently, myofunctional therapy appears as an option to treat mild and moderate OSA patients. This technique involves oropharyngeal exercises indicated by a speech therapist [5, 6].

The application of positive airway pressure (PAP) during sleep is the "gold standard" for the treatment of patients with moderate (AHI $\geq$ 15 events/hour) to severe (AHI $\geq$ 30 events/hour) OSA. Treatment of OSA with PAP was first described by Sullivan et al. in 1981 [7]. The key idea was that PAP applied for nasal route acted

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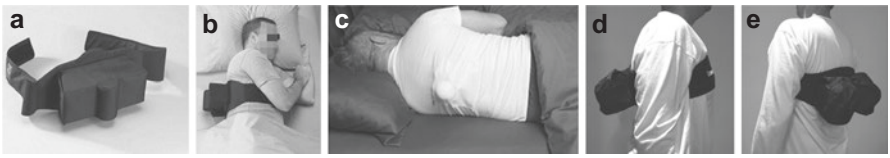

Fig. 1 Devices for positional therapy. (**a**) Chest belts; (**b**) lateral view; (**d** and **e**) inflatable dampers adjusted to provide the best curved positional support around the body. The belt and shock absorbers move with the body and prevent the supine position; and (**c**) tennis ball technique. (Image courtesy from Dr. Rafaela Andrade (**a**, **b**) and from Dr. Vivien Schmeling Piccin (**c**–**e**))

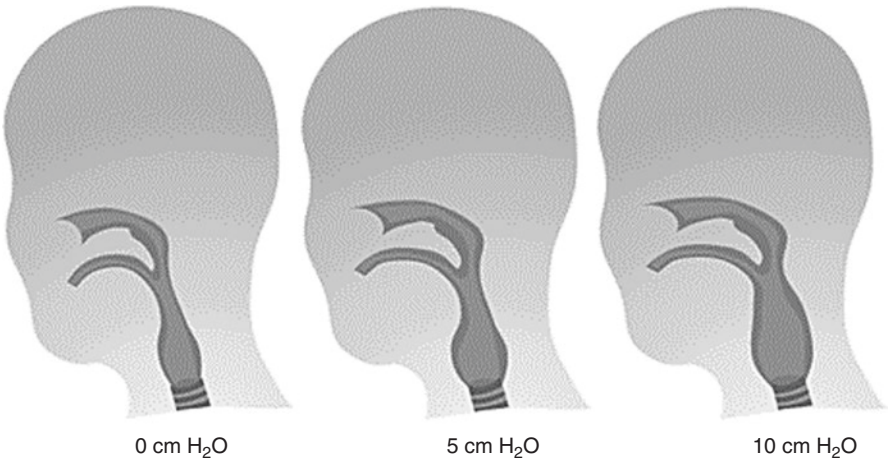

Fig. 2 A schematic illustration of a narrowed upper airway susceptible to collapse without PAP (left). A more open and stable upper airway with a PAP pressure of 5 cmH_2O (center), and with a pressure of 10 cmH_2O we can see a completely open and stable upper airway (right). (Image courtesy from Dr. Rafaela Andrade)

as a pneumatic splint to keep the pharynx stable and open during all sleep time and, consequently, maintain the upper airway patency (Fig. 2). The nasal PAP moves the soft palate and the tongue anteriorly as we can see in Fig. 3.

The reasons for the collapse of the upper airways during sleep in patients with OSA are multiple and not completely understood. The collapse of the upper airways depends on anatomical characteristics, arousal threshold, ventilatory instability during sleep, and neuromuscular control of the upper airway caliber [8]. The Starling resistor model can help to explain this mechanism of collapse and clarify the PAP concept. The Starling resistor consists of two rigid tubes connected by a collapsible tube [9]. The two rigid (bony and cartilaginous) tubes represent the nose and the trachea. The pharynx, which is a collapsible (muscular) part, makes the link (Fig. 4). If we image an overweight man, sleep during the night with complete muscular relaxation, in a supine position with gravitation action, the nasal and tracheal pressure probably was not able to maintain the pharynx open, this tube will be to collapse because of the external forces that will be higher than the nasal and tracheal forces. In this model, the pharyngeal critical pressure is the pressure at which

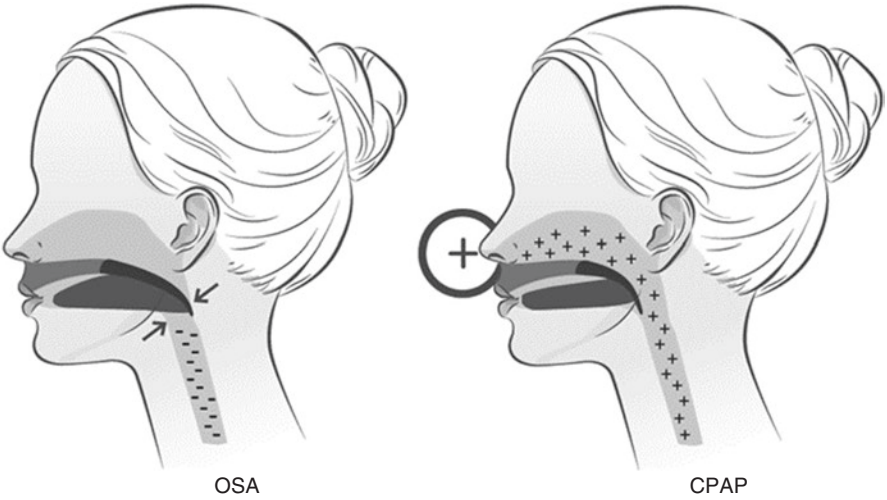

Fig. 3 A schematic illustration of the mechanism of upper airway occlusion and its treatment with PAP. The patient with OSA (left) and then (right) using nasal positive pressure with the upper airway completely open, and the tongue and soft palate anteriorly pushed. (Modified with permission from Sullivan et al. [7])

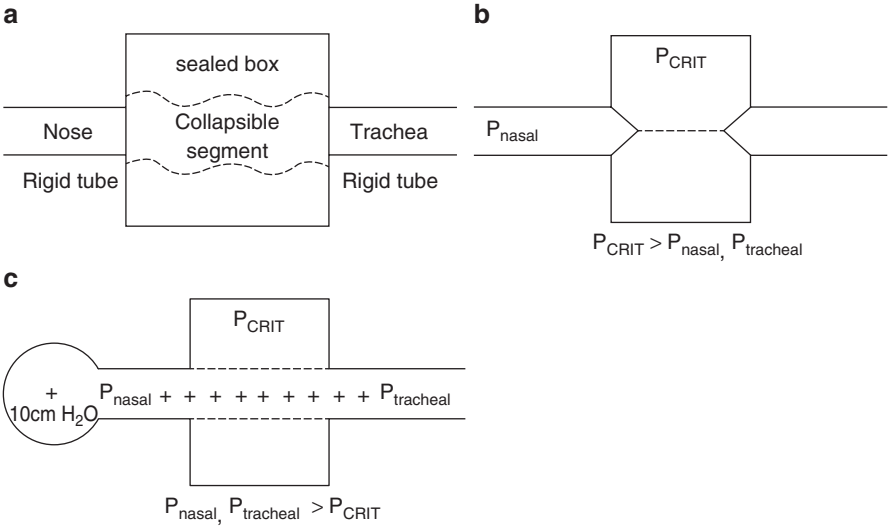

Fig. 4 Schematic illustration of the Starling resistor. (**a**) The nose and the trachea are represented by two rigid tubes connected by a collapsible segment (the pharynx). (**b**) Collapse of the pharynx. (**c**) Illustration of the CPAP mechanism with pressurization of the upper airway. (Image courtesy from Dr. Rafaela Andrade)

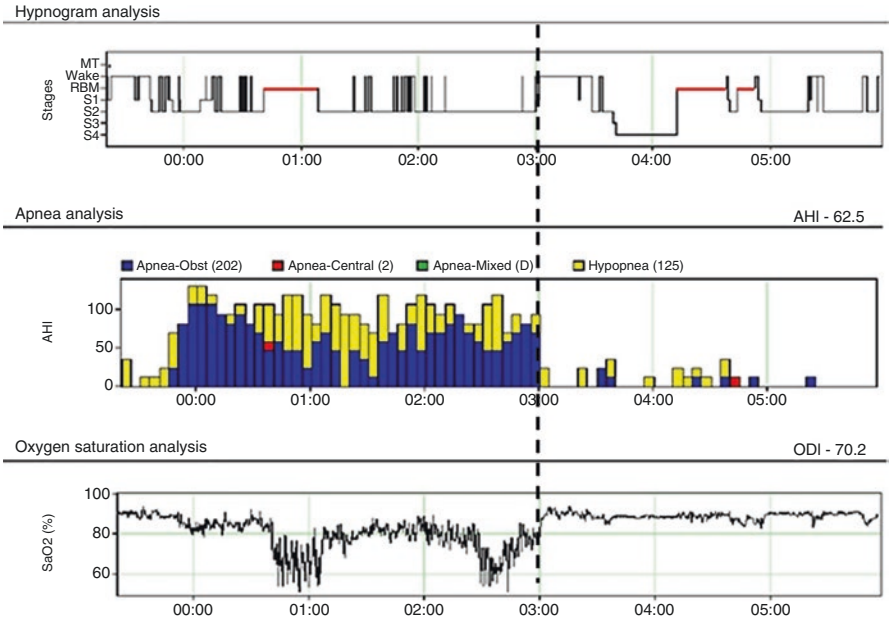

Fig. 5 A example of an OSA patient hypnogram from the Heart Institute Sleep Lab collection. A split night exam using PAP in the second half of the night (dashed line). (Image courtesy from Dr. Rafaela Andrade)

complete pharyngeal collapse occurs (Pcrit>Pnasal, Ptracheal) [10]. In the same conditions, the CPAP can continuously pressurize the upper airway, so the Pnasal, Ptracheal is higher than Pcrit, and the upper airway stays completely open as illustrated in Fig. 4c.

PAP is able to abolish respiratory obstructive events and sleepiness, reduce blood pressure and the incidence of motor vehicle accidents, and improve sleep-related quality of life in adults with OSA [11]. In Fig. 5 we can see a hypnogram of split night polysomnography that shows in the first part of the night a sleep fragmentation on top followed by a lot of obstructive apneas (blue) and hypopneas (yellow) and significant oxygen desaturation. After 3 am (red line), the PAP machine was introduced, and we can clearly see a stabilization of sleep, with deep sleep, and oxygen saturation, and a significant reduction of obstructive events.

2 PAP and Bilevel Treatment: When Should I Use Them?

Among the noninvasive ventilatory modalities, the most used for the treatment of OSA is CPAP, a continuous positive pressure in the upper airway during all time [12–14], and Bilevel, two levels of positive airway pressure, is a positive inspiratory

pressure (IPAP) capable of reducing the flow limitation and increasing lung volume and, the other, positive expiratory pressure (EPAP) able to keep the upper airway open during expiration, preventing the upper airway to collapse during sleep (Fig. 6). The IPAP must be higher than the EPAP, and both have independent adjustments [15, 16]. The Bilevel was indicated in patients with OSA who need higher CPAP and have not adapted to the modality, cases of OSA associated with hypoventilation (obesity hypoventilation syndrome and neuromuscular diseases such as myopathies, dystrophies, spinal muscular atrophy, amyotrophic lateral sclerosis, multiple sclerosis, among others) and chronic obstructive pulmonary disease [12–14].

PAP can be delivered as fixed or automatic pressure. The automatic PAP is an auto adjustable pressure mode and has the objective to maintain the upper airway patency during sleep with more pressure or not according to the patient's respiratory flow feedback [12]. The American Academy of Sleep Medicine clinical practice guideline for PAP treatment in OSA adults, published in 2019, strongly recommends the use of either automatic positive airway pressure (APAP) or CPAP (fixed pressure) for ongoing treatment of OSA in adults. However, they remark this recommendation in patients with congestive heart failure, chronic opiate use, significant unstable lung disease, neuromuscular disease, history of uvulopalatopharyngoplasty, sleep-related oxygen requirements, or expectation of nocturnal arterial oxyhemoglobin desaturation due to conditions other than OSA, including hypoventilation syndromes and central sleep apnea syndromes, and higher therapeutic pressure requirements. In these cases, higher ventilatory support is necessary with other ventilatory modalities such as Bilevel and other modalities [17].

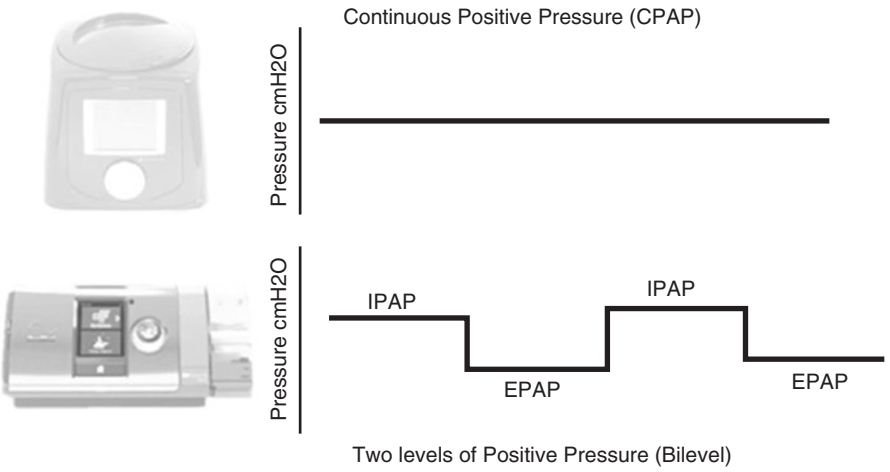

Fig. 6 A schematic illustration of how CPAP and Bilevel work. The CPAP delivers a continuous positive pressure during sleep, while the Bilevel delivers an inspiratory positive pressure during inspiration and an expiratory positive pressure during patient expiration. (Image courtesy from Dr. Rafaela Andrade)

3 Comfort Technologies: What Are They and When Should I Use Them

Both CPAP and Bilevel have comfort technologies to improve PAP adherence. They are expiratory relief pressure (a reduction on expiratory pressure during the patient expiration), ramp time (the time in minutes that PAP increases gradually until reaching therapeutic pressure), and heated humidifiers (prevent dryness of the upper airways) [13, 14, 18]. The ramp time can be used to minimize the patient's perception of excessive pressure on the face, favoring sleep induction [13]. The automatic ramp increases the PAP pressure according to the detection of obstructive events or stabilization of the breathing pattern [13, 18]. The sense awake® technologies have recently emerged. Total pressure relief occurs when breathing patterns become unstable, indicating that the patient may be awake, so the PAP pressure is reduced until sleep again and the therapeutic pressure is simultaneously restored. The physiotherapist is the most suitable professional to adapt the patient to PAP as well as to follow in the short, medium, and long terms, solving possible problems and ensuring adherence to treatment [18]. It is important to know when and how using these technologies and know the patient's history and comorbidities.

4 Talking About Adherence

Despite eliminating OSA, the effectiveness of PAP is totally dependent on adherence, which consists of the number of hours of device use per night. Unfortunately, adherence to PAP therapy is extremely variable in the literature (46–80%) [19–22]. The use of the treatment 4 h/night in at least 70% of the nights is considered to be a good treatment adherence [23]. However, in our respiratory physiotherapist clinical practice, we made all the forces to aware the patients to use the PAP device during all time of sleep, this is our goal! The predictive factors for adherence to PAP are multiple and include the severity of OSA [24], the level of excessive daytime sleepiness [25], socioeconomic status [26], the level of understanding of the therapy by the patient (education actions) [27, 28], PAP mode and pressure levels [29, 30], and the interface/mask model [31, 32]. The PAP compliance during the first month and the presence of side effects were the only independent predictors of 12 months PAP adherence [33]. Early PAP adherence had the greatest predictive value for identifying those at the highest risk of nonadherence to long-term PAP [21]. It is so important that the physiotherapist views intensive early interventions to solve the potential side effects and problems with the objective of improving long-term compliance.

For all this reason, it is so important to choose the right interface (mask). Nasal, pillow, and oronasal masks are the most commonly used and are represented in Fig. 7. Silicone, gel, and tissue can be the material used to make these interfaces. We are seeing more frequently masks extremely light and comfortable. In general, they are formed by the fitting of their parts, being easy to handle and clean by patients.

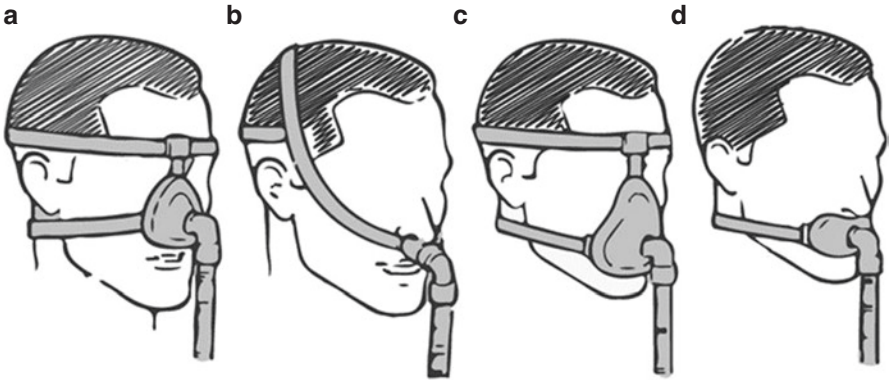

Fig. 7 An illustration of the different types of CPAP interfaces available for the treatment of obstructive sleep apnea: (**a**) nasal mask, (**b**) pillow mask, (**c**) oronasal mask, and (**d**) oral mask. (Modified with permission from Andrade et al. [34])

They are commonly found in sizes small, medium, medium wide and large, and are fixed to the patient's face by adjustable by headgear straps. All the masks have an exhalation port, which prevents the rebreathing of the exhaled carbon dioxide.

The nasal mask covers the nose exclusively and should surround it in such a way that it does not compress the wing of the nose, being immediately above the upper lip and close to the angle of the eye. Some nasal masks have forehead support as a stabilizing component of the mask. This support point allows two parallel tapes to depart from the upper region to fix the mask, and two more tapes from the lower region, composing a fixation in four points. Currently, the nasal mask is becoming increasingly lighter and with minimal contact with the patient's face and nose. The majority of modern interfaces have the tracheal output above the head (Fig. 8).

The nasal pillows consist of two intranasal pillows and emerged as an alternative to the nasal mask. Is a great choice for patients with mustache and claustrophobia because its 2 tapes come out to fix the mask in the upper and posterior region of the head, composing a fixation in 2 points.

The oronasal mask covers the nose and mouth and allows the patient to breathe through both the nose and the mouth. The oronasal interface must be positioned close to the angle of the eye, permeating the entire side of the nose to the mouth and ending below the patient's lower lip, allowing the patient to open the mouth. Oronasal masks, in general, have forehead support as a stabilizing component of the mask. This support point allows two parallel straps from the upper region of the head, and two more straps from the lower region, composing a fixation in four points. Today, a new oronasal mask has been emerging which is increasingly lighter and has minimal patient contact. Oronasal interfaces were initially described in situations of noninvasive ventilation for patients with respiratory failure and high ventilatory demand [35]. However, the oronasal mask has been progressively used in OSA patients that self-report breathing through the nose as an alternative to improve PAP compliance. One study of our group showed that the patients' self-report about

Fig. 8 Examples of masks: (**a**) Nasal mask. (**b**) Pillow mask. (**c**) Oronasal mask and (**d**) oral mask. (Image courtesy from Dr. Rafaela Andrade. (original))

the route (nasal vs. oral) of breathing is different from the real breathing route during sleep [36].

The oral interface is often made of silicone and resembles the shape of a butterfly that is positioned between the lips and the teeth. From the oral mask, two strips come out towards the back of the head to fix it to the patient's face. They have a

tongue positioning component, which keeps the tongue stabilized and prevents obstructions to the PAP flow. In clinical practice, they are rarely used.

PAP for OSA treatment was originally designed to be used with a nasal route [7]. In a meta-analysis from our group that compared nasal and oronasal PAP, the oronasal masks were associated with a significantly higher CPAP level (on average, +1.5 cmH_2O) despite a significantly higher residual AHI (+2.8 events/h) and lower adherence (−48 min/night) when compared to nasal mask [31]. In another study, our group evaluated 18 patients with OSA who slept with an oronasal mask with 2 sealed independent compartments (nasal and oral). The acute changes of the CPAP flow route during sleep from nasal to oronasal and oral routes induced obstructive events and narrowing of oropharyngeal dimensions due to a posterior displacement of the tongue as demonstrated by nasendoscopy example (Fig. 9) [37].

During stable flow limitation, oronasal CPAP led to lower peak inspiratory flow, higher driving pressure, higher inspiratory resistance, and lower upper airway dimensions, both at the retropalatal and retroglossal areas [38]. The key to explaining this behavior is the pressure transmitted through the mouth during oronasal CPAP. So, the nasal route (nasal or pillow mask) must be the first choice in the treatment of OSA patients [39]. If the patient has some nasal obstruction, it was preferable to treat the nose after beginning the PAP therapy. If a percentage of mouth breathing persists during nasal PAP use, the use of a chin strap to minimize mouth breathing is indicated (Fig. 10).

In claustrophobic patients, the use of a small mask is recommended as we mentioned above. Claustrophobia is one of the largest side effects of PAP therapy, cited by 63–84% of respondents in previous studies and associated with a greater risk of poor PAP adherence or abandonment [40]. It is characterized by a feeling of being uncomfortable with the PAP mask, positive pressure, or both, causing anxiety, worry, avoidance, and, often, insomnia. This is a delicate patient, and the PAP adaptation process is slower. A lot of studies suggest a desensitization process (graded

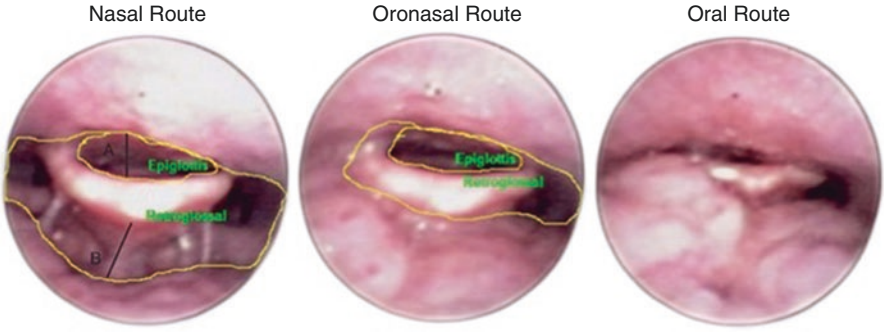

Fig. 9 Image of the upper airway of a patient during the experiment in the retroglossal region during the nasal, oronasal, and oral route. A significant reduction in the retroglossal dimensions was observed. The yellow line delimits the retroglossal and epiglottis areas. (**a**) Distance between the epiglottis and the posterior pharyngeal wall. (**b**) Distance between the epiglottis and the base of the tongue. (Modified with permission from Andrade et al. [37])

Fig. 10 Illustration of a chin strap, used to reduce mouth opening during sleep. (Image courtesy from Dr. Rafaela Andrade)

Table 1 Example of a claustrophobia patient PAP adaptation protocol

Steps	Actions
1	Use the PAP mask 1 h a day at home while awake
2	Turn on the PAP and with the mask on your face while watching TV, reading a book, or other activity – stay for 1 h
3	Use PAP for 1 h at home during naps
4	Use PAP 3–4 h per night
5	Use PAP for a full night's sleep

exposure), and each study has its protocol. But the idea is the same on them, something like five steps, and the patient only can move to another step when she/he was comfortable and without anxious feelings during the step [41]. The CPAP pressure was increased gradually by 1 cmH_2O per time (Table 1).

Beyond the type of mask, patient education, and patient's socioeconomic status, telemedicine has been emerging as a useful tool in increase PAP adherence. When the patients are engaging in the therapy by their adherence applicative (daily information about compliance, air leaks, and residual respiratory events) and when he

knows that the physiotherapist has a tool that helps to solve problems quickly and accurately, in the clinician's platform, this encourages the patients to use more the device [19, 42].

5 Talking about PAP Adaptation Process

The process of adapting PAP therapy to the patient is a great challenge for the physiotherapist and requires a careful look from the moment of the evaluation, analyzing the polysomnography and complementary exams, as well as the application of questionnaires and scales and the choice of the appropriate interface [13, 18]. Problems such as nasal obstruction (which occurs in approximately 40% of patients), intolerance to mask, dryness of the mouth and nose, fragmentation of sleep, the noise emitted by the equipment, skin irritation, intolerance to positive pressure, and escape through the mask and/or mouth are situations that negatively influence PAP adherence. The clinical benefits as reducing daytime sleepiness improve the cardiovascular system, and improving quality of life is directly proportional to the time of use of the device during sleep.

During the follow-up process, the physiotherapist periodically re-evaluates the patient, using data from memory cards, analyzing reports, graphs, and flow curves as well as the patient's perception of improvements of the initial symptoms. These reports mainly include the residual AHI, mask leak, equipment usage time, and types of respiratory events, thus allowing the physiotherapist to readjust parameters and modify the conduct. Currently, new devices already provide this data remotely via wireless that enables telemonitoring to be carried out as we mentioned before [17, 43]. The sleep and respiratory physiotherapists are the most suitable professionals to adapt the patient to PAP as well as to follow in the short, medium, and long terms, solving possible problems and improving PAP adherence [18]. The following is an example of a protocol for physiotherapist use, based on the task force carried out by the American Academy of Sleep Medicine [43].

I. *First consultation*

(a) Investigate

- Sleep habits (agitated, insomnia e daily habits)
- If the patient breaths well through the nose; if does or did any ENT (ear, nose, and throat) treatment; or it has undergone any nose, tonsils or snoring surgery
- Cognition alterations (slow thinking, forgetfulness)
- Mood disorders (irritability, depression, and anxiety)
- History of smoking and alcohol addiction
- Ongoing physical activity and diet regimen
- Other health problems

(b) Explain the disease, risk factors, types of available treatments for each instance, what to look for, and consequences of the lack of treatment.
(c) Elucidate the importance of weight loss and sleep hygiene (sleep positioning, alcohol addiction, medications and benefits of a physical activity program, etc.).
(d) Mask adaptation and the PAP equipment.

II. *The first, the third, and the sixth month of PAP Use*

(a) Evaluate the treatment adherence
(b) Investigate possible causes of mask and equipment intolerance

III. *After this period, the patient may return every 6 months in order to verify treatment adherence and possible causes of treatment intolerance.*

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Central Sleep Apnea: An Overview

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Central sleep apnea (CSA) is characterized by the temporary loss of the production of respiratory stimuli from the pacemaker in the pontomedullary region of the central nervous system (CNS). The absence of the central ventilatory stimulus results in loss of movements of the main ventilatory muscles (diaphragm, thorax, and abdomen). The central events are depicted in the polysomnography by the absence of inspiratory effort throughout the entire period of apnea (absent airflow). The CSA is also associated with the absence of abdominal thoracic movement captured by respiratory inductance plethysmography. However, in obstructive sleep apnea, the movements of the respiratory muscles remain in the absence of airflow [1].

1 Methods for the Evaluation of Central Sleep Apnea

1.1 Esophageal Pressure

The esophageal pressure (Pes) is the most accurate method for the differential diagnosis of central and obstructive hypopnea since it directly evaluates intrathoracic pressure when inserted into the esophagus. Because it is invasive, this method of evaluation is rarely used in sleep laboratories.

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1.2 Respiratory Inductance Plethysmography

Chest and abdominal movements are detected by respiratory inductance plethysmography (belts), widely used to evaluate respiratory movements. The belts are very efficient in capturing the asynchrony of respiratory incursions that occur during apnea and obstructive hypopnea or in the breathing phase associated with the reduction of the central respiratory drive [2].

Central apnea and hypopnea are characterized by the absence of a synchronous proportional reduction in thoracic and abdominal ventilatory incursions, while obstructive apnea and hypopnea are characterized by the paradoxical movement of the chest as opposed to the abdominal movement (gray arrow in Fig. 1).

The prevalence of CSA is estimated at around 5–10% of the cases of respiratory sleep disorders, according to the International Classification of Sleep Disorders, third edition (ICSD-3). Variations in the hemodynamic profile of patients with congestive heart failure (CHF) may cause changes in the presence of central apnea during sleep with changes between nights and within one night [3]. According to the ICSD-3 [3], CSA is classified into six types of apnea:

1. *Cheyne-Stokes breathing (CSB)* – high ventilatory drive characterized by a *crescendo-decrescendo* pattern of breathing between respiratory events. CSB

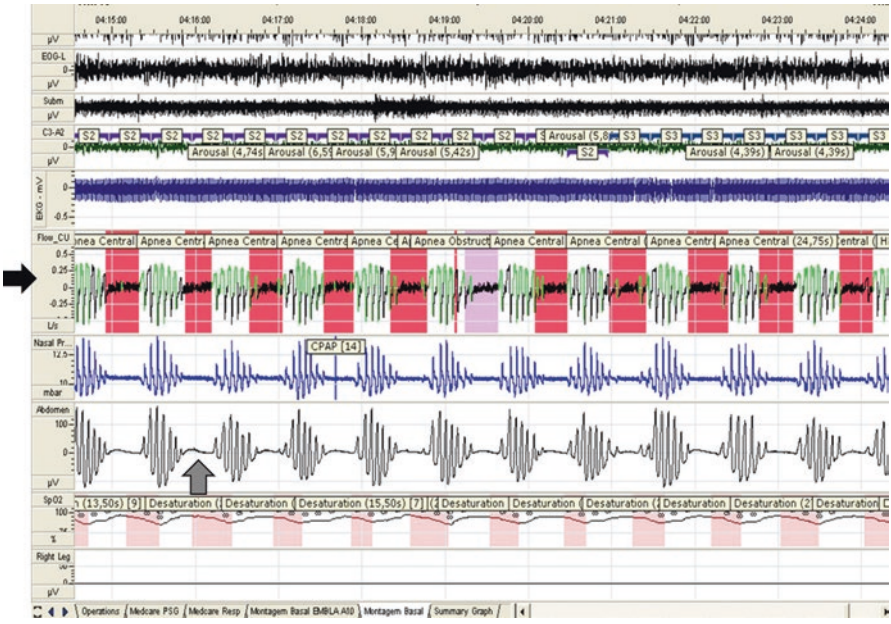

Fig. 1 Cheyne-Stokes breathing. In this 10-minute window of a polysomnogram examination, note the *crescendo-decrescendo* pattern at the flow line (black arrow), the central apneas (red bars), and the lack of abdomen movement (gray arrow). This patient was using a PAP device at a fixed pressure of 14 mmHg. (Image Courtesy from Dr. Luciana Palombini (original figure))

is a form of periodic breathing, with central apneas or central hypopneas at the nadir of effort [1]. According to the American Academy of Sleep Medicine, CSB is classified when there are consecutive episodes of three or more central apnea or hypopnea, separated by a ventilatory pattern with amplitude in increasing-decreasing, and with a cycle duration of at least 40 seconds, most commonly lasting from 45 to 90 seconds. Besides, the presence of five or more central apnea and/or hypopnea per hour of sleep is recorded by at least two hours of monitoring. CSB is commonly seen in patients with congestive heart failure.

2. *Primary or idiopathic CSA (no established etiology)* – central apnea when the sleeping pressure of carbon dioxide (PCO_2) drops below the apneic threshold. It is an uncommon disorder of unknown etiology. It is characterized by shorter cycles of CSA, with early awakenings occurring shortly after the end of apnea. The restart of ventilation is more abrupt, different from the restart growing in CSB. CSB is not present, and there is no evidence of daytime or nocturnal hypoventilation. The patient does not present hypercapnia when awake (PCO_2 greater than 45 mmHg). The diagnosis is performed by polysomnography, with the presence of five or more apnea and hypopnea per hour of sleep, with the number of central events greater than 50% of the total number of apnea or hypopnea and in the absence of CSB.
3. *High-altitude periodic breathing* – healthy individuals who are at altitudes above 2500 meters (in some situations these symptoms may also occur above 1500 meters). The ventilatory pattern is characterized by alternating periods of hyperpnea followed by central apnea, cyclically lasting 12–20 seconds. The percentage of individuals who have periodic breathing during sleep increases with altitude, and it can be observed in 25% of individuals who are above 2500 meters and in 100% above 4000 meters of altitude. The PSG shows the presence of central apnea and hypopnea, especially during non-REM sleep at the frequency of five or more sleep events/hours.
4. *CSA due to a medical disorder without CSB* – in this group of disorders, CSA is recognized due to a medical or neurological condition. It is found in individuals with heart disease, kidney disease, or neuromuscular, degenerative, or traumatic diseases, who present central apnea in the absence of CSB [4]. A mixture of obstructive and central sleep apneas may be present, and a simultaneous diagnosis of OSA is not excluded. Sleep-related hypoventilation may be present.
5. *CSA caused due to medication or substance* – CSA is thought to be caused by potent long-acting opioids or other respiratory-depressant prescriptions. Indeed, the use of opioids for long periods cause respiratory depression by the direct action on μ-receptors on the spinal cord. Individuals may also present hypoventilation and obstructive apnea associated with the use of narcotics. In PSG, the presence of central apnea and hypopnea without CSB is observed at the frequency of five or more sleep events/hours (Fig. 1).
6. Central emergent apnea *associated with treatment (or "complex" sleep apnea)* – this disorder is not explained by any other cause of central apnea and is characterized by the presence of obstructive events in the diagnostic (basal) poly-

somnography, with the persistent onset of central events (apnea or hypopnea) associated with PAP therapy. The diagnosis of this disease is made in the PSG of PAP titration, with the appearance of five or more central apnea and/or hypopneas, with the number of central apnea and hypopneas greater than or equal to 50% of the total number of respiratory events and in the absence of CSB [5]. Patients usually present symptoms of daytime sleepiness or disrupted sleep. Also, patients with central emergent apnea associated with treatment (PAP or Bilevel) are thought to have instability in ventilatory control or a sleep state instability that seems to be exacerbated by PAP or Bilevel.

Breathing frequency and deepness are regulated by a negative feedback control system, which *aims* to maintain, at relatively constant levels, the partial PCO_2 and pressures of arterial oxygen (PO_2), even in the presence of hypoxemia, hypocapnia, or hypercapnia caused by lung or chest wall disease [6]. The ventilatory response varies widely between the wake period and the sleep period, as well as between REM sleep and NREM sleep. Central apnea events rarely occur during the wake period, as well as during R sleep stage. However, during NREM sleep changes in the ventilatory pattern are chemically controlled by PCO_2's blood levels. Mild reductions in PCO_2 levels lead to a central ventilatory response with the cessation of breathing (apnea threshold), stimulated by hypocapnia and caught by the central and peripheral chemoreceptors that command this response. NREM sleep respiratory oscillations may be increased by spontaneous sleep awakenings, which promote transient hyperventilation with consequent hypocapnia, initiating central apnea events, primarily during NREM sleep, and which persist until the elevation of PCO_2 above the apnea threshold. The duration and magnitude of hyperventilation will determine the level of hypocapnia and the consequent appearance of central apnea during stable sleep [1].

During sleep, the normal respiratory rhythm is maintained by a complex feedback mechanism best explained by the "loop gain" concept. "Loop gain" can be defined as the magnitude of the ventilatory response to ventilatory disorders with increased or decreased breathing [1]. This term describes the dynamic feedback of several ventilatory stabilizing mechanisms: (i) the ventilatory control center and the chemoreceptors, the ventilatory response to PO_2 and PCO_2 above or below normal values; (ii) lung and respiratory muscles and their effectiveness in the elimination of CO_2 by the ventilatory response; and (iii) delayed circulation between the lungs and peripheral and central chemoreceptors. More on the "loop gain" concept is in the next chapter.

CSA does not occur as an isolated event, occurs in apnea/hypopnea cycles alternated with hyperpnea, and may initiate a cascade of events that perpetuate ventilation instability. This instability may include the inertia of the central ventilatory control system, narrowing of the upper airways, occlusion, hypoxia, hypercapnia, and transient awakening. Consequently, regular rhythmic breathing will only be resumed when PCO_2 levels are 4–6 mmHg above basal PCO_2 [7]. This sequence explains why CSA does not occur as an isolated event, often accompanied by obstructive and mixed events in the same patient [8].

Regarding the pathophysiology of CSA, there are two main mechanisms responsible for the appearance of central events – (a) secondary to alveolar or hypercapnic hypoventilation and (b) secondary to hyperventilation or non-hypercapnic:

(a) *CSA secondary to alveolar hypoventilation (hypercapnic)* – Individuals with marginal ventilatory status or reduction of the ventilatory drive during the waking period may present some degree of diurnal hypercapnia. Inevitably, the ventilatory changes reported during wakefulness, in addition to other behavioral influences, cause hypercapnia by hypoventilation also during sleep [9]. In the presence of hypercapnia, there is an increase in alveolar ventilation, causing a small increase in ventilatory frequency, which results in a large change in PCO_2 values. Thus, the occurrence of a spontaneous awakening of sleep, associated with a small increase in ventilation, may reduce PCO_2 below the threshold of apnea causing central apnea [1]. The different diseases causing diurnal hypercapnia include neuromuscular diseases such as post-polio syndrome, amyotrophic lateral sclerosis, stroke, central alveolar hypoventilation, multiple sclerosis, Arnold Chiari malformation, muscular dystrophy, and abnormalities in ventilatory mechanics, such as kyphoscoliosis, among others.

(b) *CSA secondary to hyperventilation (not hypercapnic)* – The most common mechanism of central apnea is hypocapnia after hyperventilation and is characterized by a transient instability between the ventilatory control system and normal or increased alveolar ventilation. This type of central apnea is commonly observed in patients with heart failure, who may present hypocapnia during the wake period. Patients with heart failure present an increase in circulatory time, which contributes to the conversion of a negative feedback system into a positive one, contributing to the persistence of compensatory hypoventilation and hyperventilation [7].

2 Risk Factors for Central Apnea

Central sleep apnea may occur during the shifts of sleep stages, in normal sleep, associated with increasing age or related to some clinical disease. Physiological and pathological factors may influence susceptibility to the onset of central sleep apnea, such as:

2.1 Sleep Stage

The transition from the waking period to NREM sleep (stages 1 and 2) may be associated with the recurrent appearance of CSA, explained by the oscillation between the wake period and superficial sleep, with a reciprocal oscillation of PCO_2 near the apnea threshold [10]. Transient awakenings cause brief periods of hyperventilation,

followed by hypocapnia, which results in CSA. Usually, these events cease with the deepening of sleep and the stabilization of PCO_2 above the apnea threshold. The appearance of CSA in the transition of the sleep-wake period is a normal phenomenon [11]. CSA usually does not occur during REM sleep, and this can be explained by a lower ventilatory response, the presence of hypercapnia, and hypoxia during this sleep stage and thus a reduced "loop gain," in addition to possible inhibition of respiratory accessory muscles. The reduction of the activity of the accessory muscles may worsen the hypoventilation during REM sleep in patients with paralysis or diaphragm dysfunction, with consequent reduction of the current volume to insignificant levels, and may generate a false CSA (pseudo-CSA). Thus, CSA during REM sleep represents transient hypoventilation rather than hypocapnia after hyperventilation [12].

2.2 Age and Gender

CSA is more prevalent in older adults than in middle-aged individuals, according to epidemiological studies. The prevalence of CSA is 1.7% in middle-aged adults vs. 12.1% in old-age adults [13]. The physiological oscillations of sleep may precipitate CSA in the older ones, as in this group the susceptibility to the appearance of CSA induced by mechanical ventilation with a nasal mask is greater [14]. The increased prevalence of CSA in the older ones may be associated with the presence of comorbidities such as hypothyroidism, congestive heart failure, and atrial fibrillation [15]. CSA is less common in women, with prevalence around 0.3% compared to 7.8% in men. The female menstrual cycle showed no influence on the appearance of CSA, ruling out progesterone as the cause of the difference between the sexes [16].

2.3 Clinical Diseases

Respiratory disorders are common in individuals with congestive heart failure, having a prevalence of 51% [17]. In this study, most patients (40%) had central apnea, and 11% had obstructive sleep apnea [17]. Patients with CSA and congestive heart failure present pulmonary vascular congestion leading to hyperventilation and hypocapnia. In patients with congestive heart failure, the magnitude of hypocapnia needed to induce CSA is small since these patients have a reduced ventilatory reserve [10].

In 40% of patients with stroke, CSA is the most prevalent sleep disorder. Similarly, 30% of chronic methadone users have CSA. Besides, it is also described in patients with hypothyroidism, acromegaly, and renal failure, with improvement after hemodialysis. The presence of spinal cord injury and tetraplegia is also associated with a higher prevalence of CSA. There is a possibility that these patients present undiagnosed metabolic or cardiac diseases [11, 18, 19].

3 Clinical Picture and Diagnosis

The underlying diseases and the occurrence of CSA influence clinical characteristics of hypercapnic CSA. Patients with clinical diseases and concomitant sleep apnea may present both symptoms of the underlying disease (dyspnea and weakness) and complaints related to sleep apnea, such as sleepiness, presence of snoring, morning headache, and poor quality of sleep. Patients with non-hypercapnic CSA may have common symptoms of sleep apnea syndrome, but do not complain of daytime sleepiness. The transitions between the waking period and stage 1 of NREM sleep can cause sleep fragmentation, poor sleep quality, and insomnia complaints [17].

4 Clinical Treatment

The strategy for treating patients with CSA takes into account the clinical condition, comorbidities, and polysomnographic findings. Therapeutic options may include pharmacological therapy, the use of supplemental oxygen, phrenic nerve stimulation, and PAP therapy. Below are described the therapeutic options, except for the PAP for CSA, addressed in the following chapter of this book.

4.1 Pharmacological Therapy

There are no clinical studies with good scientific evidence demonstrating efficacy in the use of pharmacological therapy for CSA. Little evidence supports the use of acetazolamide or theophylline as a treatment. Acetazolamide is a carbonic anhydrase inhibitor diuretic that causes metabolic acidosis with stimulation of the ventilatory center in response to PCO_2 increase during apnea. Theophylline in turn improves sleep respiratory disorder by increasing central ventilatory drive and cardiac contractility; however, its use may also increase the risk of cardiac arrhythmia and sudden death in these patients. In general, respiratory stimulants are not recommended for routine treatment of CSA [20, 21].

4.2 O_2 and CO_2 Supplementation

Many studies have demonstrated the positive effect of using oxygen supplementation in patients with CSA associated with heart failure. Oxygen therapy mitigates CSA by attenuating the magnitude of hypoxemia and consequently reducing the hyperventilation response after the apnea episode. Patients with non-hypercapnic CSA with high chemoreceptor response may benefit from O_2 therapy by the stabilizing effect of

the ventilatory center promoted by it. The most likely explanation, however, would be the increase of brain PCO_2 by the displacement of hemoglobin carbon dioxide by the increase of oxygen levels (Haldane effect) [22]. The American Academy of Sleep Medicine recommends the use of night oxygen as a standard treatment for CSA related to heart failure. In turn, CO_2 supplementation suppresses CSA in these patients by raising PCO_2 above the apnea threshold. However, this therapy is not a practical one, given the need for a closed circuit to provide supplemental CO_2 [23].

4.3 Stimulation of the Phrenic Nerve

Phrenic nerve stimulation is a physiologically attractive intervention that can be a treatment strategy for patients with CSA. An electrical stimulator is surgically implanted promoting a unilateral stimulus of the phrenic nerve. This treatment has already been approved by the FDA (Food and Drug Administration) American Regulatory Agency based on a randomized study that demonstrated a marked improvement in the central apnea index, oxygen levels, sleep parameters, and quality of life of these patients. Phrenic nerve stimulation seems to be a promising therapy; however, it needs long-term outcome studies, safety, and comparative efficacy [24].

5 Final Words

The pathogenesis of central sleep apnea varies according to general clinical conditions, with the reduction of the ventilatory drive during sleep and blood gas oscillations, especially PCO_2, being the common denominator among all cases of central apnea.

Hypocapnia is the most frequent cause of non-hypercapnic CSA; however, in some conditions depression of the respiratory rhythm may be responsible for the presence of CSA, as in chronic opioid use. Also, the etiological and pathophysiological heterogeneity of the baseline justifies an individualized therapeutic approach for each patient [8]. There is no standard treatment for patients with CSA. These patients require individualized and customized, frequently monitored treatment due to different causal factors.

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Central Sleep Apnea: Physiotherapeutic Approach

Juliana Arcanjo Lino and Vivien Schmeling Piccin

Central apnea occurs when the pontomedullary pacemaker fails in generating breathing rhythm. Without brainstem inspiratory neural output there is no work of the inspiratory thoracic pump muscles resulting in the loss of inspiratory ventilatory effort, which is characterized polygraphically by the absence of naso-oral airflow and thoracoabdominal excursions. On sleep medicine, the silence of the inspiratory effort should last at least ten seconds to be considered central sleep apnea (CSA) [1].

The International Classification of Sleep Disorders (ICSD-3) identifies eight different forms of CSA: (I) central sleep apnea with Cheyne-Stokes breathing, (II) central sleep apnea due to a medical disorder without Cheyne-Stokes breathing, (III) treatment-emergent central sleep apnea, (IV) central sleep apnea due to high-altitude periodic breathing, (V) central sleep apnea due to a medication or substance, (VI) primary central sleep apnea, (VII) primary central sleep apnea of infancy, and (VIII) primary central sleep apnea of prematurity [2].

Instead of the CSA classification by the ICSD-3, the underlying pathophysiology of central sleep apnea is due to hyperventilation or hypoventilation. According to the pathophysiological mechanisms that trigger specific central breathing patterns, the subtypes of central sleep apnea – hypercapnic, hypocapnic, or

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normocapnic – are characterized. This knowledge is especially important to determine appropriate treatment strategies [3–5].

Positive airway pressure therapy (PAP) is indicated for the treatment of hypocapnic, hypercapnic, or normocapnic CSA [6]. Other treatment strategies [7] have also been described in the literature, such as the supply of supplemental oxygen [8, 9]; respiratory center stimulants, such as acetazolamide and theophylline [10, 11]; the increase in inspired CO_2 – supplied directly or through the application of dead space [12, 13]; and, more recently, phrenic nerve stimulation [14–16]. Opioid dose reduction and weight loss both are also options that can improve central apnea [4]. Interventions that improve cardiac function can also attenuate central sleep apnea, especially periodic breathing, common in patients with underlying cardiovascular disease [17].

In recent years, the influence of bed positioning on the rostral displacement of fluid to the chest and neck regions has also been reported, contributing to pulmonary congestion, and increased cervical circumference, causing central and obstructive events, respectively. In this case, the simple recommendation to raise the head of the bed has been effective in the treatment of central apneas, especially in patients with cardiovascular disease [18, 19]. In clinical practice, these treatment strategies can be used in a combined way according to the complexity of each case, and, of course, it requires the experience of the physiotherapist to effectively use the different therapeutic techniques.

Close monitoring of patients with CSA using telemonitoring and detailed graphical analysis (i.e., analysis of respiratory flow curves when using PAP or bilevel pressure therapy) is also essential, especially in cases where the establishment of optimal conducts proves to be more difficult [20, 21].

This chapter presents the detailed physiotherapeutic approach in central sleep apnea with Cheyne-Stokes breathing, CSA due to a medical disorder without Cheyne-Stokes breathing, and CSA emerging from treatment, which represents the greatest clinical challenge in routine care of patients with sleep-disordered breathing.

1 Central Sleep Apnea with Cheyne-Stokes Breathing

Cheyne-Stokes breathing (CSB) is probably the most common form of the types of CSA [2]. Characterized by periods of hyperventilation in an increasing-decreasing pattern of tidal volume, alternating with periods of central apnea or hypopnea, with a respiratory cycle duration usually greater than 40 seconds, CSB presents highly prevalent morbidity but unfortunately is still underdiagnosed in cardiovascular diseases [5, 22].

The CSB is associated with arterial oxygen desaturation, episodes of hypercapnia, sleep fragmentation, and activation of the sympathetic nervous system which, chronically, can be harmful to the heart [23]. In fact, several studies have shown that CSB is a strong independent marker of poor prognosis and increased morbidity and mortality in patients with heart failure (HF) [22, 24, 25]. The pathophysiology of CSB in HF is directly associated with instability of respiratory control, which can be explained by a high *loop gain*. High chemosensitivity is responsible for

exaggerated ventilatory response secondary to PCO_2 fluctuations. Patients with HF are in a chronic state of hyperventilation, and, consequently, their eupneic PCO_2 level becomes remarkably close to the apnea threshold. Thus, when the patient falls asleep, the PCO_2 does not rise normally, but the apnea threshold is established at a higher level making it easier for an apnea event to be evoked by a minimal increase in ventilation, typically due to spontaneous arousals [26–28].

Among the main elements that contribute to hyperventilation in HF, pulmonary congestion is correlated with increased pulmonary capillary pressure and can be aggravated in the supine position during the night [29]. It partly explains why the CSB is usually observed more expressively at the end of the night [Fig. 1]. Similarly, this overload fluid can be observed also in chronic kidney disease [30]. As renal failure and HF are characterized by fluid overload, these observations suggest that hypervolemia may contribute to the pathogenesis of CSA in both conditions, through the redistribution of fluids during the night from the legs to the lungs, especially into the interstitial lung tissue [19, 31].

In clinical practice, the treatment of CSA with CSB is still controversial and should be individualized according to the clinical history of each patient. The PAP has been studied in the treatment of CSA in recent years [22, 32]. The Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure trial (CANPAP study) [33], with 258 patients with HF and CSA, showed that continuous PAP (CPAP) was associated with improvement in intermediate outcomes, including the apnea-hypopnea index (AHI), left ventricular ejection fraction (LVEF), and mean oxyhemoglobin saturation at night. However, there was

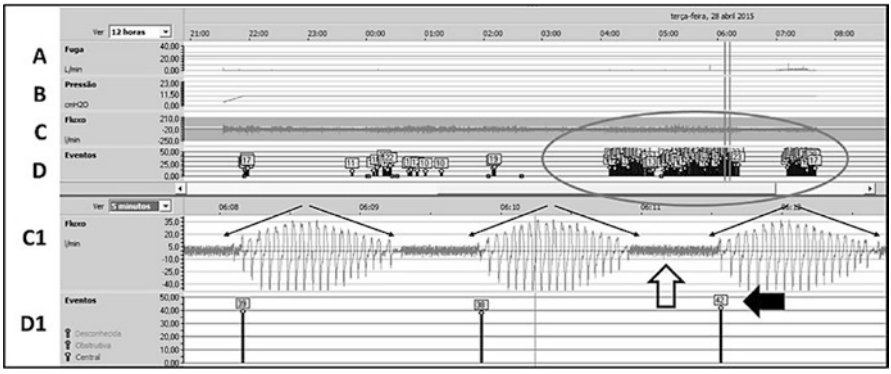

Fig. 1 Screen of a graphical data presentation for the ResScan™ system, extracted from positive pressure equipment by the company ResMed. (**A**) unintentional leak; (**B**) CPAP pressure; (**C**) respiratory flow curve; (**D**) residual respiratory events (obstructive apnea, central apnea, hypopneas, or events of increased airway resistance), during the entire night of CPAP uses; (**C1**) respiratory flow curve; (**D1**) residual respiratory events, in five-minute window of observation. The small arrows highlight the increasing-decreasing breathing pattern (CSB), indicative of respiratory instability; the open arrow shows a central apnea event; the dark arrow shows the marking time of a central apnea event. Circle shows in which moment during the night the increasing-decreasing breathing pattern indicative of CSB (showed at C1) was observed. (Image courtesy from Dr. Juliana Arcanjo Lino (original figure))

no difference in mortality rates between the two groups (with and without CPAP). On the other hand, a post hoc analysis of the results of this study demonstrated that the early suppression of CSA by PAP for an AHI below 15 per hour can improve the LVEF and patient survival with HF [34].

Another therapeutic alternative to PAP could be the adaptive servo-ventilation (ASV), a noninvasive ventilation modality that provides a fixed expiratory pressure to correct obstructive events and an inspiratory pressure, which varies according to minute ventilation, in addition to a backup respiratory rate that can be used to suppress central apneas. However, the Adaptive Servo Ventilation in Patients with Heart Failure trial (SERVE-HF study) conducted with 1,325 patients with severe HF and reduced ejection fraction (<45%), randomized to usual treatment plus ASV or usual treatment alone showed that there was an unexpected 34% increase in cardiovascular mortality in the ASV group [35]. Since then, the use of the ASV has not been recommended for use in patients with HF and ejection fraction <45%.

In our routine, the use of fixed PAP has been effective in suppressing central apneas by promoting an increase in oxygen level and a reduction in respiratory instability, responsible for variations in breathing. Furthermore, PAP works not only in the upper airway, but the positive pressure transmitted in the lungs can be beneficial for patients with HF and renal failure since PAP is a form of treatment for acute lung edema. Therefore, it works by improving the ventricular function in patients with HF, by decreasing the preload and afterload [3, 36]. Moreover, the study of Nerbass et al. [37] that evaluated the acute effects of CPAP on hemodynamic and cardiac performance in patients with hypertrophic cardiomyopathy demonstrated that the application of a 10 cmH_2O proved to be safe in patients with hypertrophic cardiomyopathy, without causing acute effects on blood pressure, heart rate, cardiac output, stroke volume, and LVEF.

Another great technique in CSB management is positional therapy, a traditional procedure already known among physiotherapists. The simple elevation of the head of the bed has been able to reduce the rostral displacement of fluids to the lungs and, with this, contribute to the reduction of central sleep apneas. Although the combination of CPAP therapy with bed positioning in clinical practice has been shown to be a good strategy for controlling central apneas due to overload fluid, it is important that the entire multidisciplinary team is attentive regarding the optimized medication use (especially diuretics) and the patient's health stabilization, with attention to all risk factors for the body fluid increase (e.g., inadequate diet).

Below we describe a clinical scenario where CSB was found, and we discuss our management approach.

2 The Man with Periodic Breathing and Sleepiness

Male patient, 82 years old, sedentary, ex-smoker, with a history of systemic arterial hypertension and dyslipidemia, ventricular arrhythmia, and complaints of daytime sleepiness and difficulty concentrating. He was referred for treatment with positive

pressure in the upper airways. At the physiotherapeutic evaluation, he presented: body mass index (BMI), 23.9 kg/m^2; neck circumference, 49 cm; Modified Mallampatti Scale, 2; and Epworth Sleepiness Scale, 13. Diagnostic polysomnography (PSG) showed severe sleep-disordered breathing (AHI: 60.1/h), with a central apnea index (CAI), 25.1/h; an obstructive apnea index (OAI), 0.7 h; and a hypopnea index (HI): 34.1/h. Titration PSG revealed a slight reduction in the AHI to 44.9/h, with a predominance of hypopnea events (HI: 42.1/h) over apnea events, and suggested CPAP treatment with a pressure of 9.0 cmH_2O.

Although the titration PSG suggested a pressure of 9.0 cmH_2O, we found more appropriate starting CPAP therapy with lower pressure (fixed pressure of 6.0 cmH_2O, with expiratory relief turned off), since residual AHI at titration PSG was high (probably due to central hypopneas) and considering a high-loop-gain patient. The patient was adapted to a nasal mask. During the positive pressure adaptation program, the patient was followed up weekly, with clinical evaluations, respiratory flow curve analysis, and also maintaining remote monitoring for appropriate positive pressure adjustments if necessary. After a week, a 7:41h CPAP average use was observed, a residual AHI of 8.1 events per hour (CAI: 5.8/h), and satisfying leak control. At respiratory flow curve analysis, we observed (by respiratory pattern) a ventilatory instability, suggestive of Cheyne-Stokes breathing, mainly at the end of the night (Fig. 1). Considering the presence of cardiovascular morbidity, we supposed that this periodic breathing observed at the end of the night would be associated with liquid displacement to the lungs. Therefore, our approach was to maintain a fixed pressure of 6.0 cmH_2O plus the elevation of the head of the bed (15 cm), to reduce the fluid shift displacement from the legs to the upper body.

In the third week, the patient reported an improvement in daytime sleepiness, without complaints of discomfort with therapy. Data from the last 7 days showed an AHI of 6.8 h (CAI: 4.0/h). In the respiratory flow curve analysis, periods of periodic breathing were also observed, suggestive of CSB, especially at the end of the night. Our approach was to reduce the pressure from 6.0 to 5.8 cmH_2O and increase the ramp from 25 min to 45 min, allowing a gradual increase in the pressure level up to the therapeutic pressure and reducing the instability of the respiratory system (to give to the respiratory center more time to adapt to the positive pressure). Considering the importance of multidisciplinary treatment, we contacted the cardiologist to optimize antihypertensive medication and suggested the use of compression stockings during the day, to avoid the accumulation of fluid in the legs.

After a period of 2 months, we observed a good therapeutic result, with the patient maintaining a median hour of CPAP use of 7:10 h and a residual AHI of 7.2/h. The patient was well adapted to positive pressure therapy, reporting improvement in daytime sleepiness and quality of sleep. Despite the antihypertensive medication optimized by the cardiologist, elevation of the head of the bed, and fine adjustments of PAP parameters (such as fixed pressure mode and increased ramp time), the patient still had residual AHI with a predominance of central events and periodic breathing, according to the data analyzed by remote monitoring (Fig. 2).

Leak l/min	Median:	**7.1**	Percentile 95%:	**29.4**	Maximum:	**89.8**
Events/hour	AI:	**6.3**	HI:	**0.9**	AIH:	**7.2**
Apnea index	Central:	**5.5**	Obstructive:	**0.3**	Unknown:	**0.5**
RERA index						**0.3**
Cheyne-Stokes Breathing						**49 minutes (9%)**

Hours of use

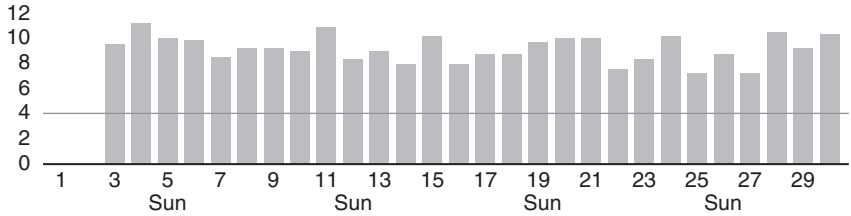

Fig. 2 Screen of the sample report, extracted from AirView – ResMed™. The dark arrow shows total apnea-hypopnea index (AIH); the open arrow shows central apnea index (CAI), Sun, Sunday. (Image courtesy from Dr. Juliana Arcanjo Lino (original figure))

However, these respiratory events have not interfered with the patient's sleep quality, as they report improvement in daytime sleepiness. In addition, we remember that post hoc analysis of the CPAP trial [33] demonstrated that early suppression of central events by PAP for an AHI below 15 per hour appears to be associated with improvement in left ventricular ejection fraction and survival improvement in HF failure patients.

2.1 Central Apnea Due to a Medical Disorder Without Cheyne-Stokes Breathing

CSA due to a medical condition without CSB is usually encountered in neurological diseases, in which stroke has been shown to be one of the most common clinical conditions associated with this kind of sleep-disordered breathing (SDB). Forty percent of the patients demonstrate central apnea as the predominant type of sleep disorder after a stroke (Fig. 3) [5, 38]. The mechanism of CSA after stroke has been discussed to be a direct consequence of the injury of central nervous system structures, leading to a lack of central input from the brain to the muscles of respiration [39, 40].

The PAP treatment of CSA without CSB recommends the use of the lowest and effective pressure, capable of treating existing obstructive events and, at the same time, reducing the ventilatory control instability and the central events. In clinical practice, it is not recommended the use of automatic CPAP, as it can trigger an

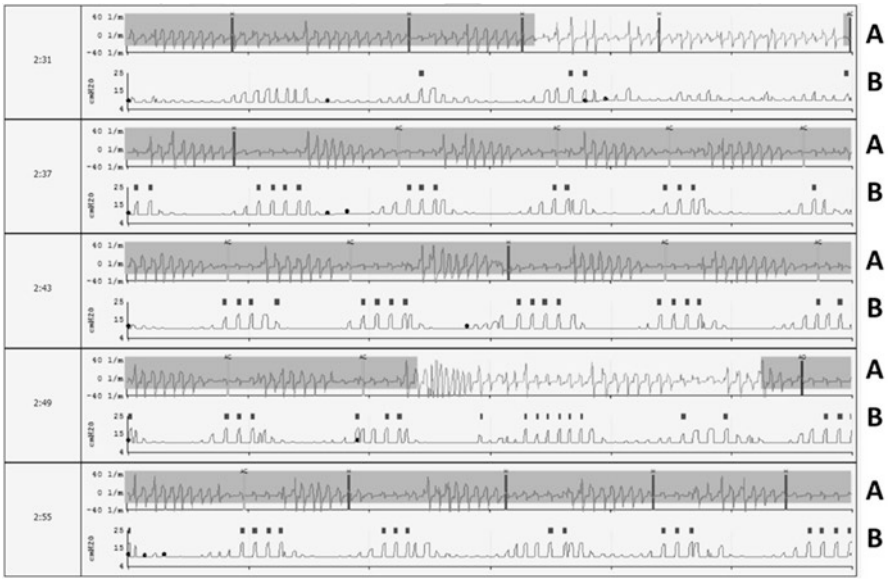

Fig. 3 Screen of a graphical data presentation for the EncorePro 2™ system, extracted from a Philips Respironics servo-ventilator. (**A**) respiratory flow curve; (**B**) pressure support. The gray hatch in (**A**) shows the breathing pattern after a stroke, with an increasing-decreasing respiratory pattern. Note in (**B**) the servo-ventilator sending mandatory breaths in apnea events and considerably decreasing the ventilatory support at central breathing events, to stabilize the patient's breathing pattern. (Image courtesy from Dr. Vivien Schmeling Piccin (original figure))

inhibitory reflex of the respiratory center, and arousals increase at the same time also resulting in periodic breathing events (especially in patients with high loop gain). In practice, the use of expiratory relief and automatic ramp must be avoided whenever possible, as they can also trigger ventilatory control instability precipitating periodic breathing.

3 Treatment-Emergent Central Sleep Apnea

A new addition to the International Classification of Sleep Disorders is the treatment-emergent central sleep apnea (TECSA), a respiratory disorder classified in the recent past as complex sleep apnea syndrome [2]. In TECSA, the patient exhibits predominantly obstructive events during diagnostic sleep testing, but central apneas or central hypopneas emerge or persist during treatment for obstructive sleep apnea. TECSA has been observed after various treatment modalities for OSA, like mandibular advancement device, maxillomandibular advancement surgery, nasal surgery, tracheostomy, or myofunctional therapy, but is more often reported during the initiation of PAP therapy. The potential mechanisms leading to TECSA included

ventilatory control instability (expressed by high loop gain in patients with OSA and the presence of upper airway (UA) narrowing during central apneas and hypopneas), low arousal threshold, activation of lung stretch receptors, and prolonged circulation time [41, 42].

The greatest question regarding treatment-emergent central sleep apnea using PAP therapy is if it requires a specific intervention considering that some central respiratory events could be spontaneously resolved over time with ongoing treatment with CPAP therapy [41, 43]. In our experience, as physiotherapists, the answer to this question is yes, principally because, although there is still some controversy about the optimal method for treating TECSA, central apneas persist in some patients even with regular CPAP therapy. Even supposing that ASV and BiPAP with respiratory backup rate could be used to treat TECSA, with significantly CSA improvement, there is no strong evidence that supports the use of these PAP modalities over the traditional CPAP therapy [41]. And we must consider the cost of the ASV and BiPAP compared with the CPAP device. In the clinical routine, the use of CPAP treatment without expiratory relief and fixed pressure has been shown to be the best cost-effective choice for resolving TECSA over time, improving the stability of the ventilatory control system. In practice, we also observe a great TECSA improvement with the addition of traditional physiotherapy techniques to the PAP therapy (especially, positional therapy).

Below we describe a clinical scenario where TECSA was found, discussing our management approach in the context of current guidelines and relevant literature.

4 The Man with Non-restorative Sleep and Difficult Daytime Sleepiness

A 59-year-old male was referred to the PAP therapy adaptation program, complaining of non-restful sleep, nightmares, snoring, and hypersomnia. He had a clinical history of pituitary adenoma. PSG revealed OSA with an apnea-hypopnea index (AHI) of 32/h. Auto-PAP was prescribed at 5.6–13 cmH_2O. Wireless monitoring data during a follow-up visit at 2 weeks of therapy revealed an average hours of CPAP use of 5:14 h. Residual AHI was normal at 3.3/h, but the patient still complained of non-restorative sleep and daytime sleepiness. At the analysis of the respiratory flow curve, we observed some CSA events and a respiratory pattern indicating instability of ventilatory control (Fig. 4).

Considering the respiratory instability observed, the therapeutic model was adjusted to a fixed pressure of 9.0 cmH_2O. Because of a persistent respiratory instability without flow restriction, a gradual decrease in the pressure level up to a pressure of 7.0 cmH_2O was made aiming for the breathing pattern improvement. Despite the increase in the average time of use of CPAP (from 5:14 h to 6:13 h) and the patient's report of better comfort, a more restful sleep sensation, and an improvement in daytime sleepiness, certain periods of respiratory instability during sleep were still noticed (Fig. 5).

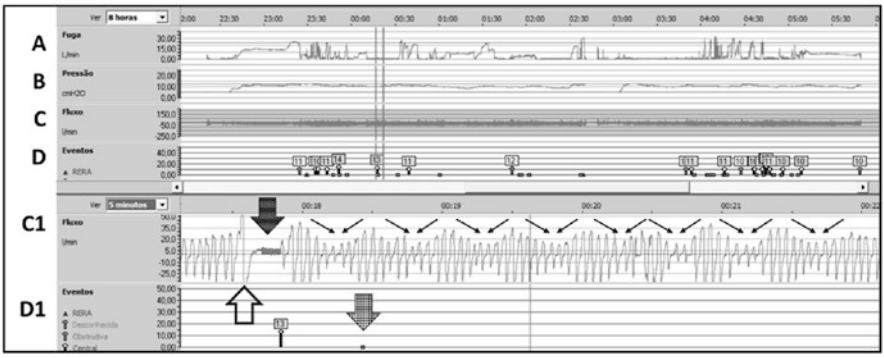

Fig. 4 Screen of a graphical data presentation for the ResScan™ system, extracted from positive pressure equipment by the company ResMed. (**A**) unintentional leak; (**B**) CPAP pressure; (**C**) respiratory flow curve; (**D**) residual respiratory events (obstructive apnea, central apnea, hypopneas, or events of increased airway resistance), during the entire night of CPAP uses; (**C1**) respiratory flow curve; (**D1**) residual respiratory events, in five-minute window of observation. The open arrow shows a physiological sigh event, with a considerable increase in respiratory flow; the dark shaded arrow shows a central apnea event in response to the decrease in the gasometrical level of carbon dioxide caused by the increase in respiratory amplitude in the previous respiratory cycle; the light shaded arrow shows the marking of a hypopnea event; the small arrows highlight the increasing-decreasing breathing pattern, indicative of respiratory instability. Note that this pattern was not detected by the algorithm and was only observed by graphical assessment of the respiratory flow curve (not because there is a problem with the equipment, but because the patient's breathing pattern sometimes has specific characteristics that influence the perception of the breathing pattern by the device's sensors). (Image courtesy from Dr. Vivien Schmeling Piccin (original figure))

Interestingly, the events of respiratory instability were distributed at specific times during the night, raising the hypothesis that they could be associated with an upper airway collapse during REM sleep, by reason of reduced muscular tonus at this sleep phase [44]. However, we could not ignore that these respiratory events could be also associated with positioning during the night, mainly due to palatal prolapse (as the presence of upper airway narrowing in patients with high loop gain or lower arousal threshold can be a possible trigger to CSA events) [45]. Analyzing the patient's data more deeply, we found that the patient had a soft palate elongation (Fig. 6) and a characteristic expiratory flow curve indicating the palatal prolapse (Fig. 7).

These data corroborated a probable palatal prolapse that, added to the hypothesis of high loop gain presented by the patient, could be the factor responsible for the ventilatory disorder, resulting in the emergent central apneas.

According to the Deacon-Diaz et al. [49] study, the product of "control gain (CG)" (represented by the sensitivity of central and peripheral chemoreceptors) versus "plain gain (PG)" (represented by the effectiveness of the lungs to alter blood gases, plus the increase in factors that lead to a collapse of the UA), determines the magnitude of the LG (Fig. 8), and, considering that was not our intention to infer in the CG, the possibility of intervention in the PG was considered. We consider that the PG intervention by adding a positional device could act to decrease the

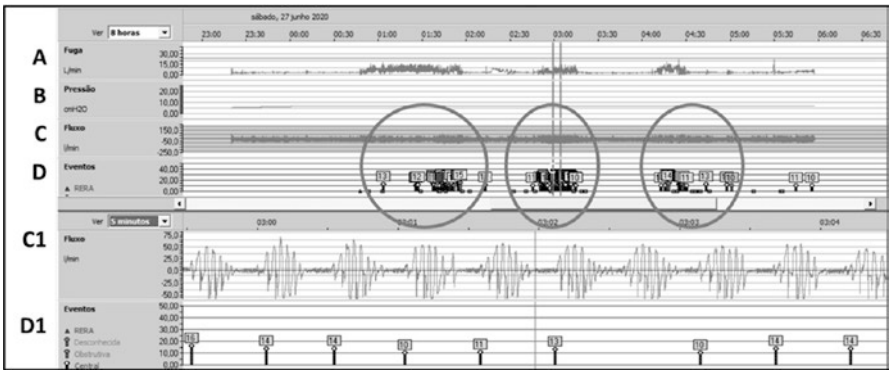

Fig. 5 Screen of a graphical data presentation for the ResScan™ system, extracted from positive pressure equipment by the company ResMed. (**A**) unintentional leak; (**B**) CPAP pressure; (**C**) respiratory flow curve; (**D**) residual respiratory events (obstructive apnea, central apnea, hypopneas, or events of increased airway resistance), during the entire night od CPAP uses; (**C1**) respiratory flow curve; (**D1**) residual respiratory events, in five-minute window of observation. Circles shows in which moment during the night the increasing-decreasing breathing pattern indicative of respiratory instability (showed at C1) was observed. (Image courtesy from Dr. Vivien Schmeling Piccin (original figure))

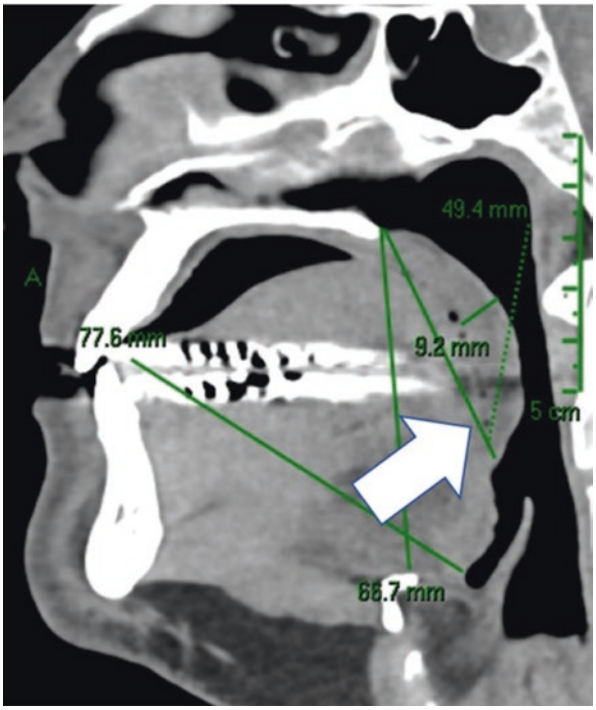

Fig. 6 Computed tomography of sinuses showing elongated soft palate (white arrow). (Image courtesy from Dr. Vivien Schmeling Piccin (original figure))

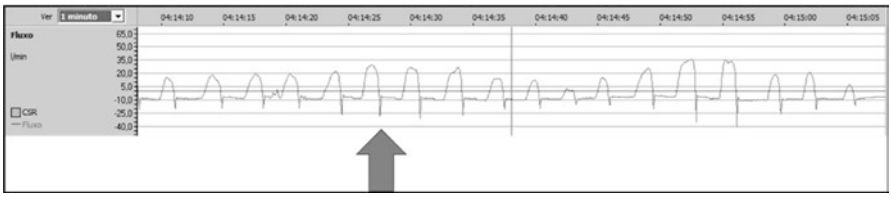

Fig. 7 Screen of a graphical data presentation for the ResScan™ system, extracted from positive pressure equipment by the company ResMed, showing the respiratory flow curve with restriction of the expiratory flow curve (spine at the expiratory curve, highlighted by the arrow), characteristic of prolapse palatal event. (Image courtesy from Dr. Vivien Schmeling Piccin (original figure))

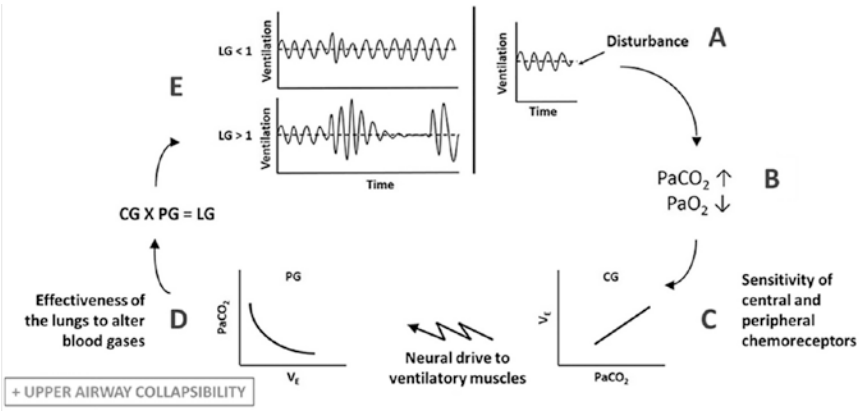

Fig. 8 "Control gain" versus "plain gain" (represented by the effectiveness of the lungs to alter blood gases, plus the increase in factors that lead to upper airway collapsibility) determines the magnitude of the loop gain. (**A**) Breathing disturbance causes a reduction in ventilation below eupnea; (**B**) reduced ventilation increases arterial CO_2 and reduces arterial O_2; (**C**) control gain (CG) represents the sensitivity of the peripheral and central chemoreceptors to blood gases and modulates the magnitude of neural drive to ventilatory muscles; (**D**) plain gain (PG) is the effectiveness of the lungs to change blood gases; (**E**) the product of control gain and plain gain determines overall loop gain (LG). If the loop gain is less than 1 (LG < 1), the fluctuations in ventilation will dampen out, and breathing will stabilize. If the loop gain is greater than 1 (LG > 1), the fluctuations in ventilation will increase in amplitude, and instability will be self-perpetuating. (Modified with permission from Deacon-Diaz [49])

magnitude of the respiratory response to a probable palatal prolapse since it was observed that the response magnitude was greater in certain periods of the night (Fig. 5) (maybe due to a supine position). In fact, the study by Joosten et al. (2017) warns about the dynamic LG increase with the adoption of the supine position during sleep, in patients with obstructive sleep apnea [46].

A positional therapy (PT) with a positioning vest was introduced as an adjunct to the pressure treatment of obstructive sleep apnea [Fig. 1 on chapter "Obstructive Sleep Apnea: Physiotherapeutic approach"], keeping the therapeutic pressure fixed

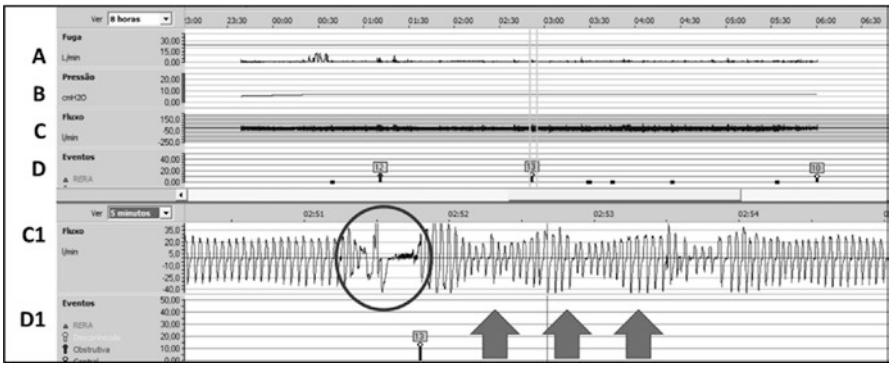

Fig. 9 Screen of a graphical data presentation for the ResScan™ system, extracted from positive pressure equipment by the company ResMed. (**A**) unintentional leak; (**B**) CPAP pressure; (**C**) respiratory flow curve; (**D**) residual respiratory events (obstructive apnea, central apnea, hypopneas, or events of increased airway resistance), during the entire night of CPAP uses; (C1) respiratory flow curve; (D1) residual respiratory events, in five-minute window of observation. The circle shows a sigh. Arrows show that after the sigh, there was an altered ventilatory response, but not an exacerbated ventilatory response. (Image courtesy from Dr. Vivien Schmeling Piccin (original figure))

at 7.0 cmH_2O. After a period of 36 days, we observed a good therapeutic result, with the patient maintaining a median hour of CPAP use of 6:40 h, the percentile 95% hours of use of 7:04 h, and a residual AHI of 6.1 events per hour. The patient was satisfied with the actions implemented for the treatment of OSA, referring a better sleep and significant improvement in daytime sleepiness and quality of life. But unfortunately positional therapy is not easy to maintain during sleep, and PT devices have not been widely adopted in part due to the poor treatment adherence observed [47]. In our case, the residual AHI was contaminated by nights of not using the PT. In the assessment of the respiratory flow curve during sleep when the patient was wearing the positional device, a high LG component was still present, observed by the change in the respiratory pattern after a physiological event of resuscitative sigh, but with a more controlled ventilatory response to the respiratory event (Fig. 9).

Treatment adherence with new vibratory positional devices has been shown to be high, possibly due to enhanced patient comfort with their petite design [47]. Based on our results, we consider that this kind of dispositive must be considered when a treatment-emergent central sleep apnea appears to be due to supine position during the night. In fact, the management strategy of TECSA aims to eliminate abnormal respiratory events, stabilize sleep architecture, and improve comorbidities. Although continuous positive pressure, preferably CPAP, is the standard treatment therapy for these cases, we should evaluate the benefit of therapeutic techniques in addition to pressure therapy. On the other hand, even though insufficient available data support ASV as an early intervention strategy for the treatment of TECSA, if central apneas persist at the follow-up session, changing the mode of PAP to either BiPAP with a back-up rate or ASV could be considered. In part of the cases, the multidisciplinary

team needs to evaluate the use of medications (e.g., acetazolamide), oxygen therapy, or carbon dioxide supplementation to improve TECSA, since these methods have been presented in some studies as therapeutic possibilities to improve the ventilatory control stability or raise the arousal threshold for TECSA patients [41, 42, 48].

5 Final Words

Treating central sleep apnea is a challenge. Accurate knowledge of the physiology of sleep and the respiratory system, as well as the pathophysiology of CSA, clinical characteristics, associated morbidities, and polysomnographic findings, is essential for the CSA diagnosis and for the development of the patients' approach. It is also important to know that the treatment of CSA must be multidisciplinary, and more than one treatment strategy can be combined when necessary.

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Upper Airway Resistance Syndrome: An Overview

Luciana Palombini, Luciane Impelliziere Luna Mello, and Avram R. Gold

Sleep-related breathing disorders (SBD) include a range of respiratory abnormalities during sleep, leading to disruption of the sleep architecture and diurnal consequences. Obstructive sleep apnea (OSA) is the most recognized disorder, but many believe that SBD are a spectrum of disorders from snoring to severe OSA [1]. A variety of phenotypes have been suggested to identify the different presentations of SBD [2]. Upper airway resistance syndrome (UARS) can be viewed as one phenotype of SBD.

UARS is an SBD characterized by an increase in upper airway resistance associated with an increase in respiratory effort leading to sleep fragmentation, non-restorative sleep, and waking symptoms, including excessive daytime sleepiness, tiredness, and fatigue. There is still controversy as to whether UARS and OSA are separate entities or are a part of the same disorder [3].

Guilleminault and associates first described UARS in 1993 in a group of 48 patients with idiopathic hypersomnia. Electroencephalography with esophageal manometry demonstrated that these patients experienced awakenings associated with an increase in respiratory effort (Fig. 1). Treating the patients with PAP during sleep resulted in an improvement of their daytime sleepiness [3].

1 Prevalence

The prevalence of UARS in the general population is not well established yet, and studies have used different criteria. In a retrospective study that identified UARS in a sample derived from a mixed military population using esophageal manometry (a

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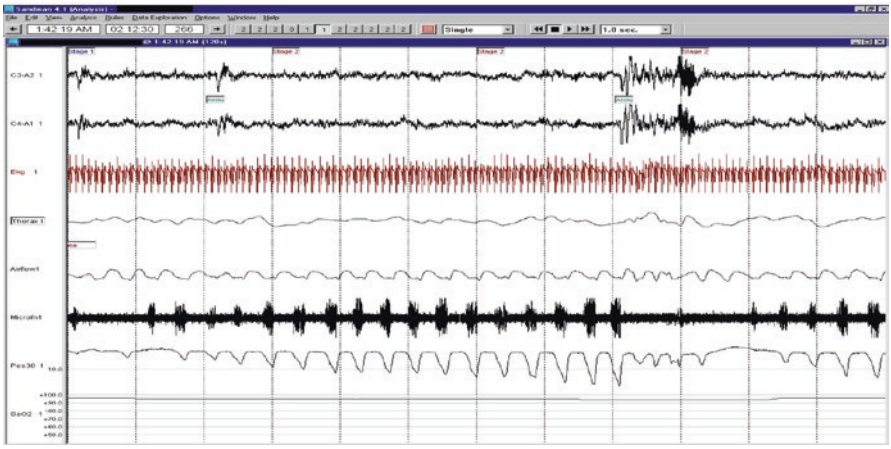

Fig. 1 Respiratory effort-related arousal indicated by esophageal pressure. (Image Courtesy from Dr. Luciana Palombini) (original figure)

research tool not used in clinical polysomnography), a UARS prevalence of 8.4% was observed [4]. However, in a more recent study of a sample from the general population of São Paulo, using the presence of inspiratory flow limitation associated with symptoms to identify UARS, the prevalence was 15% [5].

2 Pathophysiology

UARS pathophysiology is related to partial upper airway obstruction during sleep with OSA. Although the increase in upper airway resistance associated with UARS is not enough to satisfy the criteria of OSA, the increase in upper airway resistance lead to increased respiratory effort and presence of flow limitation, which can lead to significant consequences in sleep architecture and is often undetected by the patient. Individuals with UARS present a higher frequency of oral breathing, abnormalities in the nasal structure, and increased lateral pharyngeal wall volume, compared to individuals with no sleep breathing disorder [6].

UARS is typically observed in younger, thinner individuals and, in some reports, with no male predominance compared to OSA. Patients with UARS present complaints of tiredness and excessive sleepiness. They also present insomnia, restless sleep, depression, and anxiety. An association between UARS and fibromyalgia was described in patients with pain complaints [7, 8]. Other symptoms include dry mouth, excessive sweating at night, and morning headache [7]. UARS has also been described as a triggering factor for sleepwalking in children [9].

It has been demonstrated that those patients with UARS may present worse complaints of poor sleep quality and diurnal consequences compared to patients with OSA, but the mechanism for this finding is not known yet [10]. Different aspects

related to specific phenotypes describing individual differences not yet established may be involved [8].

The stress response has been suggested as a mechanism involved in the different clinical manifestations of sleep breathing disorders. Gold et al. demonstrated that sleepiness and fatigue are correlated with the level of somatic arousal, a manifestation of the SNS component of the stress response among UARS patients [8]. However, this aspect needs to be more evaluated, and new studies are necessary to define this factor in the pathophysiology and clinical manifestations of UARS patients.

3 Methods for evaluation

UARS patients can present on physical examination different abnormalities, such as, narrow external nasal valves, internal nasal valve collapse, hypertrophy of the nasal turbinates, and septal deviation. Craniofacial changes in UARS are also described [11]. Cold extremities, postural hypotension, or lower blood pressure have been described in patients with UARS [11, 12].

The first PSG criterion for UARS is absence of OSA criteria. The PSG in the UARS presents events indicative of partial obstruction of the upper airway, including increased respiratory effeort, presence of RERAs [13] and airflow limitation [14]. As mentioned, a quantitative criterion for these events for the diagnosis of UARS is not yet defined.

RERA is currently defined as a sequence of breaths characterized by increased respiratory effort or flattening of the airflow curve of the nasal pressure cannula,

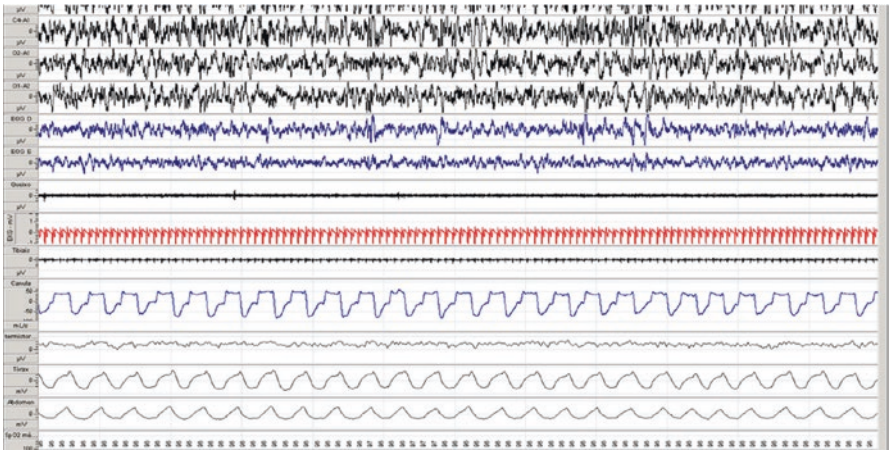

Fig. 2 Polysomnography showing airflow limitation. (Image Courtesy from Dr. Luciana Palombini (original figure))

leading to awakening (that does not reach the criterion for apnea and hypopnea). RERAs have a duration of 10 seconds.

Airflow limitation is defined as an increase in respiratory effort without a proportional increase in airflow. Airflow limitation may be indicated by the flattening flow curve by the nasal pressure cannula (Fig. 2). Periods of airflow limitation are associated with increased respiratory effort, and this event in PSG has been used as an indirect indicator of increased upper airway resistance [13–15]. According to the authors, the nasal pressure cannula can be used instead of esophageal manometry to detect RERA-type events.

The airflow limitation or increased breathing effort, in the absence of awakenings, is not recognized today as a sleep respiratory abnormality by the American Academy of Sleep Medicine (AASM). The presence of airflow limitation has been associated with different consequences, including fibromyalgia, periodic limb movement, somnambulism, preeclampsia, alternating cyclic pattern, changes in systemic blood pressure, and increase of carbon dioxide pressure at the end of expiration [14, 16]. Airflow limitation can also occur in healthy individuals. A study carried out in a sample of the general population showed that up to 30% of the total sleep time of healthy people can have airflow limitation [5]. These findings were not replicated, and possible confounding factors should be considered, such as nasal obstruction.

Other polysomnographic methods have been described to evaluate the increase in upper airway resistance during sleep, among them, the critical pressure technique, but this non-technical technique is also not validated [17].

UARS is associated with sleep fragmentation. Sleep fragmentation may be indicated by an increase in awakenings characterized by fast EEG frequencies, according to standardized definition of AASM [18], but more sensitive methods have been suggested, among these, analysis of the cyclic alternating pattern (CAP). CAP is a marker of instability and sleep fragmentation. CAP includes slow-wave sleep awakenings, EEG synchrony with delta waves, and K-complex [19]. The CAP analysis showed a correlation with sleepiness and fatigue scales in patients with UARS [9].

4 Treatment

Treatment options for UARS include behavioral treatment similar with OSA, including weight loss and nasal evaluation, PAP [20], oral appliances (OA), and surgical treatment. Hypnotic medications, such as zopiclone as adjuvants [21], can also be used to assist in treatment complaints. OA are a therapeutic option for UARS as they anteriorize the jaw and the tongue, in order to reduce the obstruction in the oropharynx. Treatment with OA has shown to reduce the awakening index, lower negative esophageal pressure, increase sleep efficiency percentage and the minimum oxygen saturation, and reduce subjective excessive daytime sleepiness and snoring in UARS patients [22, 23]. The benefits of oral devices in UARS were also demonstrated in a recent double-blind randomized study which improved sleep quality, complaints of depression, and stress symptoms [24, 25].

Surgical treatment of UARS has also been suggested [26]. Surgeries performed include septoplasty, turbinectomy, laser-assisted uvuloplasty, uvulopalatopharyngoplasty, genioglossus advancement, mandibular osteotomy with myotomy, and hyoid suspension. However, it is necessary well designed long term follow up studies to establish surgical treatment in UARS patients [26].

5 Final words

UARS can lead to significant impairment of the sleep quality and consequently quality of life. Although recognized in clinical practice, UARS is still under-diagnosed and under-treated. It is important, however, for the health professional to know that there are different phenotypes of SBD in addition to OSA that needs to be recognized and have appropriate treatment. Studies confirming significant outcomes and effective treatments for the establishment of UARS in sleep medicine are necessary.

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Upper Airway Resistance Syndrome: Physiotherapeutic Approach

Evelyn Brasil

Upper airway resistance syndrome (UARS) is a syndrome of increased upper airway collapsibility during sleep. The upper airway collapsibility during sleep of patients with UARS is halfway between that of normal subjects and that of patients with mild-to-moderate sleep apnea.

There is a lack of scientific evidence on literature about the treatment of UARS, as most of the research is case series by now. Treatments for UARS range from surgical procedures, oral appliance devices, pharmacological treatment, radiofrequency thermal ablation, and the use of positive airway pressure (PAP) [1]. From the existed investigations, the number of patients treated has been too low and the protocols too limited to be delivered at appropriate outcome recommendations. Still, many of the attempts have shown positive results, suggesting the possibility of several treatment possibilities.

1 Positive Airway Pressure

PAP is one of the most studied treatments for UARS, which can significantly reduce nocturnal awakenings and diurnal clinical symptoms such as excessive daytime sleepiness and fatigue. PAP can also improve sleep consolidation as seen in the example of a hypnogram, decreasing sleep-disordered breathing (Fig. 1), increasing N3 stage as seen in polysomnographic examination (PSG), and reducing SL, as seen in multiple sleep latency test (MSLT).

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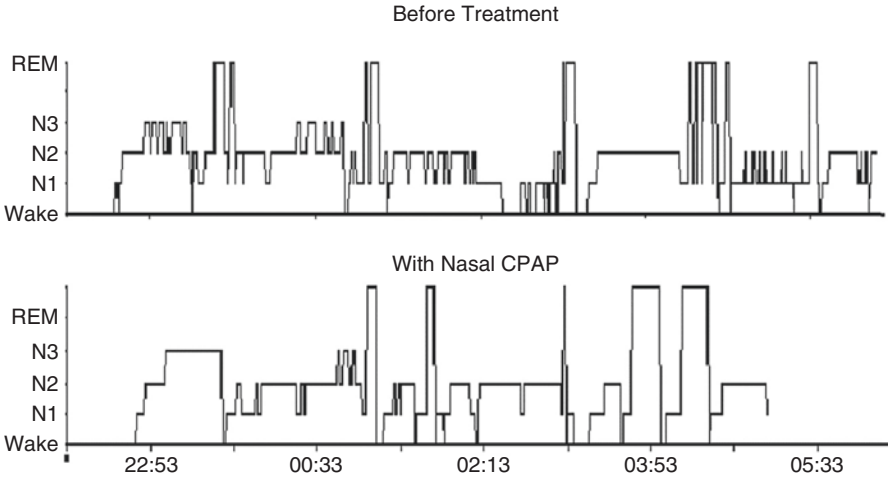

Fig. 1 Hypnograms (plots of sleep stages against time) before and after treatment with positive airway pressure (PAP) that demonstrate increasing sleep consolidation (decreasing sleep stage shifts) for a participant receiving therapeutic nasal continuous PAP (CPAP) (age 43 years; BMI 30 kg/m^2; baseline AHI 5/h; baseline RERA index 23/h). (Abbreviations: *N1* non-rapid eye movement stage 1 sleep, *N2* non-rapid eye movement stage 2 sleep, *N3* slow-wave sleep, *REM* rapid eye movement sleep stage). (Reprinted with permission from Amin et al. [2])

PAP delivered by a nasal route has been effective for UARS, improving daytime symptoms, as evaluated both by objective (PSG) and subjective (questionnaires) measures [3]. An investigation along with participants with idiopathic excessive sleepiness, who had not been diagnosed with other sleep disorders, demonstrated improvement in sleep as seen by the decrease of a number of awakening, increase of N3 stage, and improvement of excessive daytime sleepiness complaints after 4 weeks of treatment with PAP, titrated at a pressure of 7 cmH_2O (±1 cmH_2O). Considering that the individual who has UARS does not have a classically defined amount of apnea and hypopneas, the titration pressure of this investigation was based on the analysis of esophageal pressure measurements [3].

Snoring and excessive daytime sleepiness improve with PAP in patients with UARS [3–5]. Improvement in snoring and systemic arterial hypertension without the use of medication has also been reported in the literature, despite no improvement in subjective symptoms [5].

As for OSA or CSA, there is evidence on the PAP titration for treatment, as the UARS is an entity not fully recognized, and, therefore, no guideline on the treatment exists. But what is the pressure to set up for UARS? The pressure of the regulated PAP must be the lower one as to eliminate the flow limitation and to maintain the upper airway open, as we see in clinical practice. In one study, the mean therapeutic pressure found was 7 cmH_2O with a variation of 4–9 cmH_2O [3]. When comparing fixed PAP (continuous PAP, CPAP) with automatic PAP, another study

showed that there was greater adherence to automatic PAP compared to CPAP; however, in both ventilatory modalities, there was an improvement of excessive daytime sleepiness [6].

A pilot study investigated if the change in symptoms correlated with the change in sleep stage shifts after and before treatment with CPAP via nasal route (compared to sham CPAP) and found evidence that sleep-disordered breathing played a role in daytime symptoms of male veterans of war [2]. The change in sleep stage shifts among all participants from pre- to post-treatment PSG examination was well correlated with a positive change in symptoms such as pain, fatigue, sleep quality, and physical and mental components of quality of life [2]. This may have occurred as nasal CPAP is able to splint the pharyngeal airway during sleep, removing stressors such as pharyngeal collapse during sleep and thus decreasing the number of sleep stage shifts.

In women with preeclampsia and flow limitation, an investigation showed that the increase in night blood pressure (that occurs in this population) was eliminated with the use of automatic PAP ranging from 4 to 10 cmH_2O. This range of pressure was sufficient to minimize the increase in night blood pressure [7].

Postmenopausal women with insomnia, treated with hormone therapy, presented frequent awakenings, associated with UARS, tending to worsen the climacteric symptoms. In the investigation, some of the participants were treated with PAP or nasal surgery, both associated with cognitive-behavioral therapy (CBT). The results indicated that PAP associated with CBT improved excessive daytime sleepiness [8].

In clinical practice, due to low adherence, PAP is indicated as a therapeutic test and maintained through adherence and improvement of symptoms. The use of PAP improves the patient's subjective symptoms of UARS; however, adherence to long-term therapy is low. A study demonstrates that although initial acceptance of PAP is high, long-term adherence is low, as about 98% of individuals gave up long-term treatment [9]. In another investigation, the use of PAP in patients with respiratory disturbance index < 5 and awakening rate > 20/hour was evaluated [10]. From the 11 patients assessed, only 19% accepted the use and showed low adherence to PAP therapy (2.8 hours ±1.5 hours) in 6 months [10].

In addition to low adherence to PAP, an American study shows that of the 94 individuals diagnosed with UARS, in a 4-year follow-up, no participant started treatment with PAP. In the United States, this is due to the lack of coverage of treatment with PAP by the health insurance, which considers qualified to receive PAP only individuals with sleep apnea. In Brazil, there is no coverage of the treatment of respiratory sleep disorders by private health insurance or government health insurance [11].

In addition to PAP treatment, there are studies demonstrating the improvement of the airway circumference and symptoms with positional therapy and inspiratory muscle training in cases of sleep apnea [12, 13]. Nevertheless, we still have no investigations evaluating inspiratory muscle training or positional therapy in patients with UARS.

2 Final Words

PAP has been shown to be effective in the treatment of UARS; however, acceptance and adherence to therapy are low, and there is no consensus or guidelines for the use of PAP for UARS. Both for the use of PAP, as for the other therapeutic modalities for UARS, there is an urgent need for randomized controlled studies with follow-up as for new and innovative investigations on treatment.

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Narcolepsy: An Overview

Fernando Morgadinho Santos Coelho and Ana Carolina Dias Gomes

Narcolepsy is a sleep disorder that is characterized by excessive daytime sleepiness (EDS) and manifestations of REM sleep disorders such as hallucinations, sleep paralysis, cataplexy, and sleep fragmentation. Narcolepsy is divided into narcolepsy type 1 (NT1), with cataplexy and/or hypocretin-1 (HCRT-1) deficiency, and narcolepsy type 2 (NT2), without cataplexy and normal levels of HCRT-1 [1].

Narcolepsy is prevalent in 0.02–0.18% of the populations of the United States of America and Western Europe. Its prevalence is slightly divergent when different races or ethnicities are analyzed, varying in Japan and other Asian countries between 0.16% and 0.18%. Among Israeli Jews, a prevalence of 0.002% was noted. No epidemiological studies on the disease were found in the Brazilian population, but it is estimated that the rates are similar to those in Western Europe and the United States of America.

There is a bimodal incidence distribution at 15 and 35 years old. The symptoms of narcolepsy can start more rarely in childhood, and in 5% of patients, it starts before puberty. In the third edition of the International Classification of Sleep Disorders (ICSD-3), narcolepsy is part of central disorders of hypersomnolence: NT1, NT2, idiopathic hypersomnia, Kleine-Levin syndrome, insufficient sleep syndrome, and hypersomnia secondary to a clinical illness or medication and associated with psychiatric disorders. It is important to note that EDS is not necessarily caused by comorbid psychiatric illness, they simply need to be diagnosed in the same patient at the same time [1].

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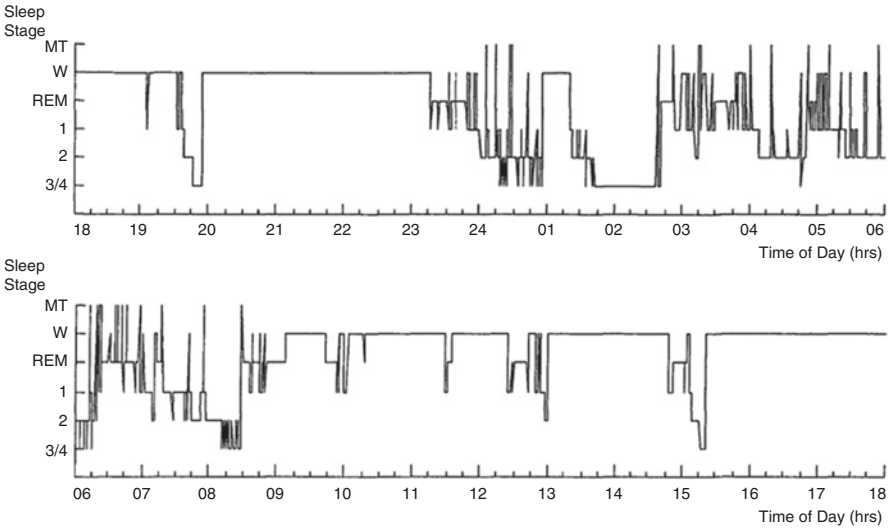

Fig. 1 Example of a typical histogram from a day-sleep individual with narcolepsy. There are frequent nocturnal awakenings (fragmented nighttime sleep) and several episodes of sleep during the daytime. Note that N3 stage was represented by stages 3 and 4, the old nomenclature. (Reprinted with permission from Rogers et al. [28])

Although cataplexy is the most specific symptom of narcolepsy, practically pathognomonic, EDS is the cardinal symptom, present in all individuals (Fig. 1). Narcolepsy patients usually have other clinical manifestations, such as cataplexy (60%), fragmented nighttime sleep (45%), hallucinations (68%), and sleep paralysis (49%) [2].

Narcolepsy patients have more comorbidities than the general population. There is an increased frequency for other sleep disorders, including periodic limb movements during sleep, sleep-disordered breathing, and REM sleep behavioral disorder. Other associated medical diagnoses are depressive symptoms, obesity, higher prevalence of pain, anxiety disorders (panic attacks or social phobias in about 20% of patients), and more than 50% of patients report severe fatigue.

Epidemiological studies have shown that obesity (defined as a body mass index $\geq$30 kg/m^2) is a twofold higher risk in narcolepsy patients than in the general population. At the onset of symptoms, there are a few possibilities to explain increased body weight in many patients, such as lower tolerance to exercise and slow oxidative metabolism with worst lifestyle and increased cardiovascular risk.

1 Clinical Picture

EDS is essential to the diagnosis of narcolepsy, and it is usually the first symptom to manifest. Cataplexy, in patients with NT1, occurs most frequently within one year of onset with gradual development over the years and small fluctuation when the clinical picture is established [1].

The other symptoms of REM sleep instability, although prevalent, are not mandatory for the diagnosis of the disease: hypnagogic and hypnopompic hallucinations, sleep paralysis, and fragmentation of night sleep [1].

1.1 Excessive Daytime Sleepiness

Patients with EDS are more susceptible to potentially fatal occupational and vehicular accidents. There is an impact in cognitive performance that manifests itself as difficulty in memory and maintaining attention, loss of memory, decreased ability to strategically plan, impaired fine motor coordination, difficulty in controlling impulses, and obscure reasoning [4]. EDS can be temporarily suppressed by physical exercise, and narcoleptic patients tend to feel refreshed after a short nap [1].

1.2 Cataplexy

Cataplexy is the most prevalent symptom after EDS in NT1, and it is an important behavioral and clinical biomarker of narcolepsy. Cataplexy is characterized by sudden and involuntary episodes of loss of muscle tone during wakefulness with preservation awareness and is usually triggered by strong positive and negative emotions.

Cataplexy occurs more frequently within 1 year of the onset of the EDS, but in rare cases, it may precede the onset of drowsiness or begin up to 40 years later. Cataplexy can either decrease with age or increase in frequency and severity.

The cataplexy attack is easily recognized when the clinical features are typical and the doctor is aware of these features. The lack of knowledge of this entity in the medical field is still common. The cataplexy phenotype differs widely among patients, and since patients are rarely examined during a cataplexy attack, their presence needs to be established based on clinical interviews only becoming a complex task [2].

Cataplexy is most commonly bilateral and symmetrical, and the most affected sites are the jaw, knees, cervical region, and lower limbs; however, it can be generalized and result in falls. When partial, attacks can be very subtle and sometimes only recognized by experienced observers. Not infrequently, they affect one side of the body. Weakness of the cervical region with cephalic ptosis is common, and facial involvement can lead to dysarthria. Extraocular musculature and diaphragm are spared during episodes, although patients sometimes describe shortness of breath [1].

Attacks start suddenly and usually evolve over several seconds, especially in generalized ones. Positive motor phenomena are not uncommon, with muscle spasms or small myoclonus (jerks), with a preference for facial muscles.

Although many emotions can potentially lead to cataplexy, joy is the most frequently associated. Actions such as laughing, telling a joke, and making a witty observation are typical examples. Cataplexy attacks usually range from 30 seconds

to 2 minutes, usually bilateral and symmetrical, without sleep. If a trigger is maintained, consecutive attacks can follow or appears as a single episode.

The frequency of cataplexy is variable, ranging from less than one attack per month to more than 20 per day. Factors such as the sudden withdrawal of drugs for cataplexy can result in *status cataplecticus*, in which attacks occur continuously [1].

It is often difficult to assess descriptions during the first contact with a patient if a muscle weakness reflects genuine cataplectic episodes or just physiological muscle fatigue associated with laughter or intense physical activity. In a recent epidemiological study, 6.5% of the reported population experienced "sudden and abrupt weakness" in association with laughter or other emotions [2].

Attacks similar to cataplexy are reported after the use of medications (lamotrigine and modafinil) and in a small number of other neurological diseases (Norrie and Niemann-Pick type C disease) [3, 4].

1.3 Fragmented Nighttime Sleep

The nocturnal sleep of these patients can be fragmented due to multiple awakenings, compromising its quality. This is a common finding, and it may even be the main complaint about some of the patients.

1.4 Hypnagogical and Hypnopompic Hallucinations

Hypnagogic hallucinations are defined as vivid dreams that occur in the transition from waking to sleep. Hypnagogic hallucinations occur in the transition from sleep to awakening. Hallucinations usually have a multimodal or "holistic" character, often combining visual, auditory, and tactile phenomena. Hallucinations are more common in people with NT1 (63%–77%), less common in people with idiopathic hypersomnia (25%), and have intermediate rates in people with NT2 (42%).

1.5 Sleep Paralysis

Sleep paralysis describes the disturbing temporary inability to voluntarily move muscles in sleep-wake transitions. Despite being awake and aware of the environment, the affected individual is unable to move his limbs or even open his eyes. The experience can take several minutes and can be very distressing. Other symptoms can include ptosis, blurred vision, and diplopia, probably as a result of drowsiness.

Sleep paralysis is prevalent in NT1 (53%–69%), relatively uncommon in idiopathic hypersomnia (20%), and has intermediate rates to these other two groups in

NT2 (35%). Unlike cataplexy, sleep paralysis is very nonspecific, with approximately 10% of the general population present.

In 2017, a study evaluated patients with NT1 and NT2 to assess exercise tolerance, which is one of the best prognostic markers of all-cause mortality in the general population, and it depends on daily energy expenditure or the amount of daily exercise. The study revealed that patients NT1 and NT2 have less tolerance to exercise and obtained interesting results [5].

Cardiopulmonary fitness is inversely related to the degree of EDS in NT1 and NT2 patients and the number of cataplexy attacks per month in NT1. They concluded that the fact that patients are less physically active (e.g., performing household chores), the day-to-day activities have reduced exercise tolerance with less muscle recruitment [5].

Patients with narcolepsy have several factors that may explain this low tolerance to exercise, such as EDS, episodes of cataplexy triggered by exercise, high fatigue prevalence, and obesity.

These patients are less active, in general, regarding actigraphy in another study, despite treatment with modafinil, a stimulant used to treat EDS. There are also reports that 48% of narcolepsy patients complained of difficulties in playing sports. In another sample of NT1 and NT2, only 19% reported playing any recreational sport. There is still a variable only mentioned in the studies, which is the highest prevalence of depression in NT1, which can also contribute to less physical activity [5].

When compared with controls and NT2, patients with NT1 had lower basal metabolism. It was noted that there was a 35% reduction in strides per day in NT1 when comparing them with the daily activities of a healthy adult non-sedentary [5].

Narcolepsy is associated with a higher cardiovascular risk when registering a greater prevalence of obesity and diabetes [6]. These patients should perform structured physical activities to improve exercise tolerance, as well as potentially improve the overall cardiovascular profile since diagnosis. The physiotherapist and the physical education professional can play a central role in the treatment of these patients by leading the prescription of activities for these patients.

1.6 Diagnosis

The diagnostic criteria based on the ICSD-3 are:

Criteria A and B must be met:

A. The patient has daily periods of irrepressible need for sleep or daytime lapses of sleep occurring for at least 3 months.
B. The presence of one or both:

    1. Cataplexy (as defined in Essential Resources) and an average sleep latency of ≤8 minutes and two or more periods of sleep-onset REM periods (SOREMP) in a Multiple Sleep Latency Test (MSLT) performed according

to standard techniques. A SOREMP (within 15 minutes of sleep onset) on PSG the night before MSLT can replace one of the SOREMPs on MSLT.

2. Hypocretin-1 level in the CSF, measured by immunoreactivity, is ≤110 pg/mL or < 1/3 of the mean values obtained in normal subjects with the same standardized test.

The EDS can be graded subjectively by applying scales such as the Epworth Sleepiness Scale (ESS), the Karolinska Sleepiness Scale, and the Stanford Sleepiness Scale. The last two allow the assessment of EDS at the moment of its application, having as a disadvantage the fact that there may be variation in somnolence from one moment to another. ESS, on the other hand, refers to the possibility of napping in everyday situations in the last 30 days [7]. The clinical instruments for quantifying EDS should not be evaluated in isolation, and it is necessary to contextualize the clinical condition of each patient. Recently, a new tool was incorporated to monitor the patients with narcolepsy [8]. The Narcolepsy Severity Scale quantifies the EDS and other symptoms of NT1 patients, and it is useful to follow them [8–10].

The MSLT measures the physiological tendency to fall asleep in monotonous situations, as patients tend to get more sleepy in these situations. The test must be conducted according to the parameters of the American Academy of Sleep Medicine manual. It is recommended that the patient undergo a PSG on the night preceding MSLT.1 The average sleep latency in MSLT below 8 minutes was the best cutoff point in the context of the diagnosis of narcolepsy, with approximately 90% of adult patients with narcolepsy with latency below that level [1].

It is necessary to pay attention to situations that can make differential diagnosis difficult through tests. Sleep deprivation can result in a false-positive result, and, therefore, this test should only be requested for patients who are sleeping well (about 7–9 hours in adults, there is the possibility of individual variations). The assessment of an adequate sleep period before the exam, by an actigraphy or a sleep diary, must be done, at least 1–2 weeks, before polysomnography/MSLT. Several drugs can affect the results of MSLT. Sedative medications that interfere with the average latency for sleep onset or REM sleep suppressant medications, especially serotonergic antidepressants, should be discontinued, if possible, before MSLT. It is necessary to evaluate the half-life of these medications and also if there is an abuse of illicit substances to avoid false-negative results.

For the diagnosis of narcolepsy, the presence of EDS must be confirmed by MSLT, when the average latency for sleep onset is less than 8 minutes and there are two or more periods of REM sleep at the beginning of sleep – SOREMPs. The two SOREMPs must be present in the MSLT and can also be considered in the baseline polysomnography (PSG), performed the night before the MSLT (SOREMP ≤15 minutes in the PSG). PSG and MSLT are objective ways to assess sleep-related parameters [1–11].

In addition to clinical findings, there are markers frequently found in patients with narcolepsy such as the human leukocyte antigen (HLA)-related allele, the HLA-DQB1*0602 allele that may be present in 95% of patients with cataplexy [12].

About 24% of patients without cataplexy will have low levels of HCRT-1 in the CSF, and 10% of patients diagnosed with NT2 will later manifest cataplexy, which will result in a change in diagnosis to NT1.1 There are still 8% of type 2 narcoleptics who present intermediate levels of HCRT-1 in the CSF (> 110 pg/mL and ≤ 200 pg/mL) [1].

1.7 Prognosis

Narcolepsy patients have difficulty performing daily life activities and socializing, mainly due to cataplexy attacks and EDS. These patients have a poor quality of life that is similar or inferior to patients with epilepsy or obstructive sleep apnea syndrome [2].

The quality of life of these patients worsens, even more, due to the delay in obtaining a diagnosis and symptom control. The average delay for diagnosis reaches more than 10 years after the onset of symptoms even in Europe, for example. When considering that the majority of patients will present the onset of symptoms in the second decade of life, they would remain untreated during a crucial period of their education and the initial period of their career [2–13].

These patients often have slower responses to external stimuli and varying degrees of difficulty concentrating [13].

2 Narcolepsy and Childhood

The clinical presentation of narcolepsy in childhood is quite different; EDS can be difficult to assess and can be expressed as excessively long night sleep or the recurrence of naps in the previously interrupted daytime period (ICSD-3).

In addition, children may paradoxically exhibit hyperactive behavior, behavioral problems, and worsening school performance. Inattention, lack of energy, insomnia, hallucinations, or a combination of them can lead to an incorrect psychiatric diagnosis of schizophrenia and depression. In this population, the presence of auxiliary symptoms, such as sleep paralysis or hypnagogic hallucinations, can also be difficult to confirm, depending on the child's expression ability.

Early puberty and obesity can also develop near the onset of symptoms. REM sleep behavioral disorder may be present from the beginning as well; it is important to pay attention to the PSG request.

Cataplexy is infrequent before the age of 4 years old with a different phenotype of typical cataplexy triggered by positive emotions. It is common the involvement of the face, eyelids, and mouth, associated with a clear non-association with emotions can occur. Along with the protrusion of the tongue, this characteristic pattern was called cataplectic facies. Children with cataplexy may also have positive motor phenomena, ranging from dyskinetic movements or perioral dystonic movements or

even stereotyped movements, similar to epileptic seizures. In children, the anticipation of a reward can also be a precipitant [1].

Due to the clinical differences, the diagnosis of NT1 in children can be a challenge also because of the difficulties in performing the MSLT and the lack of normative values for children under 6 years of age. If the MSLT is iffy, it is recommended to repeat it after some time. CSF hypocretin-1 becomes a very important test since HCRT-1 is already low or undetectable at the onset of symptoms.

3 Differential Diagnosis

Insufficient sleep syndrome, circadian rhythm disturbances, use of medications and illicit drugs, and sleep-disordered breathing can develop EDS with possible false-positive MSLT. It is important to perform PSG during the night before MSLT to observe the patient's sleep, as well as for 2–4 weeks before the test to ensure that they have been sleeping properly. Chronic fatigue syndrome and depression can mimic narcolepsy too, but it does not show the typical findings in MSLT (Table 1) [1].

Cataplexy should be distinguished from similar complaints, which are occasionally seen in normal individuals. Sensations of muscle weakness are occasionally reported when a healthy individual laughs out loud. Cataplexy should be distinguished from hypotension, transient ischemic attacks, fall attacks, epileptic seizures, neuromuscular disorders, vestibular disorders, psychological or psychiatric

Table 1 Differential diagnosis of central hypersomnolence

	NT1	NT2	Idiopathic hypersomnia	Kleine-Levin syndrome
Excessive daytime sleepiness	Yes	Yes	Yes	Yes[a]
Cataplexy	Yes	No	No	No
Hallucinations	Common	Common	Rare	Rare[a]
Sleep palsy	Common	Common	Rare	Rare[a]
Sleep fragmentation	Common	Common	Rare	No
Hyperphagia and hypersexuality	No	No	No	Common[a]
Total sleep time/24 h	Normal	Normal	Higher	Higher[a]
Refreshed after a short nap	Yes	Yes	No	No[a]
MLTS – average sleep latencies	≤8 minutes	≤8 minutes	≤10 minutes	≤10 minutes[a]
SOREMP-PSG + MLST	2 or +	2 or +	No	No
Hypocretin-1 CSF level (pg/mL)	≤110	>200	>200	>200

NT1 narcolepsy type 1, *NT2* narcolepsy type 2, *MSLT* multiple sleep latency test, *SOREMP* sleep-onset REM period, *PSG* polysomnography exam, *CSF* cerebrospinal fluid
[a]During EDS attacks

disorders, and sleep paralysis. Clear improvement with antidepressant medications is a clue for the diagnosis of cataplexy in some cases.

Idiopathic hypersomnia is distinguished from NT1 by the absence of cataplexy and the lack of two or more SOREMPs in the MSLT. In contrast to patients who have narcolepsy, patients with idiopathic hypersomnia generally have high sleep efficiency, sleep drunkenness, and non-refreshing naps [1].

Kleine-Levin syndrome is a rare syndrome characterized by prolonged EDS periods (weeks to months), most commonly seen in males and teenagers. The patient sleeps 18 hours or more, per day, and has hyperphagia and hypersexuality [1].

There are many clinical differences, and objective exams can help. In addition to the clinical findings, the HLA-DQB1*0602 allele and the HCRT-1 levels in the CSF can be used as markers previously discussed [12].

3.1 Comorbidities

Other sleep abnormalities have also been described in narcolepsy, including periodic limb movements during sleep, sleep-disordered breathing, and REM sleep behavior disorder. There is a higher prevalence of depressive symptoms, although there are conflicting reports on whether these symptoms qualify as clinical depression. Recent studies point to a high level of anxiety, panic syndrome, pain, social phobias, fatigue, and increased prevalence of obesity in narcolepsy patients with lower quality of life (about 20%). More than half of these patients report fatigue [6, 14, 15].

3.2 Pathophysiology

There is growing evidence about autoimmune changes in NT1 in genetically susceptible patients. Genetic susceptibility could be related to the strong association of NT1 with the presence of human leukocyte antigen HLA-DQB1*0602, as well as a relationship among polymorphism of alpha locus of the T cell receptors and autoimmunity [16].

There are seasonal peaks in the incidence of NT1 with a possible relationship between H1N1 infection, specific forms of vaccines (H1N1), and infection by *beta-hemolytic streptococci*. The presence in 14–26% narcolepsy patients of Tribbles homolog 2 antibodies that are related to autoimmune uveitis and the identification of autoreactive T cells drive to the immune theory. The immune system would be responsible for the loss of neurons that produce orexin or hypocretin-1 (HCRT-1) [17].

HCRT-1 is a CNS neuropeptide with a wide distribution that is produced in the lateral hypothalamus and is measured by radioimmunoassay.1 NT1 patient has a marked decrease in HCRT-1 levels in the CSF (less than or equal at 110 pg/mL), due to the loss of HCRT-1-producing neurons in brain tissue [16].

HCRT-1 has a maximum expression during wakefulness, and it is related to muscle tone through the activation of the motor system at the *locus ceruleus* and the *raphe nucleus* by the release of norepinephrine and serotonin, respectively. These neurons are inhibited during REM sleep. The balance between motor excitation and the inhibition generated by an emotional stimulus is altered in the deregulation of this HCRT-1 circuit, generating muscle atony during wakefulness, which is characteristic in NT1 patients. Cataplexy is caused by decreased excitement of noradrenergic neurons and an increased motor inhibition of GABAergic and/or glycinergic neurons. The amygdala and the medial prefrontal cortex contain neural pathways; positive emotions are the triggers for cataplectic phenomena [16].

3.3 Treatment

Non-pharmacological treatment is an essential part of treatment in patients with narcolepsy consisting of taking scheduled naps. Short naps are usually restorative in these patients. Scheduling naps throughout the day and a good night's sleep can have a great benefit to the patient, and this approach should always be associated with pharmacological treatment [2].

Unfortunately, isolated non-pharmacological treatments are generally not sufficient for the treatment of narcolepsy patients. The medications are prescribed to treat EDS- and REM-related symptoms such as cataplexy [18].

4 Pharmacological Treatment of Excessive Daytime Sleepiness

4.1 First-Line Therapy

- Modafinil – several studies with the class of evidence I
  Modafinil is the choice for the pharmacological treatment of EDS in patients with narcolepsy. The mechanism of action is not yet fully understood; the probable mechanism of action is greater presynaptic activation of dopaminergic transmission in some brain regions. It is a non-CNS stimulant with fewer side effects and a lower incidence of tolerance [19].
- Pitolisant – two studies with the class of evidence I
  Pitolisant is an antagonist/agonist inverse to histamine receptor H3. The main action is the presynaptic activation of histaminergic neurons in the brain, promoting wakefulness and improving attention and memory. The effect of pitolisant on EDS in patients with narcolepsy was similar to that of the use of modafinil [20].
- Solriamfetol – one study with a class of evidence I
  Solriamfetol is a selective dopamine and norepinephrine reuptake inhibitor with a similar release of amines to that of amphetamine-type stimulants. Solriamfetol

reduces EDS in patients with narcolepsy, and the main side effects are headache, nausea, decreased appetite, pharyngitis, dry mouth, and anxiety [21].

- Sodium oxybate (GHB) – several studies with the class of evidence I
  GHB increases the release of GABA in the hippocampus and the cerebral cortex. Other effects are the modulation of dopaminergic neurotransmission and an increase in tryptophan transport with consequent higher levels of amines and acetylcholine in the brain. The most common side effects are euphoria, amnesia, anabolic effect, aggressiveness, coma, agitation, tremors, and muscle contractions. Studies also demonstrated that GHB improves sleep fragmentation with improved EDS in patients with narcolepsy [22].

4.2 Second-Line Therapy

- Methylphenidate – one study with a class of evidence II

  It is a CNS stimulating drug, with characteristics similar to those of amphetamines. It is important to advise the patient not to use the medication on the weekends or for two days during the week to avoid tolerance. Side effects such as insomnia, high blood pressure, irritability, headache, and palpitations are common. Patients being treated with these drugs should be monitored and their complaints assessed [19].

4.3 Third-Line Therapy

- Amphetamines – no study with a class of evidence I–IV
  Amphetamines are stimulants with a higher prevalence of abuse and risk of adverse cardiovascular events. The use of lisdexamfetamine to treat EDS in patients with narcolepsy has been reported in many cases [23].
- Caffeine – one study with a class of evidence II
  Caffeine is a derivative of xanthine which is a selective antagonist of adenosine receptors (A1 and A2a). Possible higher doses necessary to promote wakefulness in patients with narcolepsy can induce anxiety, tremors, headache, and gastrointestinal irritation. However, a recent study demonstrated the benefit of lower doses of caffeine to control EDS in patients with narcolepsy [19].
- L-carnitine – one study with a class of evidence II
  L-carnitine is an amine that participates in the metabolism of lipids, playing a fundamental role in the transport of these from the cytoplasm to the mitochondrial matrix to be oxidized. There is a dysfunctional fatty acid beta-oxidation pathway in patients with narcolepsy, and a randomized placebo-controlled study showed the effectiveness of oral L-carnitine in reducing EDS by increasing the action of the enzyme L-carnitine-o-palmitoyl transferase in this population.

Recent findings point to the safe and useful use of L-carnitine during pregnancy in patients with narcolepsy [24].

5 Pharmacological Therapy of Cataplexy

5.1 First-Line Therapy

- Sodium oxybate (GHB) – several studies with a class of evidence I
  GHB is the drug of choice to treat cataplexy. It is an approved drug for the treatment of narcolepsy in children too. There is a higher concentration of sodium in the medication that can elevate blood pressure levels. It should be taken in bed, due to the risk of falls and trauma due to very short sleep latency [22].
- Dual antidepressants – venlafaxine (no study with evidence class)
  Dual antidepressants have double action with an increase in the synapses of both serotonin and norepinephrine. The main side effects are similar to other antidepressants that inhibit serotonin uptake: loss of fine coordination, mental confusion, weight gain, sedation, nausea, insomnia, and altered sexual function; and in rare cases of drug combination, they can cause arrhythmias and death. Venlafaxine is widely used in clinical practice, although there are no studies with a minimum level of evidence [19].
- Pitolisant – one study with a class of evidence I
  Pitolisant is also effective in reducing cataplexy. The use of pitolisant does not seem to lead to abuse and is well tolerated. Common side effects include headache, insomnia, and nausea, especially at the beginning of treatment [20].

5.2 Second-Line Therapy

- Tricyclic antidepressants – clomipramine (one study with a class of evidence IV)
  Tricyclic antidepressants block membrane transport of presynaptic neurons with increased concentration of monoamines in synapses with action on postsynaptic neurons. These drugs have many possible side effects such as dry mouth, impaired vision, intestinal constipation, urinary retention, postural hypotension, weight gain, difficulty concentrating and learning, tachycardia and mania, coma, delirium, cardiac arrhythmias, respiratory depression, and death. The doses used to control cataplexy are lower than those used to treat depression, with a lower prevalence and severity of side effects [19].
- Serotonin reuptake inhibitor antidepressants – fluoxetine (two studies with a class of evidence III) and citalopram (one study with a class of evidence IV)
  Serotonin reuptake inhibitor antidepressants increase the concentration in the serotonin synaptic cleft by inhibiting their reuptake by the presynaptic neuron. The side effects seen are loss of fine coordination, mental confusion, sedation,

weight gain, nausea, insomnia, and altered sexual function and, in rare cases of drug association, can cause arrhythmias and death [19].

5.3 Third-Line Therapy

- Monoamine oxidase-B inhibitors – selegiline (one study with a class of evidence II)
  Monoamine oxidase-B inhibitors block the monoamine oxidase-B that degrades serotonin, norepinephrine, and dopamine in the synapse with a consequent higher effect of these neurotransmitters on postsynaptic neurons. Sedation, confusion, tremors, excitement, weight gain, dry mouth, intestinal constipation, urinary retention, and cardiac arrhythmias can all be side effects [19].
- Baclofen – one study with a class of evidence II
  Baclofen is a $GABA_B$ agonist drug, commonly used in neurological patients to control stiffness, pain, and spasticity. There is evidence that baclofen can provide sleep benefits by reducing sleep latency and increasing slow-wave sleep, increasing the total sleep time. There is also a possible benefit of using baclofen to control cataplexy [25].

6 Future Perspectives for the Treatment of Narcolepsy

There is ample evidence of an autoimmune mechanism of NT1. Some studies to modulate the immune system have been made to control the disease. A few series of patients treated with intravenous immunoglobulins have been published, but with negative or transitory results [26].

The improvement in narcolepsy symptoms after the use of steroids and immunomodulatory treatments (alemtuzumab and rituximab) has been described; however, more studies need to be done to define the effectiveness of these immune therapies [26].

The intraventricular infusion of HCRT-1 did not improve symptoms in narcolepsy patients. However, HCRT-1 agonists appear to be promising, as long as these drugs cross the blood-brain barrier [27].

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Excessive Daytime Sleepiness: An Overview

Lúcio Huebra Pimentel Filho and Fernando Morgadinho Santos Coelho

Among the daytime symptoms related to sleep disorders, daytime sleepiness is one of the most disabling. This is a frequent reason for seeking medical care on an outpatient basis and sometimes in emergency care units.

Excessive daytime sleepiness or hypersomnia can be conceptualized as difficulty in staying awake and alert with a greater tendency to fall asleep during the day unexpectedly or at inappropriate times. It is important to make it clear that it is not always necessary for sleep to occur, but only this feeling of need for daytime sleep is enough, even if the individual manages to withstand a nap. Thus, daytime sleepiness is primarily a symptom and is directly related to a subjective interpretation. However, as we will see throughout the chapter, there are some strategies to standardize its assessment, whether with subjective clinical scales or with objective neurophysiological parameters.

Patients living with hypersomnia suffer from a very heterogeneous group of syndromes and disorders. It makes its epidemiology very complex. There are several studies in association with age, sex, body mass index, work shift, snoring, obstructive apnea, and among groups of specific comorbidities; however, the prevalence in the general population is little known and varies with the methodology used. An overall prevalence is estimated at around 4–20.6%. A recent prospective study of a Swiss cohort showed an incidence of 5.1% in a 5-year follow-up. Risk factors in this survey, associated with the onset of hypersomnia, were male gender, depressive symptoms, poor subjective quality of sleep, and moderate to severe sleep apnea [1].

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Some of the other risk factors also defined in studies of incidence are depression, sleep apnea, obesity, and diabetes [2].

The recognition of hypersomnia becomes very important because it has already been defined that this symptom, in isolation, determines an increase in general morbidity and mortality. A 10-year prospective study of a large cohort showed a mortality all-causes hazard ratio of 1.43, that is, a 43% greater chance of occurring in the group with daytime sleepiness [3]. In addition to higher mortality, it implies economic and social losses.

In this chapter, we will go deeper into the study of hypersomnia, especially in the diagnosis and recognition of its causes and available guidelines for approach and treatment.

1 Diagnosis

Evaluation of patients with excessive daytime sleepiness is generally a clinical challenge. At first, despite being a relatively common complaint in neurology and sleep medicine clinics, the search for medical help in the face of symptoms is still restricted, and, in most cases, it is delayed. The reason for this is diverse and ranges from cultural issues and ignorance about sleep disorders, difficulty in accessing a specialized service, or even prejudices and dysfunctional beliefs in relation to the patient with daytime sleepiness.

The initial step in the management of patients with daytime sleepiness is to better understand the complaint and to know how to precisely identify it. During the consultation, at the initial moment, we can already see if the patient shows signs of drowsiness at that moment. Yawning, little motor activity, difficulty in attention, or even demand for coffee can be indirect signs for the diagnosis. During the interview, it is important to assess whether the patient has daytime episodes when he has difficulty staying awake and how severity is their functional impact, even in social, professional, or school spheres. It is common for the patient, in a simple directed question, to deny having daytime sleepiness, only because he is already accustomed to the symptom or because of not taking daytime naps, but when properly assessed, it is evident that, for several moments, he has some discomfort related to the difficulty of maintaining himself awake.

A distinction that must be made during the clinical interview is whether the patient complains of fatigue and apathy or really daytime sleepiness. Fatigue is referred to as tiredness, lack of energy, and exhaustion. It is usually induced by overactivity and relieves with rest. Daytime sleepiness is referred to as a decreased ability to perform tasks that worsen at rest or in monotonous situations and relieve with sleep or nap.

Some clinical scales support this subjective assessment of the symptom. The Epworth Sleepiness Scale (ESS) is a self-administered questionnaire, a good alternative to quantify the sleepiness of patients with hypersomnia. It is an inexpensive tool, remarkably simple, and quick to execute [4]. The ESS has eight questions that show routine situations in which the patient must graduate the probability of falling

asleep, in reference to the symptoms in the last month. Each question is scored from 0 to 3, with 0 being no chance of sleep and from 1 to 3 progressively greater chance of falling asleep. The global score ranges from 0 to 24; the higher the score, the greater the daytime sleepiness. Scores greater than 9 indicates that the patient has excessive daytime sleepiness [4]. The Stanford Sleepiness Scale is also a well-established questionnaire for assessing daytime sleepiness, but it provides little information for assessing outpatients. This scale assesses the patient's state of alert at that precise moment and the propensity to sleep in that momentary situation in which it is applied. The score ranges from 1 to 7; the higher the score, the greater the drowsiness. Scores greater than or equal to 4 show significant drowsiness at that moment [5]. It can be used, in the clinical context, to guide patients with hypersomnia to better recognize and graduate their symptoms, in order to avoid performing risky tasks when at greater drowsiness, thus avoiding work and traffic accidents (please refer to chapter "Subjective assessment of sleep").

In addition to subjective assessments, it is possible, in specific contexts, to use supplementary tests to objectively quantify daytime sleepiness. There are two neurophysiological tests that provide important information for this purpose, the Multiple Sleep Latency Test (MSLT) and the Maintenance of Wakefulness Test (MWT), detailed in chapter "Objective assessment of sleep". MSLT is indicated for the investigation of patients with hypersomnia and is especially important for the diagnosis of narcolepsy and other central origin hypersomnias. MSLT is the multiparametric analysis – electroencephalogram (EEG), electrooculogram (EOG), and chin electromyography (EMG) – of five naps performed during the day. The exam starts two hours after the end of the night polysomnography, and it continues with five opportunities of naps in a calm, dark, and silent environment. The patient is instructed to try to sleep. It is assessed whether the patient falls asleep before 20 minutes of recording, and if it happens, it is observed the first 15 minutes of sleep to assess the sleep stages reached in that period. The most important data used in the interpretation of the result is the mean sleep latency, that is, how long it takes for the patient to start sleeping, from the beginning of the record until the first time of sleep. The mean sleep latency of these five records is suggestive of EDS if it is less than 10 minutes. The lower the average sleep latency, the greater the patient's propensity to nap in monotonous situations [6]. MWT is a neurophysiologic exam very similar to MTLS, especially in data collection, but it has some peculiarities. This exam is not largely used in the diagnosis of hypersomnia, but it can be useful in the clinical follow-up of patients, and it is used in the legal documentation of excessive daytime sleepiness in some countries for labor purposes or vehicular driving. The patient is monitored with EEG, EOG, and EMG of the chin and positioned comfortably in the bed, seated with indirect light in a quiet environment. In this case, the patient is instructed to try not to sleep. Latency to sleep onset is also monitored within four 40-minute opportunities, assessing the mean sleep latency [7].

Once the patient is identified as having hypersomnia, physicians need to identify the cause of this symptom. From this moment on, we will present the main causes of hypersomnia, organized in diagnostic groups with their particular aspects of epidemiology and management.

2 Causes

2.1 Insufficient Sleep Syndrome (Chronic Sleep Deprivation)

Insufficient sleep syndrome, which is named in the third classification of sleep disorders (ICSD-3) [8] or chronic sleep deprivation, is the most common cause of excessive daytime sleepiness, especially in young patients. Although more prevalent during adolescence, when the need for sleep is greater, insufficient sleep syndrome occurs at any age and in both genders.

In addition to daytime sleepiness, patients may experience other symptoms such as irritability, difficulty concentrating and paying attention, distractibility, reduced motivation, dysphoria, fatigue, and lack of coordination. Secondary symptoms can become the patient's primary focus, making diagnosis difficult.

In addition to the consequences directly related to daytime sleepiness as already mentioned in this chapter, these patients add greater cardiovascular risk and higher overall mortality due to shortened total sleep time.

For the diagnosis of insufficient sleep syndrome, complementary to the clinical interview with a usual sleep schedule during workdays and days off, a sleep diary can be requested, in which the patient records his subjective perception of a period of sleep and waking up time for a few days or weeks. Objective data can be assessed with actigraphy, which is the gold standard for sleep schedule analysis. Actigraphy is the recording through a movement sensor of periods of activity and rest, allowing the objective interpretation of sleep times and circadian rhythm.

The treatment of insufficient sleep syndrome is based on the simple rationale of prolonging total sleep time. Despite being a simple guideline, it is often difficult to perform due to poor patient compliance, especially when social conditions are unfavorable.

2.2 Hypersomnia Due to a Medical Condition

Hypersomnia secondary to clinical disease is also a diagnosis recognized by the ICSD-3 [8]. There are several clinical or neurological conditions that are associated with daytime sleepiness. Thyroid dysfunction, kidney and liver failure, hypovitaminosis B12 or D, severe anemia, Parkinson's disease, Alzheimer's disease, neuromuscular diseases, structural brain injuries, and head trauma are some examples.

Patients may experience increased total nighttime sleep, daytime sleepiness, prolonged naps, or attacks of sleep during the day. Treatment of the underlying condition tends to improve the symptoms of hypersomnia. In the presence of residual

symptoms, the diagnosis should be reviewed, and the possibility of another associated cause for daytime sleepiness should be considered.

2.3 Hypersomnia Due to a Mental Disorder

Hypersomnia secondary to a psychiatric disorder can be diagnosed when there is an association between drowsiness and a psychiatric disorder. The diagnosis of hypersomnia associated with a psychiatric disorder can be a challenge because very commonly the patient is intensely focused on symptoms related to daytime sleepiness, hiding other psychiatric symptoms. Several psychiatric disorders are related to hypersomnia, but the most common are major depressive disorder and bipolar affective disorder type 2. In addition, somatoform disorder, schizophrenia, and personality disorders can also be associated [9].

Hypersomnia associated with psychiatric disorders is more common in women than men. In patients with depression, the prevalence of daytime sleepiness is around 5–50%, according to the hypersomnia diagnostic criteria.

2.4 Hypersomnia Due to Drugs Use

The use of medications can also be a causative or worsening factor of daytime sleepiness. There are several classes of medications with sedative effects: some are used for this purpose (hypnotic drugs), and others appear as an adverse effect. In patients with daytime sleepiness, it is important to assess whether they are using these drug classes: benzodiazepines, non-benzodiazepine hypnotics (Z-drugs), antipsychotics, sedative antidepressants (tricyclics, mirtazapine, trazodone, doxepin), anticonvulsants, opioids, and first-generation antihistamines. Dopaminergic agonists can also lead to daytime sleepiness like sleep attacks. There is a different individual tolerance to all these medications, and some patients are more susceptible to severe symptoms even at low doses. Elderly and patients with altered clearance metabolism (hepatic or renal failure, according to the drug's metabolism pathway) are especially sensitive.

In addition to the use of medications, the use of some substances can also induce daytime sleepiness, such as alcohol, marijuana, and sedative teas. Withdrawal of stimulating substances and medications can also lead to rebound drowsiness. This can happen in the abrupt cessation of the continuous and frequent use of caffeine and amphetamines.

The treatment in this context will be directed to the reduction of dose or suspension of the medication-related to the symptom. The cost-benefit of the sedative effect should be evaluated in relation to the desired beneficial effect with the medication. Whenever possible, evaluate other therapeutic possibilities.

2.5 Hypersomnia Related to a Circadian Rhythm Disorder

Disorders of circadian rhythm are also common causes of excessive daytime sleepiness. Patients with advanced sleep phase (preferred sleep time earlier than the majority of the population) experience daytime sleepiness in the late afternoon or early evening, and patients with delayed sleep phase experience sleepiness mainly in the early hours of the morning. The diagnostic tip is to assess sleep schedule, their regularity, and especially in the most socially free periods, such as weekends and holidays.

More recently, a new phenomenon related to sleep deprivation and the circadian rhythm has been described, the so-called social jet lag. The "social jet leg" is a time difference between working days and days off. The phenomenon occurs when there is a difference in the midpoint of sleep (bedtime and waking time divided by 2) between working days and rest days greater than 2 hours. Several recent studies show independently higher cardiovascular risk and overall mortality in these patients [10].

The treatment of daytime sleepiness in these cases is dependent on the treatment of the rhythm disorder. Guidance on the regularity of bedtime, searching for a sleep schedule more similar to biological demand, and orientation on times of greater exposure to light can help in the synchronization of the circadian rhythm. The use of melatonin may also be indicated in the treatment of the delayed sleep phase.

2.6 Hypersomnia Due to Sleep Disorder

Various sleep disorders can trigger daytime symptoms such as fatigue, daytime sleepiness, irritability, difficulty concentrating, and learning. Faced with a patient complaining of EDS and signs of poor sleep quality, the investigation should be directed to sleep disorders, and, if indicated, nocturnal polysomnography should be requested.

Polysomnography is a complementary exam that registers several physiological variables during sleep: latency for sleep in minutes, latency for REM in minutes, total recording time in minutes, total sleep time in minutes, sleep efficiency in percentage, sleep stages (N1, N2, N3, and R), arousals per hour of sleep, apnea and hypopnea index, and oxyhemoglobin saturation, as well as body and limb movements. The registration of other variables can also be done depending on the clinical needs of each clinical suspicion. The use of more complex neurological channels in the EEG record, as well as more electrodes for capturing muscle activity in extremities or for detailing bruxism, may be necessary.

Restless legs syndrome, periodical limb movement syndrome, sleep-disordered breathing, bruxism, and parasomnias are part of the differential diagnosis to be excluded [11]. Obstructive sleep apnea (OSA) is a common cause of daytime sleepiness. OSA associated with daytime sleepiness affects 3–7% of the adult male

population and 2–5% of adult women. Both sleep apnea and sleepiness secondary to sleep apnea are more common in men; this statistic equalizes when women reach menopause. Some symptoms act as a warning for the diagnosis; the most common are easily recognized such as snoring and apnea. Other less classic symptoms, but very helpful in the diagnosis, especially when the consultation is carried out without the presence of companions, are nocturia, dry mouth, morning headache, non-restorative sleep, night sweating, and sleep fragmentation.

2.7 Hypersomnia of Central Origin

Excluding the differential diagnoses mentioned so far, there is a set of rarer hypersomnia named hypersomnia of central origin. Diseases such as narcolepsy, Kleine-Levin syndrome, and idiopathic hypersomnia must be recognized, and the differential diagnoses must be remembered. These diseases lead to a significant reduction in quality of life, as well as a high risk of personal and professional accidents. The delay in diagnosing these diseases is greater than 10 years with a significant impact on the quality of life of these patients [12].

Health professionals need to be well prepared and motivated to make diagnoses of rarer sleep disorders. Efforts by university circles have been made trying to reverse this scenario with continuing education on the topic for patients and health professionals.

Narcolepsy is a chronic neurological disease, with important social, personal, and family repercussions. Narcolepsy is characterized by excessive daytime sleepiness, characterized by short-term recurrent sleep attacks, fragmentation of night sleep, and other REM sleep phenomena, such as cataplexy, sleep paralysis, hypnagogic, and hypnopompic hallucinations. First-degree relatives of narcolepsy patients have a risk of developing drowsiness of central origin about 20–40 times greater than normal individuals in the general population. However, a family pattern for cataplexy alone rarely occurs [13]. Until now, narcolepsy does not have curative treatment. Symptomatic medications are prescribed with the intention of controlling the main symptoms of the disease. Non-pharmacological measures should also be taken with guidance on sleep hygiene, scheduled naps, physical activity, and routine activity regularity [14].

Idiopathic hypersomnia is a sleeping disorder of unknown cause. The diagnosis is defined through neurophysiological evidence of daytime sleepiness, that is, average sleep latency in MLST less than 8 minutes and absence of REM sleep changes. Any other cause of daytime sleepiness should be excluded. Despite being a diagnosis of exclusion, patients with idiopathic hypersomnia have some characteristics that suggest the clinical condition. In general, they are patients with excessive sleepiness with increased total sleep time 24 hours a day. They present permanent sleepiness, different from the sleep attacks characteristic of narcolepsy. Naps of patients with idiopathic hypersomnia are also different from those present in patients with narcolepsy, being generally prolonged, lasting more than 1 hour, and usually not

repairing [15]. Another symptom suggestive of idiopathic hypersomnia is sleep inertia. This can be defined as a prolonged difficulty waking up with a frequent return to sleep, irritability, difficulty in performing cognitive tasks, irritability, automatic behavior, and confusion. Autonomic symptoms have been reported, such as orthostatic hypotension, changes in thermal perception, and Raynaud's phenomenon. Treatment must have behavioral and pharmacological approaches. Guidance to family members and the use of stimulants improve the quality of life of these patients.

Kleine-Levin syndrome is a very rare disease, but a classic cause of recurrent hypersomnia, characterized by recurrent-remitting episodes of severe EDS associated with cognitive, psychiatric, and behavioral changes. The duration of the episodes is variable, usually around 10 days, and can last up to 30 days. The episodes have an evident functional impact. Common behavioral symptoms are hyperphagia, hypersexuality, coprolalia, or copropraxia. Patients commonly report a symptom of lack of realization, with difficulty in stating what is real or dream. In the intervals between crises, the patients do not present cognitive or psychiatric symptoms nor sleepiness [16]. There is no specific and effective therapy, and treatment involves medications with different effects. Lithium carbonate and carbamazepine have been used with inconsistent responses to increasing crisis intervals. Usually, there are frequent spontaneous remissions with advancing age.

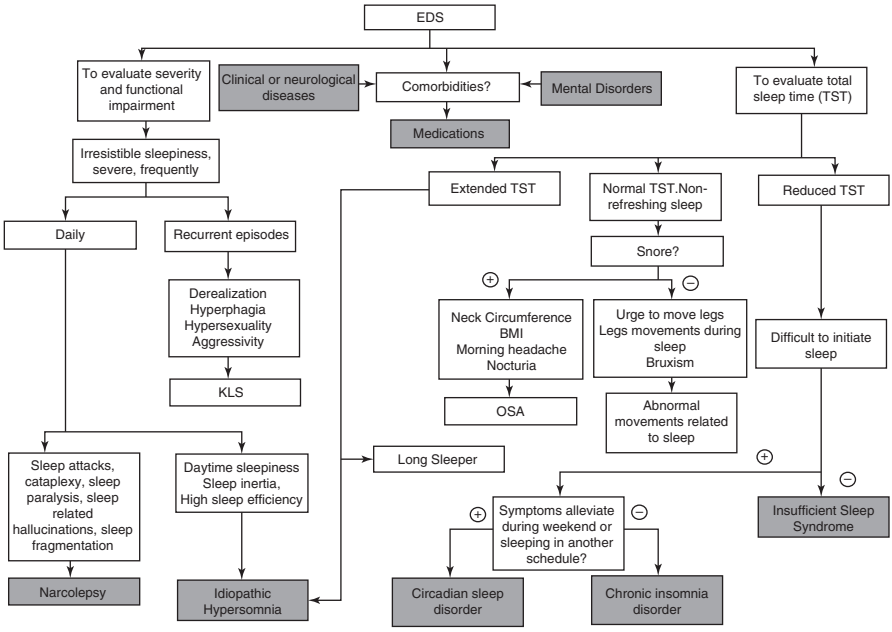

Fig. 1 Proposal for the management of excessive daytime sleepiness and its differential diagnosis. (EDS excessive daytime sleepiness, KLS Kleine-Levin syndrome, TST total sleep time, OSA obstructive sleep apnea)

3 Final Words

Excessive daytime sleepiness is a common sleep complaint, and for its proper management, it is important to understand the groups of causes of hypersomnia to direct the medical interview, the physical and neurological examination, and the complementary investigation. We highlight seven etiological groups to be considered: insufficient sleep syndrome, clinical and neurological diseases, mental disorders, sleep disorders, use of drugs or substances, rhythm disorders, and, more rarely, hypersomnia of central origin (Fig. 1). The treatment of hypersomnia will be directed to its underlying cause, and, in specific cases, when necessary, symptomatic treatment with the use of stimulants may be done.

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Excessive Daytime Sleepiness and Narcolepsy: Physiotherapeutic Approach

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Excessive daytime sleepiness (EDS), as seen in the previous chapter, is a symptom of many diseases (Fig. 1) and can be a debilitating and an overwhelming condition. EDS may indicate an undiagnosed sleep disorder or other condition, and it can also impair development and daily function. Moreover, EDS makes it difficult for patients to adjust to school/work and concentrate on their responsibilities. The disease diagnosis needs to be done by a physician and will help to direct and focus the physiotherapeutic treatment. For that, physical therapy might help in the management of the symptom and in the treatment of the disease itself, identifying the modifiable risk factors which could alleviate or prevent EDS, such as sedentary behavior. Consequently, the general and main aim of PTs treating EDS is to maintain vigilance.

A patient with narcolepsy tends to be more overweight or obese, less physically active than people without this condition, can be in an isolating condition overwhelming of his sleep attacks, and tends not to have a routine. Physical therapy can help within the management of EDS by exercising and having orientation on an increase of physical activity, outdoor, with other people, and making it a routine at a specific time. Also, sleep hygiene tips, ensuring good sleep hygiene, scheduled naps, and nighttime sleep can help with pharmacological treatment, indispensable for narcolepsy. Yet, few investigations have been conducted and no consensus on the

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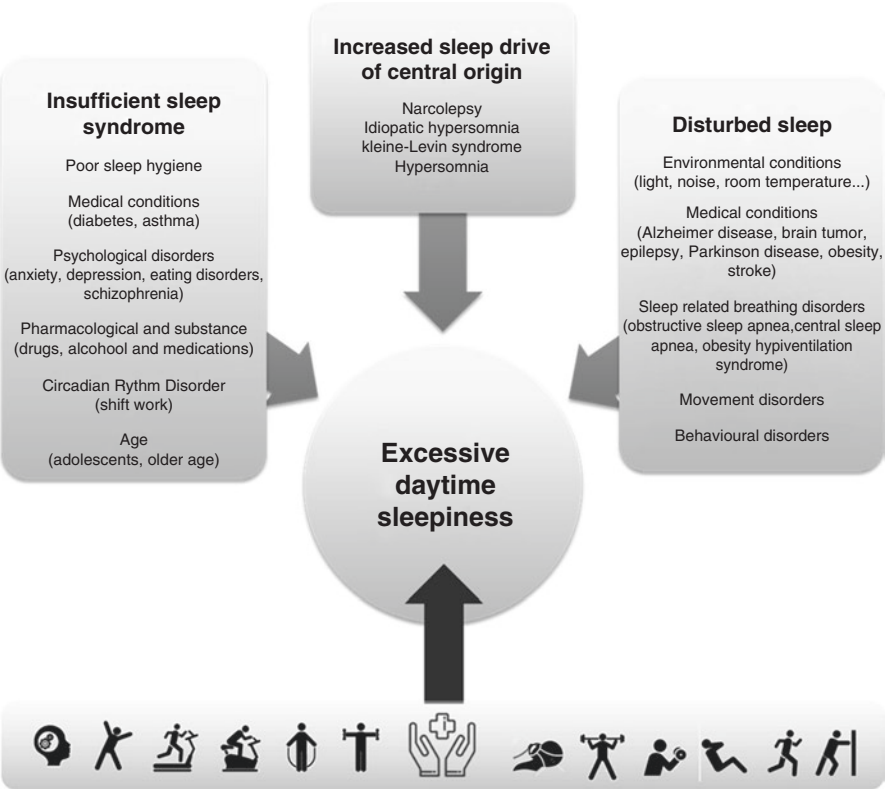

Fig. 1 Excessive daytime sleepiness is a symptom of many diseases and conditions commonly treated by the physical therapist. Physical activity, exercise, and positive airway pressure therapies can act as a countermeasure along with pharmacological treatment

theme, warranting further investigations for both the effectiveness and the mechanisms of physical activity for EDS.

Two epidemiological investigations in general population samples showed that approximately 20–40% of patients with sleep apnea reported EDS with diurnal repercussion [1, 2]. During the PTs initial evaluation of a patient with sleep apnea, there must include an investigation of life habits, sleep perception, pre-bedtime care, stimuli before bed, the sleep environment, and the reporting of the night of sleep. The gathering of this information is quite important for the beginning of treatment, which can also be done using positive airway pressure (PAP) therapy. In clinical practice, many patients do not relate to EDS at the first session, mainly because with daily life, they had not recognized it, because of external stimuli, such as work, movement, use of stimulating beverages, and others that mask the complaint of EDS. It's up to the PT to get to know the EDS, making the patient observe and understand it, in order to treat it. It is important to observe the EDS, as it can affect the predisposition for physical activity and adherence to it. Thus, in addition to the effective treatment with PAP therapy, for the control of obstructive respiratory

events and care for the emerging central events that may occur, having the behavioral evaluation of the patient is an important point for the care of the physiotherapy practice. Lack of regular exercise has shown to be a significant predictor for EDS in patients with sleep apnea [3].

1 Exercise and Physical Activity

For EDS exercise might help directly and indirectly. There is no consensus until now on exercise improving EDS neither in an acute (short bout) or chronic (regular) manner. Indirectly, exercise can improve obesity, muscular performance, inflammation, diabetes, metabolic syndrome, and sleep apnea [3, 4], which impact EDS, having it as a symptom.

From observational studies, we know that lack of exercise is associated with increased EDS in children [5, 6], adults [7], and older ones [8, 9]. Lack of exercise has also been known as an independent predictor of EDS in men with sleep apnea, being independent of the degree of apnea [3]. Also, strength training (55 minutes, 3 times a week, for 12 weeks, 3 sets of 10–12 repetitions with a 1-minute rest interval between sets) reduced EDS in adolescents [10].

In addition, evidence on weekly engagement in leisure-time moderate physical activity (e.g., walking) was significantly associated with a 30% lower chance of reporting EDS [11], indicating that a non-sedentary way of life is a choice to prevent many diseases and EDS. The significance of moderate-intensity physical activity cannot be neglected, as moderate-intensity physical activity is associated with numerous health benefits compared with high-intensity physical activity. Nevertheless, for those already engaged in moderate-intensity physical activity, supplementary health benefits may perhaps be achieved with higher intensity and/or duration. One investigation on low-to moderate-intensity physical activity (e.g., tai chi program) performed for 6 months including older adults complaining of sleep demonstrated that tai chi participants reported reduced EDS (assessed by the ESS) compared with controls [12]. With a broad range of age, between 18 and 85 years, another investigation showed that the relative risk of often versus never having EDS decreased by a factor of 0.65 for those meeting physical activity guidelines compared with their counterparts not meeting the guidelines [13]. Taken together evidence points out that meeting physical activity guidelines, including exercise, is of importance for all, and also for sleep and EDS.

The mechanism through which exercise, specifically, improves EDS is not clear and depends on the disease or condition investigated. Regular exercise has anti-inflammatory effects, altering cytokine responses such as C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6), and in this manner may prevent EDS [14–16]. Another possibility is that exercise improves sleepiness by influencing mood [17]. Furthermore, exercise improves metabolic factors, such as visceral fat and insulin resistance [18, 19], that have been shown to be independently associated with EDS [20, 21].

In patients with sleep apnea, polysomnographic contributing factors of EDS were shorter sleep latency, increased sleep efficiency, and worse nocturnal oxygenation than their counterparts without EDS [22]. In patients with sleep apnea, hypoxemia can be a foremost determinant of EDS. Investigations focused on the possible coexistence of obesity hypoventilation syndrome (OHS), which is a known cause of EDS [23]. The lower nocturnal oxygen saturation and the increased EDS might be due to OHS. Low nocturnal blood oxygen saturation has a fundamental role in EDS, whether or not it is related to OHS [23]. However, EDS is not always associated with low nocturnal blood oxygen saturation in sleep-related breathing disorders, and that other factors are involved. Impaired autonomic cardiac modulation has also been suggested as a mechanism in which it has led to autonomic arousals and might be an additional cause of EDS [24]. Considered together, two independent factors are associated with the pathogenesis of EDS in patients with sleep-disordered breathing: first, a low nocturnal oxygen saturation, probably caused by OHS, and second, an enhanced sympathetic cardiac modulation during the night, probably caused by repeated nocturnal autonomic arousals. In this sense, EDS might be caused by increased sympathetic activity and/or increased nocturnal hypoxemia.

From a clinical standpoint, we suggest that physical activity (including exercise) should be part of the comprehensive clinical assessment of patients with EDS and that regular exercise should be recommended to those patients that are sedentary or have sedentary behavior.

2 Cognitive-behavioral Therapy for Excessive Daytime Sleepiness

Cognitive-behavioral therapy (CBT), discussed in detail in chapter "Optimizing Behavior Strategies for Sleep" of this book, is similarly used in the management of narcolepsy recently. It is proposed that CBT for narcolepsy should have three components:

(i) Behavioral component: begins with specific techniques designed at changing sleep-disordered behaviors or sleep-related disorder variables that are not well-suited (e.g., sleep satisfaction and nap training).
(ii) Cognitive component: intended at modifying beliefs, emotions, and motivations that may play a critical function in maintaining narcolepsy (by this means increasing the frequency of symptoms) and point out the psychosocial effect of the disorder.
(iii) Educational component: instruct the patient about the nature of the disease, the mechanism of pharmacological approach, and precautions regarding the use of medication to accomplish a global awareness of the condition. The acceptance of treatment and the therapeutic relationship becomes important aspects for treatment success, and the use of strategies becomes a type of therapeutic contract [25].

A review on CBT for narcolepsy presents the good effects of the treatment along with pharmacotherapy [25]. Approaches might help with EDS, such as considering having a regular sleep schedule, getting enough sleep during the night according to National

Sleep Foundation Recommendations (see chapter "Normal Sleep: Interindividual Differences and Sleep Variability", Fig. 1), and taking an exercise break to improve alertness. There are behavioral approaches to treat narcolepsy symptoms: (i) structuring nocturnal sleep habits (maintain a regular sleep schedule, avoid changes in sleep time and sleep deprivation, learn relaxation techniques to avoid extreme stimulus before sleep); (ii) planning naps (15- to 20-minute naps after lunch and before 5 PM are highly effective); (iii) diet (avoid caffeine beverages and drinks; healthy eating habits are useful to ensure sleep); (iv) counseling or other assistance (for lifestyle organization, psychotherapy, special considerations at school and work, working during the day) [26].

EDS was one of the variables that determined cardiopulmonary fitness in an investigation with patients with narcolepsy [27]. Cardiopulmonary fitness was inversely related to the degree of sleepiness in patients with narcolepsy type 1or 2. In narcolepsy type 1, cardiopulmonary fitness was also inversely correlated to the number of cataplexy attacks in a month. In addition, the authors found lower cardiopulmonary fitness in patients with narcolepsy compared to the general population [27]. Therefore, one limitation that the authors point out is the fact that the volunteers with narcolepsy of this study were in use of stimulants, which may have influenced the results of cardiopulmonary fitness (prolonging endurance exercise time and reducing the perception of effort, even though the effect of stimulants on cardiovascular function is still controversial). Moreover, the pharmacological state-of-the-art treatment for narcolepsy is the use of stimulants or wake-promoting compounds, and the results were from a treated population of patients with narcolepsy on stable medication. One point that we want to make noticeably clear is the fact that we propose physical therapy as an adjunct therapy for narcolepsy, along with pharmacological treatment.

3 Final Words

Following the possibilities that the physiotherapist can have with the patient with EDS, either by narcolepsy or sleep apnea, more studies are still necessary to prove the evidence of physical activity by itself. Investigations are worth with PAP therapy, its pressure adjustment and relief, control of interface leakage, and thus improvement in sleep fragmentation, as well as its adjuvant orientations, such as sleep hygiene, posture during sleep, and sleep routine, habits and beliefs.

When we score the EDS related to sleep apnea, it is important to remember that in addition to polysomnographic characteristics, the initial clinical evaluation must raise life habits, sleep perception, and behavioral aspects during the day and pre-sleep - all this information may be useful during the evaluation of the evolution of the treatment plan.

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Parasomnias

Giselle de Martin Truzzi, Cristina Frange, and Fernando Morgadinho Santos Coelho

Parasomnias are a verbal, motor, or experiential phenomenon that occurs during entry into sleep, within sleep, or during arousal from sleep. Parasomnias may occur during non-rapid eye movement sleep (NREM), rapid eye movement sleep (REM), or during transitions to and from sleep, and are classified accordingly: NREM-related, REM-related, and "other parasomnias" (e.g., sleep enuresis) [1]. The word parasomnia derives from the Greek "para" meaning "alongside" and the Latin word "Somnus," meaning "sleep."

Some parasomnias are considered a primary sleep phenomenon, while others may be secondary due to medication or psychiatric disorders, for example. The evaluation of parasomnias depends on an accurate history, age of onset, and time of the night of the episodes, comprising a detailed anamnesis and a clear description of the events. Refer the patient to a physician in case of suspected parasomnias. Video polysomnography is used to evaluate the parasomnias; as the events may not occur every night, multiple nights of video PSG may be needed.

NREM sleep parasomnias often occur in the transition from the deepest to the most superficial stages, about 2 to 3 hours after the onset of sleep, predominantly in the first half of the night. Most of these manifestations resolve spontaneously [2].

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REM sleep parasomnias are more prevalent in the second half of the night, and the chance of spontaneous remission is lower than in NREM sleep parasomnias [3, 4].

1 NREM-Related Parasomnias

1.1 Disorders of Arousal

Confusional arousals are brief episodes of incomplete arousal from sleep, characterized by awakening with mental confusion and often go unnoticed unless reported by the bed partner or parents. It occurs very often in younger children, with almost 2–7% of adults present confusional arousals [5]. Patients don't usually walk out of bed and there is no autonomic arousal (tachycardia, tachypnea, and diaphoresis), and behavior may be inappropriate or actions and responses may be slower than usual. A confusional arousal episode usually lasts up to 5–15 minutes. It is a very common condition in children and usually resolves by the age of 5 years old.

Sleepwalking (somnambulism) consists of a series of complex behaviors that occur during NREM sleep, with evidence of a familial role in the development of sleepwalking. Patients may walk out of bed, with the individual in altered absent consciousness, the eyes are usually open, and may have somniloquy (talking during sleep). In addition to ambulation, the episodes have evidence of persistent sleep, altered consciousness, and impaired judging during ambulation – which can lead to inappropriate behaviors or dangerous ones. Patients are difficult to arouse when sleepwalking. When awakening from such an episode, there are tachycardia, mental confusion, amnesia, and abnormal behaviors. The prevalence varies in children, ranging from 3.5% and 14.5%, and in adults between 0.6% and 34% [6]. Sleepwalking can be calm or agitated, with varying degrees of complexity and duration, and may also be accompanied by sleep terrors.

Sleep terrors (night terrors, *pavor nocturnus*) are sudden arousals from sleep accompanied by loud screams, crying, and the autonomic nervous system and behavioral manifestations of intense fear. There is often intense autonomic discharge (e.g., tachycardia, tachypnea, flushing of the skin, diaphoresis, mydriasis, and increased muscle tone). The patient frequently sits up in bed and does not remember what happened. The sleep terror episode may be accompanied by incoherent vocalizations. Sometimes there is prolonged inconsolability associated with a sleep terror in children or adults. It typically occurs in prepubertal children, diminishes in adolescence, and is uncommon in adulthood [1, 7].

Importantly, a given episode may be a mixture of the mentioned types of disorders of arousal, all of them with confusion during the episode and partial or complete amnesia.

1.2 Sleep-Related Eating Disorder

Recurrent episodes of involuntary eating and drinking during arousals from sleep are called sleep-related eating disorders. They are associated with diminished levels of consciousness and subsequent recall, with problematic consequences. Eating

episodes occur involuntarily during partial arousals from sleep with subsequent partial recall. Patients usually don't remember having eaten during the night. This condition can be idiopathic but can be associated with a primary sleep disorder, another clinical condition, or the use of a sedative-hypnotic medication [1].

2 REM-Related Parasomnias

2.1 REM Sleep Behavior Disorder

REM Sleep Behavior Disorder (RBD) is characterized by complex motor activity or vocalization during sleep (i.e., loss of muscle atony during REM sleep) associated with dreaming [1]. *Dream enactment behavior* or *acting out one's dream* is observed when the patient presents motor activity, as "staging, acting" the dream, without suppression or muscle atony [8].

Data on the prevalence of the disease in the population are still scarce and limited since it has a low prevalence and part of the diagnostic criteria requires video polysomnography, which makes the diagnosis expensive and limited. In addition, in many cases, the change is not observed and reported by the patient and/or roommate [9]. For diagnosis, in addition to clinical history, it is necessary to observe, with the video polysomnography the absence of muscle atony during the period of recording REM sleep. In polysomnography (PSG) findings, there are sustained muscle activity in REM sleep on chin electromyography (EMG) and transient muscle activity during REM on chin or limb EMG (Fig. 1).

RBD predominates in males and increases with age. It usually begins in the fifth or sixth decade of life. In younger patients, it may also be related to narcolepsy type 1 and the use of antidepressants. It is also related to the use of alcohol, lower educational levels, depression, anxiety, and posttraumatic stress, among others [10]. An important characteristic of RBD is that it is the greatest prodromal marker of α-synucleinopathies, and it may be present before the development of these diseases. A-synucleinopathies are neurodegenerative diseases in which there is an accumulation of α-synucleins in nerve cells, as Parkinson's disease, Lewi body dementia, and multiple system atrophy [11].

The patient with RBD has a clinical history of complex movements and/or vocalization during the dream, which may include laughing, crying, cursing, singing, clapping, punching, slapping, kicking, gesticulations, and chewing, among others. The movements are often aggressive and can cause physical trauma to the patient and roommate. After waking up, the patient may be alert and able to report the dream, consistent with the motor activity he presented while sleep [1].

RBD can be classified as idiopathic, due to medication or identifiable changes [12], or even secondary, when caused by neurodegenerative diseases, autoimmune diseases, lesions or tumors in the central nervous system, tautopathy associated with anti-IgLON5 antibodies, after stroke, medications (in particular the use of antidepressants) [13], and narcolepsy [14]. RBD has a strong association

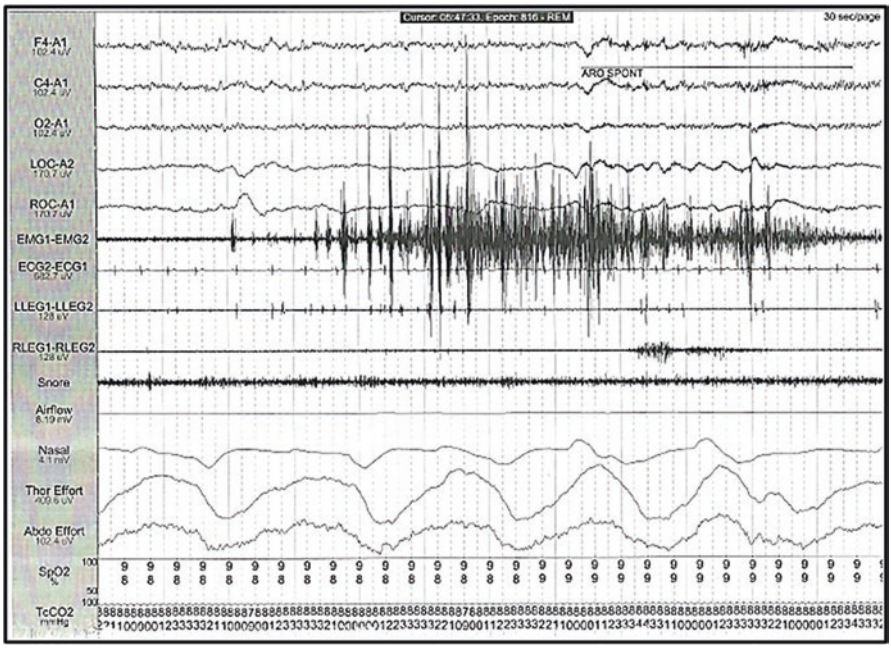

Fig. 1 Thirty-second (epoch) window page of polysomnography showing the loss of muscle atony during REM sleep stage in the arm electromyography (EMG1-EMG2). Note also brief movements in left and right legs (LLEG1-LLEG2 and RLEG1-RLEG2). (Image courtesy from Dr. Fernando Morgadinho Santos Coelho)

with neurodegenerative diseases, and that idiopathic RBD is an important prodromal of α-synucleinopathies. Older patients have a 33% risk of developing a neurodegenerative disease within 5 years, and 91% in 14 years after the onset of RBD [15].

There is no treatment that can prevent the progression to this disease. However, early monitoring and recognition of neurodegenerative disorders can lead to early treatment and monitoring of the patient, and neuroprotective measures, which can be beneficial in the evolution of the disease [16].

2.2 Recurrent Isolated Sleep Paralysis

Recurrent sleep paralysis is characterized by an inability to move at sleep onset (hypnogogic) or on awakening (hypnopompic), lasting from a few seconds to minutes. Patients are awake and have full memory of the event. Episodes can cause anxiety and fear of sleep and although the diaphragm is not affected, there may exist a sensation of dyspnea. In sleep paralysis, there is partial memory preservation of the event, and there are no stereotyped movements.

The age of onset of sleep paralysis is variable but is more common in adulthood and middle age. Prevalence can range from 4.7% to 41% of the population

[5], which may have had at least 1 episode during life. Predisposing factors are sleep deprivation, irregular sleep periods, sleep disruption, and stress. Sleep paralysis is common in narcolepsy and idiopathic hypersomnia (and the term *isolated* refers to the absence of these diseases). Treatment is not normally necessary in isolated cases, and sleep hygiene measures are an effective way to control sleep paralysis.

2.3 Nightmare Disorder

Nightmare disorder is characterized by repeated occurrences of extended, dysphoric, and well-remembered dreams. They are disturbing mental experiences that generally occur during REM sleep and that often result in awakening. When awakening the patients quickly are oriented and alerted. Details of the content of nightmares are usually recalled by patients. Patients may also present increased prevalence of mood disorders (persistence of nightmare effect, anxiety, dysphoria), sleep resistance (fear of sleep or subsequent nightmares, bedtime anxiety), cognitive impairment (intrusive nightmare imagery, concentration, impaired memory), behavioral problems (bedtime avoidance, fear of the dark), fatigue, and daytime sleepiness [17].

Nightmares occur in around 60–75% of children. Both sexes are equally affected until adolescence when girls are more affected. In adults, about 2–8% have nightmare disorders (18) being more frequent in psychiatric disorders, including posttraumatic stress disorder, borderline personality, and substance abuse, stress, and anxiety. The posttraumatic stress disorder dreams may occur out of NREM stages N2 and N3, during REM sleep, and at the onset of sleep. Cognitive-behavioral treatments have been used to treat nightmares with success.

3 Final Words

Treatment of parasomnias includes avoiding precipitating factors (e.g., sleep deprivation and medications) environmental precautions and eventually the use of medications to control the presented condition. There is no evidence of physical therapy interventions for these disorders. The treatment of the parasomnias by a physician is important for the reduction of clinical manifestations and protection of the patient and bed partner, yet physiotherapists may refer the patients to a physician in case of suspicious parasomnia.

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Part IV
Sleep in Specific Conditions

Sleep-Wake Disturbances in Childhood and Adolescence

Giuliano da Paz Oliveira and Marcia Pradella-Hallinan

Adequate sleep is essential for the child's growth, development, learning and well-being. Insufficient and/or poor-quality sleep are associated with increased occurrence of mood disorders, behavioral disorders, and learning difficulties due to inattention. Similarly, untreated sleep apnea in childhood is associated with increased irritability, inattention, emotional dysregulation, unsatisfactory academic performance, impairment of growth. Although more rarely, systemic arterial hypertension and pulmonary hypertension can also be related to some sleep-related breathing disorders [1–3].

Sleep disorders are very common in the pediatric population, with a worldwide prevalence ranging from 20 to 40% [4–6]. A Brazilian study using validated child sleep questionnaires estimated an alarming prevalence of sleep disorders of 25.5% among individuals aged 0–19 years [7]. It is also noteworthy that sleep habits of the child are very rarely approached by health-care professionals in order to identify, prevent and treat possible sleep disorders [8].

The American Academy of Sleep Disorders (AASM) developed a consensus published in 2016 with the amount of sleep needed to promote health among children and adolescents, according to each age group [Table 1]. Infants aged less than 4 months were not included in this consensus due to the great variation of normality regarding duration and sleep patterns [9].

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Table 1 Recommendation of AASM consensus (2016) on total sleep time according to each age group in children and adolescents

Age	Total sleep time
4–12 months	12–16 hours (including naps)
1–2 years	11–14 hours (including naps)
3–5 years	10–13 hours (including naps)
6–12 years old	9–12 hours
13–18 years old	8–10 hours

Table 2 Characteristics of sleep biology and ontogenesis according to each age group of childhood and adolescence

Age	Characteristics of sleep
0–6 months	Categories: awake, quiet sleep, active sleep and indeterminate sleep (transitional sleep) At 6 months, begins to consolidate the night sleep Initiates sleep by REM. REM sleep represents 50–60% of total sleep time
6 months–2 years	One or two daytime naps Starts sleep by NREM. REM sleep represents 25–30% of total sleep time
2–6 years	Transition from two naps to one. Nap usually disappears after 5 years. REM sleep is concentrated in the second half of the night
6–12 years	No naps, 9–12 hours of night sleep
12–18 years	Delayed sleep phase syndrome is common during teenage years

1 Sleep States from Newborn to Adolescent

The characterization of the sleep patterns is based mainly on the electroencephalographic tracings and behavioral characteristics [Table 2].

Up to 6 months of life, the child's states of consciousness are classified into 4 categories: awake, quiet sleep, active sleep and indeterminate sleep (transitional sleep) and indeterminate sleep (transitional sleep). The newborn falls asleep in REM sleep and remains in this state of sleep for about 60% of the total sleep time. This percentage can reach 80% preterm neonates.

Around 6 months the baby comes to sleep up to 6 hours uninterrupted, a period in which the longest night sleep begins to consolidate. Still in this phase, infant initiates the sleep cycle in NREM sleep, which is the predominant phase (70–75% of the total sleep time).

Between 2 and 5 years old, the child usually sleeps between 10 and 14 hours a day, with only one nap during afternoon, which usually disappears around 5 years old. In this phase, a predominance of REM sleep occurs in the second half of the night, as observed in adults.

Adolescents after 12 years of age begin to present a typical alteration called delayed sleep phase syndrome, that is characterized by difficulty in falling asleep at a socially acceptable time and by the need to wake up later. Depending on the social

demand (e.g., going to school in the morning), this factor can contribute to the occurrence of sleep deprivation and its consequences [10–12].

2 Sleep-Related Breathing Disorders

2.1 Obstructive Sleep Apnea in the Pediatric Population

In the pediatric population, the peak incidence of obstructive sleep apnea (OSA) occurs in preschoolers, a period in which there is an imbalance between the growth of palatine tonsils and adenoid, concerning the growth of the upper airway, that allied to the physiology of sleep/muscle relaxation favors the occurrence of obstructive respiratory events [13, 14].

Unlike the adult, the diagnosis of sleep apnea in the child requires the presence of an apnea index (AHI) greater than 1 event per hour of sleep, often accompanied by multiple awakenings and oxyhemoglobin desaturation. The following table summarizes the indications of polysomnography (PSG) in the pediatric age group [Chart 1] [13].

Adenotonsillectomy is the most widely used treatment for children with OSA. In cases of moderate or severe OSA in which adenotonsillectomy did not show satisfactory results or was contraindicated, the use of continuous positive airway pressure (CPAP) devices should be considered. The greatest limitation of the use of CPAP in children is the low adherence. Also, the chronic use of these devices can lead to facial deformities due to the pressure of the mask on the facial bones. Care with choosing the best mask can minimize these effects [14, 15].

The treatment of the child's OSA should always be multidisciplinary. It is known that about 20% of the children submitted to adenotonsillectomy continue with residual apnea resulting, in its great majority, of the alteration in the relation between the maxilla and mandible, of dental malocclusion. Several studies show the benefit of the use of orthodontic devices and the palatal circuit breakers that make the maxilla

Chart 1 Main indications of PSG in childhood and adolescence. Presence of two or more of the following criteria:

Snoring for at least 4 nights a week associated with restless sleep, frequent awakenings, hyperactive, aggressive, or impulsive behavior, learning difficulties, enuresis, malnutrition, recurrent upper airways infections
Apnea observed by the family
Excessive daytime sleepiness
Laborious breathing during sleep
Polycythemia
Cor pulmonale
Patient will perform any elective surgery and presents suggestive OSA symptoms
Some genetic syndromes and craniofacial malformations

expansion fast are the most indicated. Phonoaudiology has a recent and important role in the recovery of the child's stomatognathic functions, whether it has residual apnea or not. It has been proposed that the increase of muscle tone improves the upper airways patency, which provides adequate chewing, sucking, swallowing, and nasal breathing functions, and even influences phonation [16, 17].

Also, we enphasize the physiotherapist's work by correcting of postural alterations observed in the mouth-breathing child [18].

2.2 Primary alveolar hypoventilation

They comprise a group of diseases associated with an elevation in $PaCO_2$ above 45 mmHg. During sleep we can use as rules, Paco2 exhaled, measured by nasal cannula, 55 mmHg for at least 10 minutes or 10 mmHg increase in Paco2 in vigil and supine position for values above 50 mmHg and for at least 10 minutes during total sleep time [13].

Alveolar hypoventilation may occur in association with several diseases in which there is a restrictive rib cage disorder such as neuromuscular diseases associated with obesity, in central sleep apnea due to impairment of the respiratory center located in the bulb or cardiac dysfunctions, and in chronic obstructive pulmonary diseases. Associated with hypercapnia, hypoxemia is often developed, which intensifies clinical manifestations and increases morbidity. Hypoventilation may begin during sleep and is sometimes underestimated by waking evaluations. The treatment of hypoventilation syndromes will depend on the underlying causes, it is usually multidisciplinary, and it may be necessary to use ventilation devices [13, 19, 20].

The performance of respiratory physiotherapy with the use of bag valve mask is frequently recommended in any age group, and motor physiotherapy, when indicated, is used mainly for stretching and maintenance of joint mobility, without the use of load [21].

3 Insomnia

The child's insomnia is almost always a complaint from parents or caregivers and is characterized by the child's difficulty in initiating and/or maintaining long periods of sleep. A behavioral component is almost always present and can be associated with a problem of clinical, neurological, psychiatric, and even, physiological cause that served as a trigger for the difficulty with sleep, such as the eruption of teeth, for example [22].

Behavioral insomnia can be classified into association disorder and/or lack-of-limit disorder and association of these two types. However, behavioral insomnia is

an exclusion diagnosis that needs evaluation to rule out clinical causes or other sleep disorders [22, 23].

In the 3rd edition of the International Classification of Sleep Disorders (ISCD-3), insomnia was subdivided into acute insomnia (duration less than 3 months) and chronic insomnia. The criteria for the diagnosis, in addition to the difficulty in initiating and/or maintaining sleep, are the daytime symptoms, the absence of inadequate environmental factors, the presence of insomnia at least 3 times a week, and the absence of another sleep disorder that may justify the complaint [13].

The evaluation of insomnia complaints includes detailed interview questioning sleeping routines, evaluation of cognitive functions, mood, and daytime behavior. It is recommended to use sleep diaries asking parents to register bedtime and wake up times, night awakenings and naps for at least 7 days. The following table shows the summary of the main indications of complementary examinations in the context of childhood insomnia [Table 3].

3.1 Pharmacological Treatment of Childhood Insomnia

Behavioral therapy has been successfully used to treat the child's insomnia. The American Academy of Sleep Medicine consensus (2017) noted that according to published articles, 80% of children treated with behavioral therapy for insomnia showed significant and lasting improvement for up to 6 months with techniques of absolute or gradual extinction of negative associations with sleep, positive reinforcement, sleep hygiene and preventive education of parents [26].

Behavioral therapy includes guidance on sleep hygiene, physical activities, use of monitors and the appropriate times to perform them, appropriate feeding times including breastfeeding and the institution of repetitive activities (bedtime ritual). The control of stimuli close to bedtime favors the reduction of awakenings and the period of physiological and cognitive alert before sleep. In addition to relaxing massage techniques such as Shantala, there are no references to the use of physiotherapy techniques as a treatment for children's insomnia [26–29].

Table 3 Complementary tests for the etiological investigation of insomnia in the pediatric age group [24–28]

Examination	Referral
Laboratory tests	CBC, iron profile (anemia and RLS investigation) Thyroid function (investigation of hypo/hyperthyroidism)
Polysomnography	Suspected sleep-related breathing disorder, PLMD
Actigraphy	Accurate evaluation of sleep/waking periods Evaluation of circadian rhythm disorders
Electroencephalogram	Epilepsy

3.2 Non-pharmacological Treatment of Childhood Insomnia

The institution of drug treatment aims mainly to interfere in the long period of insomnia to facilitate the performance of behavioral work. Another indication is the presence of neurological, psychiatric, and child comorbidities with marked visual impairment. Melatonin is indicated and mainly used in children with autism spectrum disorders, with global developmental delays and in blind children. Melatonin reduces sleep latency and wake-up frequency and should be ingested 1 to 2 hours before bedtime. Antihistamines such as diphenhydramine, promethazine, and hydroxyzine promote blocking of H1 histaminergic receptors by reducing sleep latency and awakening due to sedation. Benzodiazepine hypnotic drugs (such as clonazepam) act as gamma-aminobutyric acid (GABA) receptor agonists, reducing sleep latency. The effect of muscle relaxation associated with this drug should be considered, especially in the suspicion of sleep-related breathing disorders [30, 31].

4 Sleep-Related Movement Disorders

4.1 Restless Legs Syndrome (RLS)

Restless legs syndrome (RLS) is a sensorimotor disorder that affects the sleep and quality of life of the child or adolescent. The affected child describes its symptom as an irresistible need to move the legs, usually accompanied by discomfort, unpleasant feeling, and/or restlessness [32–34].

The clinical course is variable, moderate to severe forms can behave as chronic and progressive. Difficulty in initiating and/or maintaining sleep, feeling that you have not slept enough, tiredness, and weakness are common complaints in children with RLS. Positive family history and the presence of periodic limb movements of the members (identified in PSG) are considered support criteria for RLS, according ICSD-3 [33, 34].

The diagnosis of RLS in the pediatric population, as it occurs among adults, is eminently clinical, as shown below [Chart 2]. If the child cannot describe their discomfort, it must have at least two of these criteria: sleep disorder, a first-degree family member with a diagnosis of RLS and periodic limb movement index (PLMDi) >5/h in polysomnography [13].

Should always be requested. Several studies show an association of RLS symptoms with a ferritin dosage of less than 50 mcg/L and that iron supplementation surprisingly improves symptoms. In addition to iron supplementation in severe RLS, other drugs can be used such as gabapentin, benzodiazepines such as clonazepam and temazepam, clonidine, dopaminergic agonists and *H. perforatum* [33, 34].

Chart 2 Diagnostic criteria for restless legs syndrome (ICSD-3) [13]

Need to move the legs, caused by an unpleasant sensation
Unpleasant feeling worsens in rest periods
Unpleasant feeling is totally or partially relieved by movement
Need for movement and the feeling of discomfort are worse at night
Symptoms cannot be explained by other medical conditions
Report of the child himself describing with his words the unpleasant sensation and/or discomfort in the legs

We did not find studies of the use of physiotherapy techniques for the treatment of RLS; however, as personal experience of the authors it is worth mentioning that the caregivers refer that vigorous massage on the legs and even the placing of cushions or heavy covers on them helps in the conciliation of sleep [33, 34].

4.2 Periodic Limb Movement Disorder (PLMD)

PLMD is characterized by repetitive, intermittent, and stereotyped movements that most frequently affect the lower limbs. Often the caregivers complain that the child has restless sleep or drops the covers or kicks, while sleeping. This complaint, to be relevant, should be associated with symptoms associated with nonrestorative sleep such as behavior and/or mood changes and learning difficulties, among others. For the diagnosis, we should request a PSG where muscle movements/contractions will be counted with a duration of 0.5 to 10 seconds and with an increase of the tibial electromyogram of at least 8 mV. A 5/h periodic movement index is considered significant. Likely RLS, blood tests may be necessary to evaluate iron metabolism and its supplementation (when indicated) may improve the symptoms [32–34].

4.3 Restless Sleep Disorder in Children

In 2020 a new sleep-related movement disorder was described. It refers to the complaint of restless sleep reported by parents or caregivers and was studied in the pediatric age group, between 6 and 18 years of age. For the diagnosis, all criteria defined by consensus must be present [Chart 3].

The authors found serum ferritin rates even lower than those observed in patients with IPS, but this was reported in oral communication (not yet published). Again, we must emphasize the importance of analyzing the iron profile in these patients.

Chart 3 Diagnostic criteria for child agitated sleep disorder [35]

Complaint of restless sleep
Observed large body movements during sleep (movements should comprise large muscle groups of the whole body, of the four limbs, arms, legs, or head)
Movements occur during sleep or when the child appears to be sleeping
Video-polysomnographic documentation of 5 or more large body movements/hour
Occurrence at least three times a week for at least three months
Restless sleep is associated with daytime behavioral/mood/cognitive complaints
Restless sleep cannot be caused by a clinical or psychiatric or environmental condition or other sleep disorder

4.4 Sleep Bruxism

Sleep bruxism is a rhythmic, involuntary movement of tightening and/or friction of teeth during sleep, associated with repeated contractions of the masseter, temporal, medial and lateral pterygoid muscles, that may or may not produce noises [13].

Polysomnographic studies showed that episodes predominate in NREM sleep. As a result of muscular effort, headache, mandibular pain, tooth wear, pain in the temporal-mandibular joint, and even limitation of mandibular movement may occur. The annual incidence of some episodes of bruxism is 15%, for the age10 group of 20 years, the most affected. Children with intellectual disability, ASD and cerebral palsy have a higher incidence [34].

Bruxism can occur in situations of stress and anxiety or association with other sleep disorders such as snoring, obstructive sleep apnea, RLS, PLMD movements and epilepsy associated with sleep. The diagnosis is clinical, but the PSG exam may be requested to confirm the diagnosis and also evaluate the occurrence of other sleep disorders [33, 34].

Dental evaluation is always recommended because it may be necessary to treat tooth wear, or its prevention, with the placement of resin protection or use of intra-oral devices in children with established permanent dentition [33, 34].

Pharmacological treatment may be used in cases with dental impairment and/or clinical symptoms. Children with severe encephalopathies and sleep bruxism can also benefit from pharmacological management. The medications used are mainly benzodiazepines (clonazepam) and alpha-agonists (clonidine) in low doses [33, 34].

5 Child Neurology and Sleep Medicine Interface

5.1 Cerebral Palsy (CP)

CP is a chronic motor condition secondary to nonprogressive brain damage in a brain during its development [36]. The worldwide prevalence of CP is 2.11 per 1000 live births and obeys an inverse proportion to gestational age and birth weight [37]. The prevalence of sleep disorders in children with CP varies from 23 to 46%. Some

variables can influence these high rates, such as: greater occurrence of pain, epileptic seizures, impaired mobility [38, 39]. The presence of sleep disorders impairs cognitive and emotional development of these children and impacting their physical rehabilitation [38].

Horwood et al. observed that the presence of untreated pain was a strong predictor for abnormal scores in the pediatric sleep scale among children with CP, with an odds ratio of 6.5 [39]. The non-pharmacological approach to pain with physical therapy may be an interesting path for the treatment and prevention of sleep disorders in patients with CP, but there are still no studies proving the effectiveness of this type of intervention. A randomized controlled clinical trial involving 142 children diagnosed with CP found that the Cranial Osteopathy technique did not promote sustained improvement in motor function, quality of sleep, and life [40].

5.2 Autistic Spectrum Disorder

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by impairment of communication and social skills associated with repetitive behaviors. The prevalence of ASD can reach 1 per 59 individuals [41]. 50 to 80% of children with ASD have problems initiating and/or maintaining sleep, and the occurrence of sleep disorders may contribute to the worsening of behavior problems [42].

Preschoolers and schoolers with ASD have a higher prevalence of behavioral insomnia and parasomnia, while adolescents with ASD have a higher occurrence of short-term sleep and excessive daytime sleepiness. Several reasons are proposed to justify the higher prevalence of sleep disorders in this group of children: alteration of endogenous melatonin synthesis, sleep neurotransmitter system dysfunction, sensory dysregulation, gene mutations related to rhythm disorders and also the increased occurrence of comorbidities (epilepsy, attention deficit hyperactivity disorder, anxiety, and mood disorders) [43, 44].

Several systematic reviews have already been carried out to evaluate the effectiveness of pharmacological and non-pharmacological treatments to approach sleep disorders in children with ASD. Unfortunately, the findings were inconclusive and often controversial. It is a clearly heterogeneous group of patients with different clinical picture and comorbidities [45].

The most evident therapeutic modalities in this context were melatonin use (0.75 to 10 mg/day), behavioral intervention (e.g., sleep hygiene, extinction, positive reinforcement, and sleep restriction), and parental education [45]. A study identified that parental massage therapy reduced the occurrence of sleep disorders in ASD patients. Although promising, this study used a sample of only 20 children; therefore it still lacks replication of its results [46]. Therefore, the role of the professional physiotherapist in parental education seems to be an effective option of intervention.

5.3 Attention Deficit Hyperactivity Disorder

Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder characterized by the presence of symptoms of inattention, hyperactivity and impulsivity that generate social, emotional and/or cognitive functioning impacts. The prevalence of ADHD is around 5% and the prevalence of sleep disorders among ADHD patients ranges from 35 to 70%, varying according to age, the subtype of ADHD, use of medications and presence of comorbidities [47, 48].

The relationship between ADHD and sleep disorders is multifaceted and complex, as sleep disorders can aggravate ADHD symptoms and even mimic them. More than half of children and adolescents diagnosed with ADHD have at least one comorbidity associated with sleep problems, such as anxiety, depression, bipolar affective disorder, ASD, obsessive-compulsive disorder, conduct disorder and Tourette's syndrome. Besides, the use of psychostimulants, first-line drugs to treat ADHD, directly affects sleep [48].

The most commonly reported sleep disorders in association with ADHD are behavioral insomnia, sleep-related breathing disorders and RLS. The promotion of sleep hygiene associated with behavioral strategies remains as first-line therapy for insomnia in the context of ADHD. Adenotonsillectomy is the main strategy for treating obstructive sleep apnea and may even contribute to improving part of the symptoms of ADHD. Sleep hygiene, avoiding medications that worsen symptoms of RLS (especially neuroleptics and serotonin reuptake inhibitors) and oral or venous iron supplementation (in some specific cases) have scientific evidence for the treatment of RLS in the context of ADHD [48]. Unfortunately, there are no specific studies addressing the role of physiotherapy for the treatment of sleep disorders in patients with ADHD.

5.4 Neuromuscular Diseases

Neuromuscular diseases are characterized by progressive weakening muscles, and may affect skeletal, respiratory and/or bulbar muscles. In some specific cases, there is heart muscle involvement. Some children experience fragmented sleep with low efficiency and oxyhemoglobin desaturation during REM sleep, even in the absence of a sleep-related breathing disorder. This phenomenon happens due to the association of muscle weakness and stiffness or chest deformities potentiated by the physiological mechanisms of REM sleep. In this situation, measuring the exhaled carbon dioxide (CO_2) during sleep is essential for evaluating possible hypoventilation during sleep. Also, children with neuromuscular diseases may experience obstructive sleep apnea which should also be treated to avoid muscle fatigue and its consequences. Polysomnographic studies of patients with neuromuscular diseases show that an increase of CO_2 of 3–7 mmHg and reduction of SpO_2 of 2% is associated with increased upper airways resistance, lower diaphragmatic contraction in the

supine position, hypotonia of intercostal muscles and accessories, reduction of central sensitivity to hypercapnia, hypoxemia, mechanical stimuli for pulmonary insufflation and reduction of central respiratory stimuli [19, 20, 49].

During disease progression, it is known that the inability to cough effectively and clean the airways can cause respiratory failure needing hospitalization in intensive care units.

Normal breathing consists of cycles of variable flowing volumes interspersed with deep breaths or sighs. Periodic hyperinflation is necessary to prevent the closure of some pulmonary units (alveoli). Patients with neuromuscular diseases may present marked weakness of both the inspiratory musculature and the expiratory musculature. This weakness causes decreased current volume and expiratory flow, resulting in decreased lung expansibility. During a normal cough, about 2.5 liters of air are expelled from the lungs at a speed of 6 to 20 liters per second (peak cough flow). High thoracic-abdominal pressure is required to generate an effective and sufficient cough flow to eliminate secretions. Therefore, for an effective cough to occur, high current volumes are required. Deep inspiration dilates the airways and increases the force of contraction of the expiratory musculature, thus making the cough effective in eliminating pulmonary secretions [49–51].

Breath-stacking technique exercises are recommended so that the patient can perform the cough effectively through the maximum capacity of insufflation, which is the largest amount of air that can enter our lungs through the bag valve mask [Table 4; Fig. 1]. The effects of breath-stacking are alveolar recruitment, increased oxygenation, stretching of the chest muscles, and help the cough. Furthermore, stacking facilitates the elimination of secretions and the use of positive pressure devices. The assisted cough maneuver can also be used in the presence of infections or the patient with increased secretion trachea-bronchial is the compression of the chest downward and inward that increases the amount of air expelled. Thus, these maneuvers give strength to the cough and eliminate pulmonary secretions [21].

Below, some practical guidelines on breath-stacking technique: [21]

- It is recommended to perform the breath-stacking technique at least 3 times a day without the assisted cough maneuver when the patient does not present secretion and/or respiratory infections. In the patient who uses positive pressure apparatus, it shall be performed on waking as soon as the positive pressure apparatus is removed and before putting the ventilation apparatus to sleep. The third breath-stack should be done preferably before one of the big meals. In patients with increased bronchial secretion, breath-stacking always before meals to avoid nausea/vomiting caused by secretion.
- The breath-stacking should not be carried out for longer than 10 minutes because it can cause dizziness and nausea.
- Always try to reach the maximum inflation capacity.
- Remember to encourage the patient to sustain the amount of air he has placed in the lungs for 6 seconds, which is necessary for air distribution to the bases of the lungs.

Table 4 Guidance on breath-stacking technique [21]

Position the patient in a seated position
Accommodate the bag valve mask around the patient's nose and mouth
Press the mask firmly (pressure upwards) so that no air escapes
Inflate bag valve mask as many times as necessary to fill the patient's entire lung (usually two to five breaths are required)
After stacking as many bag valve mask inflations as possible, quickly remove the mask, and encourage the patient to hold that amount of air for 6 seconds
In case of flu or pulmonary secretion, help the patient in the expiration (assisted cough that is performed with chest pressure during expiration)
Insist on assisted coughing as often as necessary until the patient can eliminate all lung secretion
Exercise as many times as necessary during the day, that is, every time the patient has secretion and cannot cough without help

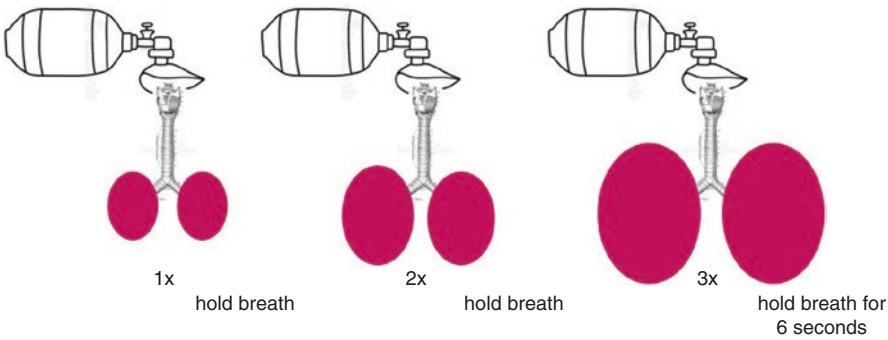

Fig. 1 Schematic drawing on breath-stacking using bag valve mask [21]

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Sleep and Aging

Ligia Mendonça Lucchesi and Ronaldo Delmonte Piovezan

Life expectancy increased by 30 years from the beginning to the end of the twentieth century worldwide and was one of the greatest social achievements of the last century, with longevity becoming the norm for most people. One of the greatest challenges of the twenty-first century will be to guarantee the quality of life of the two billion people aged over 60 who the World Health Organization (WHO) forecast to be alive in 2050, with more than 80% of them living in developing countries [1]. One of the most important factors that will determine the quality of life of this population will be sleep and its disorders, which currently affect about 50% of the population aged 60 and above and two-thirds of those who live in nursing homes [2].

Sleep undergoes a continuous process of change from birth throughout life, a process that is called sleep ontogenesis. However, studies on the changes in the need for sleep over the lifetime have not shown clear and consistent results. The changes observed during adulthood impact both the quantity and quality of sleep, as well as the distribution of each sleep stage and phase during the night. Thus, further studies on sleep ontogenesis are still required to elucidate how changes in the central nervous system (CNS) during the aging process affect sleep. These studies will also need to provide information on the social, physiological, and public health aspects, relevant to maintaining a healthy aging population.

When analyzing sleep changes throughout life, the main difficulty is to establish which changes are the consequences of normal aging, and which are due to the greater morbidity of some older subjects [3]. In fact, if we exclude the influence of pathologies, sleep should be quite similar across different age groups during adult life [4, 5]. Nevertheless, as people get older, it becomes more difficult to find individuals without any kind of disease. It is, therefore, unrealistic to aim for older adults to continue to have the same sleep patterns they did when they were younger, as the majority of individuals do not age optimally, that is, without any health

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condition, sleep disorder, or another factor that might affect their sleep. However, it is realistic to aim for the concept of healthy aging or "normal aging," in which these factors may arise but, through good treatment and management, do not result in a significant reduction in the individual's independence or quality of life [6]. Another problem may arise when comparing individuals of a more advanced age range, as the gap between biological and chronological age tends to get larger over time [3].

Older people without any sleep disorder generally have sleep efficiency (the ratio of total sleep time to the time spent in bed) of between 80% and 85%, with a progressive increase in awakenings after sleep onset (WASO) [4, 7, 8] that gradually reduces sleep efficiency. Sleep tends to become more fragmented, with awakenings lasting longer and appearing more often at the end of the night [4, 8]. Age-related changes in sleep can have both qualitative and quantitative effects and are associated with factors such as difficulty in initiating and maintaining sleep, and a reduction in the percentage of slow-wave and REM sleep [7, 8]. Among the possible influences on sleep due to aging are circadian and homeostatic factors, as well as changes in cardiopulmonary and endocrine functions [8]. During aging, there may be complaints of difficulty falling asleep and waking up too early (advanced phase). Also, there may be a return to a polyphasic pattern (e.g., more than two sleeping periods in one day). Given that changes in sleep quality and quantity in later life have implications for the quality of life and level of functioning, it is imperative to distinguish the normal age-related sleep changes from those originating from pathological processes [8]. In this respect, objective measures of sleep quality, such as polysomnography, are considered the gold standard for evaluating sleep. However, these methods are associated with high costs and are often not easily available. It should be noted that older adults can have a good perception of their sleep quality, so subjective measures such as sleep diaries and questionnaires can, in many situations, be a valid alternative [9].

The aging process also leads to shorter electrophysiological amplitudes during sleep, probably due to a smaller number of cortical neurons. Moreover, REM sleep decreases throughout life, occupying slightly less than (20%) of the total sleep time. Additionally, REM periods (rapid eye movements) are shorter and have less density [4, 7, 8].

A meta-analysis carried out with healthy individuals [7] showed that, after the age of 60, variations in the proportion of sleep stages are modest. Indeed, most changes in sleep patterns seem to occur between early and middle adulthood. From 60 years old onwards, some sleep patterns decrease slightly with advancing age. The only significant change found was the decrease in sleep efficiency, which falls at a rate of 3% per year [7] (Fig. 1).

A study by Moraes et al. [10] analyzing the effects of age on the structure of sleep during adulthood using data from the São Paulo Epidemiologic Study (EPISONO) revealed that the structure and duration of sleep underwent significant changes throughout the aging process in the general population. There was a correlation between age, sleep respiratory parameters, and periodic limb movement (PLM) [10] (Fig. 2). The apnea-hypopnea index (AHI), WASO, and the number of arousals associated with respiratory events showed a significant age-related increase,

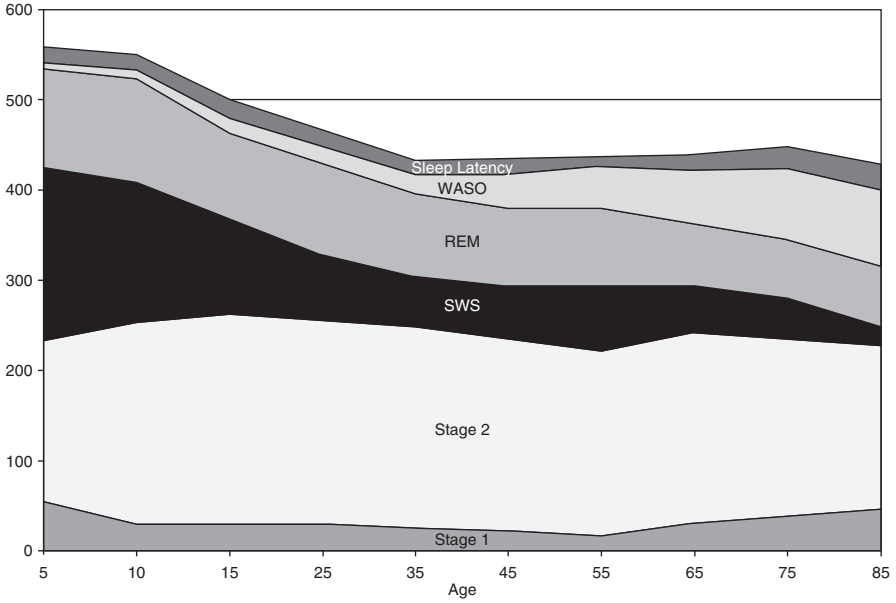

Fig. 1 Age-related trends for stages N1, N2, N3, or slow-wave sleep (SWS), rapid eye movement (R) stage, wake after sleep onset (WASO), and sleep latency (in minutes). (Reprinted with permission from Ohayon et al. [7])

Large effect	Moderate effect	Small effect
↑ Apnea-hypopnea index (AHI) Wake after sleep onset (WASO) Respiratory arousal index (RDI)	↑ Time spent with oxygen desaturation below 90% Desaturation index Periodic limb movements index (PLMi)	↑ Sleep latency (SL) REM sleep latency Stage N1 (%) Stage N2 (% and duration)
↓ Oxygen desaturation: basal, medium and minimum	↓ Total sleep time (TST) Sleep efficiency (SE) Stage N3 (duration)	↓ Stage N3 (%) Stage R (% and duration)

Fig. 2 Changes in objective measures of sleep throughout adulthood

with a large effect size. On the other hand, O_2 saturation (SpO_2) parameters during sleep presented a significant reduction. There was a moderate increase in effect size in time in the O_2 desaturation index and in the lower limb periodic movement index. There was also a moderate reduction in total sleep time (TST), sleep efficiency (SE), and the duration of stage 3 sleep. There was a slight increase in sleep latency (SL), REM latency, the percentage of stage 1 sleep, and the percentage and duration of stage 2 sleep. Finally, there was a slight reduction in the percentage of stage 3 and REM sleep (Fig. 2).

Moreover, men and women showed similar trends, but with different effect sizes. The reduction in the percentage of REM sleep significantly correlated with age in women, whereas the reduction in the percentage of SWS correlated with age in men. The periodic limb movement (PLM) index increased with age in both genders [10].

1 Impact of Sleep on Morbidity and Mortality of Older Adults

In advanced age, indicators of good sleep also can positively affect markers of cardiovascular risk. A study carried out with older adults (over 85 years old) showed that regular sleep patterns, maintenance of SWS, and a favorable lipid profile are important in respect of longevity in humans [11]. This study pointed out the importance of a strictly regular sleep pattern in both young (20–30 years) and older (60–70 years) groups. The same study also found that some older individuals showed high levels of adaptation to the age-related effects of sleep. Taken together, these results indicate the importance of sleep not only for the quality of life but also in respect of human longevity [11].

Another study investigated the association of sleep duration with the risk of all-cause mortality among older Brazilians using data from a 9-year population-based cohort study, the Bambui Health and Aging Study, undertaken in southeastern Brazil. In the multivariate analysis, using sleep duration as a categorical variable and controlling for various sociodemographic and health status measures, those who slept 9 hours or more per night had a higher risk of mortality than those who slept 7 hours (risk ratio (RR), 1.53; 95% confidence interval (95% CI), 1.12–2.09). This study highlights the fact that it is not only short sleep duration that should be considered to have possible negative outcomes [12].

On the other hand, a study in a Japanese community that associated the risk of mortality and dementia with sleep duration showed that the incidence rates of dementia and mortality from all causes (adjusted for age and sex) were significantly higher in individuals who slept less than 5.0 hours or more than 10.0 hours per day [13].

In a meta-analysis carried out with 27 cohort studies comprising 70,000 older people with follow-ups between 3.4 and 35 years, short- and long-term sleep was associated with increased all-cause mortality (RR, 1.33; 95% CI, 1.24–1.43, and RR, 1.07; 95% CI, 1.03–1.11, respectively), compared with the reference category. For cardiovascular mortality, the pooled relative risks grouped were 1.43 (95% CI: 1.15–1.78) for a long sleep and 1.18 (95% CI: 0.76–1.84) for a short sleep. Daytime napping (≥30 min) was associated with the risk of all-cause mortality (RR, 1.27; 95% CI, 1.08–1.49), compared with no daytime sleep [14].

2 Sleep Characteristics in Older Adults

2.1 Sleep Complaints

Older adults suffer from a range of sleep complaints [8], with women tending to report more than men. The symptoms most commonly related to aging are waking up too early, interrupted or very light sleep, increased periods of wakefulness during the night, and reduced total sleep time. As a result of the poor-quality sleep, there are also complaints of non-restorative sleep, waking up tired, and excessive daytime sleepiness [15].

The frequent interruption of sleep can be the result of an age-dependent change in sleep homeostasis and/or in the maintenance of wakefulness. Awakenings are often more frequent and more prolonged, lasting more than 30 minutes [7]. Older adults tend to characterize sleep as lighter and more fragile than young adults, and there may be greater responsiveness to environmental and other stimuli during sleep that previously did not lead to awakenings [7]. In respect of gender, older women have less fragmented objective-measured sleep than men; however, they are more likely to have subjective sleep problems [8].

2.2 Circadian Rhythm Changes with Aging

Age-related disorders of the sleep-wake cycle are part of complex chronobiological changes in physiological systems that accompany the aging process [8]. Changes in circadian body temperature control and the sleep-wake cycle [10] are probably associated with brain modifications including atrophy of the suprachiasmatic hypothalamic nucleus [5]. Body temperature circadian rhythmicity in aged individuals has reduced amplitude and an advanced phase in comparison to young adults [16, 17]. Although demonstrating greater flexibility than younger subjects to sleep deprivation, older subjects show less tolerance to changes in work shift patterns, a fact that may be related to both social factors and their lower homeostatic capacity [16].

Additionally, the reduction in nocturnal melatonin secretion that takes place in older adults can result in a disruption in circadian rhythm, particularly in relation to phase advancement, which is linked to a less pronounced, but an earlier, decline in body temperature in the evening, as well as an earlier increase in the morning. This can result in less time in bed, less total sleep time, and, therefore, greater daytime sleepiness [8].

2.3 Excessive Daytime Sleepiness and Naps

Excessive daytime sleepiness (EDS) directly impacts the quality of life in older adults and should not be part of normal aging. Epidemiological research has shown that older people without sleep disorders do not have EDS [15]. Daytime sleepiness

in older individuals is a common consequence of a number of sleep disorders, as well as neurological and respiratory problems [5, 15]. Although some controversy remains as to whether regular napping in older adults is healthy, it has been reported to have a negative impact on the night-time sleep quality of older people without sleep disorders [18]. However, the question remains whether napping may be a favorable compensating behavior in chronic insomniacs [4].

3 Etiological Factors

Sleep complaints and sleep disorders are frequently persistent and multifactorial in origin older patients. In addition to age-related physiological changes in circadian rhythm and sleep homeostasis, other risk factors in relation to sleep impairment can be classified as follows: (a) medical and psychiatric comorbidities, such as cardiovascular disease, arthritis, gastroesophageal reflux, depression, and the medications used to treat them; (b) social, environmental, and behavioral factors, which can compromise an individual's quality of sleep; (c) primary sleep disorders that can affect mainly the older; and (d) a combination of the factors above mentioned [6, 18].

4 Main Sleep Disorders Affecting Older Adults

With regard to the presence of sleep disorders in older people, an increase in the prevalence of insomnia; sleep-disordered breathing (SDB), including obstructive sleep apnea (OSA); movement disorders; and REM sleep behavior disorder has been reported.

4.1 Insomnia

The prevalence of insomnia in the general population has been estimated at between 10% and 20%, but some studies in older adults report higher frequencies [19]. An epidemiological study including individuals over the age of 65 showed that 42% of the participants complained of difficulties in falling asleep or staying asleep. Higher prevalences are observed in individuals with clinical and mental conditions, those using medications [15], retired or inactive individuals, or in people who are taking care of another older person [20]. Possible consequences of insomnia are depression, anxiety, cognitive decline, increased suicide attempts, clinical diseases (cardiovascular and cancer), increased fragility, and sarcopenia [19–21].

Insomnia in older subjects is related to increased mortality, risk of falls, lower quality of life, depression, and increased anxiety [19]. Insomniacs are more likely to present chronic pain, cancer, chronic obstructive pulmonary disease, and cardiovascular diseases as associated factors [20]. Nocturia, despite being very common in both male and female older individuals, is underestimated as a potential risk factor for insomnia. Many age-related factors contribute to nighttime urinary symptoms, including sleep-disordered breathing such as OSA [15, 22], and these symptoms are related to sleep fragmentation and excessive daytime sleepiness [15]. Menopause also contributes to worse sleep quality, causing nocturia, increased airway resistance, and obesity, in addition to night sweats [23]. On the other hand, the treatment of menopausal symptoms promotes a reduction in subjective insomnia and an increase in sleep efficiency [23].

Additionally, environmental and psychological factors contribute to the increased incidence of insomnia in older people. A large part of the population over the age of 65 years old often experiences social isolation (which has increased with the onset of COVID-19), financial problems, lack of exposure to sunlight, and anxiety due to fear of death and illness. Insomnia in this age group is often treated without a careful assessment of its causes, and self-medication is also frequent [23]. Additional predisposing factors for insomnia are female gender, divorce and widowhood, low education level, drug abuse, physical inactivity, and difficulties in social relationships [20, 24]. As precipitating factors, we have disabilities, the acute beginning of physical and psychiatric illnesses, and the use of medications. As for perpetuating factors, these include immobility, naps, excessive daytime sleepiness, and behavioral changes [20].

Cognitive-behavioral therapy (CBT) has shown long-term efficacy for the treatment of chronic insomnia in older adults [25]. A study confirmed that CBT not only improves sleep quality but reduces acute or long-term pain in patients with insomnia and osteoarthritis. This fact suggests that impaired sleep is not only a symptom of the painful syndrome and that improved sleep can also relieve comorbid disease [26].

4.2 Sleep-Disordered Breathing

In an analysis based on the literature, a high worldwide prevalence of obstructive sleep apnea was reported and was highlighted by country and region [27]**.** The authors concluded that there is a clear association between OSA and several adverse clinical results, including morbidity and mortality from cardiovascular disease [27]. The estimated prevalence of OSA ranged from 5% to 80% and was generally higher in older people [28]. In the epidemiological study conducted in the city of São Paulo mentioned previously, the prevalence of OSA in the 60–70 age group was 60.2% (55.9% for men and 63.4% for women) and 86.9% above 70 years (88.7 for men and 85.8 for women) [22]. In younger adults, there is a higher prevalence of OSA in

men, but after menopause, the prevalence in women becomes similar to that in men. A number of age-dependent factors could explain this progressive increase, the best known being the tendency, with age, for the upper airways to collapse due to a weakening of the pharyngoesophageal musculature, which explains snoring, and to some extent, the apnea present in this condition. Other age-dependent factors include reduced vital respiratory capacity and thyroid function, increases in body mass index, and a drop in respiratory control [22, 29, 30].

The most common daytime symptoms of OSA in older adults are excessive daytime sleepiness, impairment in daily performance and concentration, and cognitive and behavioral disturbances [22, 29, 30]. As for the symptoms and nocturnal signs related to increased AHI, the most common are snoring, abnormal motor activity, frequent awakenings, choking, nocturia, and excessive sweating [31].

Few studies have examined the consequences of OSA in older populations. It is difficult to attribute adverse outcomes to a single condition, given that this population suffers from high rates of comorbidities. As with other conditions, evidence linking OSA with health consequences may not be as robust as in young adult populations [28]. When examining sleep and body composition, it is important to consider the possible association between atypical clinical features such as weight loss, fragility syndrome, sarcopenia/sarcopenic obesity, and OSA in older adults.

The changes in muscle tissue, sleep, and the sleep-wake cycle present in older adults are associated with an increase in inflammatory signals. Aging generates several changes in different systems, but, currently, the chronic sub-clinical and low-grade inflammatory process, called “inflammaging” (inflammation and aging), is the main focus of interest. The pro-inflammatory phenotype of senescent cells can contribute to systemic inflammation in the aging phase, becoming harmful to health. These senescent cells are essential, and large amounts of proinflammatory cytokines are produced during the reproductive phase of life to repair tissue damage [32].

Several factors have been associated with an increased risk and severity of OSA. These include male gender, age, central obesity, alcohol use, craniofacial anomalies, heredity, and more recently, the period after menopause and polycystic ovary syndrome [33–35]. In addition to these, other characteristics such as excessive naps, dementia, nocturia, vertigo/dizziness syndromes, falls, and acute psychiatric conditions – including depressive/anxiety symptoms, delirium, and Charles Bonnet syndrome (a rare disease linked to visual hallucinations) – have also been linked to increased OSA [36].

In respect of the treatment of sleep apnea in older adults, the same guidelines used with younger adults should be followed, like apnea, when associated with symptoms, should be treated regardless of age. Positive airway pressure (PAP) treatment should be considered as the first option. The difficulty of adaptation to the treatment seems to be similar in older adults to that of young adults [37]. Myofunctional therapy should also be considered as a strategy to increase adherence to PAP [38].

4.3 Restless Legs Syndrome and Periodic Limb Movements Disorder

The frequency of periodic limb movement disorder (PLMD) increases progressively with age, as does the prevalence of restless legs syndrome (RLS). Many mechanisms, both central and peripheral, seem to contribute to this increase. Among the main agents are a dopaminergic deficit, also linked to iron deficiency, which is successfully corrected by the administration of L-dopa or dopaminergic agonists [39]. A family history of the disease (30–65%), a reversal of symptoms with a dopaminergic (80–90%), and PLM in sleep (80–90%) are the most frequent characteristics found in RLS [39].

Along with OSA, RLS and PLMD are frequent causes of sleep fragmentation and daytime sleepiness [40]. RLS occurs in 5–8.8% of the adult population and is associated with diverse age-related factors, including uremia, anemia, iron deficiency, Parkinson's disease, chronic obstructive pulmonary disease, hypo/hyperthyroidism, multiple sclerosis, and depression [41–43]. The drug treatment for RLS comprises dopaminergic agents, opioids, benzodiazepines, and iron replacement. Dopaminergic agents are the first-line therapy, but they can present a worsening of symptoms, with expansion to other parts of the body as the drug dose is increased. Some medications and substances such as antidepressants, antiemetics, antihistamines, alcohol, caffeine, and levothyroxine can exacerbate symptoms [44–46]. Non-pharmacological treatment options include improved sleep hygiene, avoiding smoking, physical exercise, massages, and hot or cold baths [45, 47].

In summary, it must be remembered that RLS has a high prevalence and that we should investigate associated diseases and medications that potentially worsen symptoms. For treatment in moderate and severe cases, dopamine agonists are the first line, but the monitoring of side effects is highly recommended [47].

4.4 REM Sleep Behavioral Disorder

Rapid eye movement sleep behavior disorder (RBD), also known as REM behavior disorder, is a parasomnia characterized by abnormal behaviors such as vocalizations, spasms, and motor activities during R stage, and is usually underdiagnosed. It is more common in individuals aged over 50 years old, with a significant prevalence in men [8]. There is an absence of physiological muscle atony during this phase of sleep, which is also associated with dreaming. This, therefore, can produce an imbalance between the mental activity of the dream and the absence of motor inhibition related to the dream content, leading to the individual acting out the dream. Patients also frequently report intense and vivid dreams, often of an aggressive nature, which can be associated with relatively coordinated semi-intentional movements, such as running. This motor activity can affect the bedpartner, resulting in bruises, lacerations, fractures, and direct trauma. In the anamnesis, there is a history

of restless sleep, which can occur every day, often at the end of the night when REM sleep predominates. PSG can usually confirm the diagnosis by detecting excessive motor activity during REM sleep, and audio-visual monitoring can show abnormal body movements and vocalizations [48].

RBD is generally considered to be associated with synucleinopathies, such as Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy that usually appear years before the first symptoms of these diseases. RBD is believed to predict neurodegeneration in synucleinopathy. However, growing evidence has shown that it is also found in non-synucleinopathy neurodegenerative diseases, including Alzheimer's, Huntington's diseases, and amyotrophic lateral sclerosis, among other conditions. It can be an early sign of neurodegeneration in these diseases, and also serve as an assessment of non-cognitive symptoms prior to cognitive impairments [49, 50].

The most common treatments used for RBD are clonazepam, melatonin, and ramelteon. It should be noted that drugs used to treat neurodegenerative diseases, such as monoamine oxidase inhibitors and antidepressants, can induce or aggravate RBD symptoms [50].

5 Treatment of Sleep Disorder in Older Adults: Physical Therapy and Exercise

The varied clinical presentations of sleep complaints require a multidisciplinary treatment response. The symptoms and the presence of comorbidities should be used to guide the therapeutic decision. The treatments used to manage sleep disorders include:

- The prevention and treatment of musculoskeletal pathologies using stretching exercises, muscle strengthening, proprioception, and joint mobilization to reduce stiffness and contractures. The current treatment options for sarcopenia include specific physical exercises (sometimes combined with nutritional recommendations). In addition, therapeutic approaches to normalize circadian rhythms and sleep homeostasis strategies can be used to preserve or recover muscle health in older adults [51].
- The treatment of respiratory pathologies using breathing exercises to strengthen the muscles participating in breathing, thereby increasing vital capacity. Although PAP is the most effective treatment in the complete resolution of OSA and in improving saturation rates during sleep [52], physical training, used as an additional option, can help to significantly reduce excessive daytime sleepiness [53]**.** Furthermore, the use of myofunctional therapy together with PAP has been shown to produce an increase in adherence to PAP [38].
- Fall prevention and treatment of older people with a history of falls: walking and balance training, proprioception, muscle strengthening, and home guidance.

Although this type of therapy is not directly related to sleep, it can also have a positive effect on it.

As a result of these treatments, there is an improvement in physical capacity and quality of life. Also, physical exercises can bring pain relief in older patients [50]. All of these results lead to an improvement in sleep quality.

6 Final Words

Aging can be associated with a decline in motor function, cognitive ability, and functionality. Sleep plays an essential role in all these processes, and its improvement can reduce negative outcomes in older individuals. With aging, changes occur in sleep patterns, which can become more fragmented, less efficient, and susceptible to clinical, mental, and sleep disorders. The sleep disorders that most commonly affect older adults, including insomnia, respiratory disorders, RLS, PLMD, and RBD, can be associated with the risk of geriatric syndromes, such as dementia, depression, delirium, falls, frailty, and sarcopenia.

Recent advances in physiotherapeutic approaches mean that we can improve the quality of sleep of individuals in this age group, as well as reduce the risk of falls, and the impact of other age-related conditions, with a consequent improvement in the quality of life brought about by the relief from symptoms and increased independence.

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Sleep and Gender Differences

Glaury A. Coelho

The experience of sleeping differs between women and men. The reporting of the symptoms also differs, women need more sleep than men, about 20 minutes more per night [1], and women having more complaints about sleep than men [2–4]. Women tend to have a better quality of sleep and shorter sleep latency, sleep longer, and have a higher sleep efficiency than men [5]. Distinct hormonal changes in specific time points can impact sleep health and lead to gender-specific sleep disorders [6]. Obstructive sleep apnea has a higher prevalence among men (until postmenopause at least), while insomnia and restless legs syndrome are higher among women [5, 7, 8].

For researchers, one of the fundamental characteristics to classify a social group is sex. However, the biological condition is not enough to understand supra-organic aspects, such as environmental, psychological, and socio-cultural factors that can contribute to this difference in scientific analysis. With the advent of sexology, new terms were proposed seeking to identify and clarify what was innate, and what was culturally influenced. Back in the 1950s, John Money commented on the difficulty of accepting the use of the terms *gender role* and *gender identity* by sexual medicine at the time [9]. According to his research, a person's sexual status has many criteria, besides its chromosomal charge (or genotype). In addition to sexology, there is a growing interest among sleep researchers clearly addressing the influence of sex versus gender on normal sleep and its disorders.

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1 Defining Concepts

The term *sex* refers to the dichotomy between individuals such as male and female, related to glands or gonads, sex hormones, body anatomy, and genitals. Chromosomal sex refers to XX or XY at the time of fertilization (genotype); biological sex (phenotype) refers to secondary female or male sex characters from androgen hormones; gender identity refers to that inner feeling of belonging to the female or male universe and the ability to relate to both; gender role or social role refers to the way of being of each person, how it behaves before society as a whole (Table 1). This role already begins to be defined before birth (the sex of the fetus is known previously through ultrasonography), and after it, children should follow the set of values corresponding to what society establishes as to how they should be, feel, dress, and behave as a feminine or masculine person.

The term *gender* refers to how sexual characteristics and biological differences between women and men are understood and translated into social practice and relationships between people. It is how each culture identifies what is feminine and masculine; what are the obligations, rights, and standards to be followed by women and men [10, 11]. Women tend to multi-task (many activities at once), and so some research presents that women use more their brain than men do, needing more sleep.

Sex and gender are factors that significantly influence the health of women and men [12], as well as modulating women's and men's health standards and the level of disease of the general population. In this chapter, the sexual and gender differences of both normal sleep and sleep disorders will be addressed to assist in the clinical evaluation of physical therapists.

2 Normal Sleep in Women and Men

Girls have an increased sleep duration and sleep with more quality from childhood to early adolescence. From this moment on, there is a decrease in slow wave sleep (SWS) and a circadian delay that, if accentuated, may already predispose to insomnia symptoms in adolescents [13]. However, it is considered that the early pubertal maturation of young women (compared to boys) cannot be directly associated with the decline of the SWS, since even among boys, pubertal and electrophysiological time relationships were statistically independent of the sex difference [14].

Mallampalli and Carter presented a comprehensive report on differences in normal sleep of women and men: (i) sleep onset latency is longer in women; (ii) above

Table 1 Differences in the classification between sex and gender

Chromosomal sex or genotype	Biological sex or phenotype	Gender identity	Gender role or social role
XX	Female	Woman	Feminine
XY	Male	Man	Masculine

the age of 55, women report more drowsiness than men; (iii) as the age progresses, women have less sleep time than men; (iv) men have more N1 and N2 stages than women, who have more N3 stage [15].

3 Disturbed Sleep Between Gender

Understanding the difference between women's and men's sleep disorders has so far focused on the biological dimension [4, 13, 16] and in studies with men [4]. Advanced age is a risk factor for sleep difficulties in both sexes. However, hormonal and anatomical factors influence and alter women's sleep, especially from menarche to postmenopause, requiring specialized knowledge in the conduction of their problems.

There is little scientific evidence about how psychological and socio-cultural factors intensify the differences in the sleep-wake cycle between women and men. After a night of sleep deprivation, the performance of cognitive functions in women was more impaired than men [17]. These findings can be explained by the several commitments assumed by the female role, such as double working hours between work and family, impacting on the health of workers with children [18]. Women work 7.5 hours more per week than men, and 90% of them reported doing domestic work in addition to paid work [19], thus being more disposed to sleep deprivation. This lifestyle may be related to increased surveillance [20, 21] and may also be associated with mood disorders such as anxiety and depression [22], which in turn, influence and impair sleep.

Women have an increased risk of insomnia of 40% compared to men [10], which justifies greater attention from health professionals. Insomnia in women seems to be associated with mood disorders, and insomnia in men seems to be associated with clinical comorbidities. Insomnia is also more prevalent in separated, widowed, or single women [23].

Obstructive sleep apnea (OSA) is more prevalent in men, and obesity is a relevant risk factor [24]. However, the quality of life of women with OSA is more affected than that of men [25]. The symptoms of OSA presented in women at a less severe level when compared to men, with mild snoring, minor Apnea-hypopnea index (AHI), shorter obstruction events [26] and usually report difficulties in initiating and maintaining sleep, nightmares, fatigue, and depression [2, 27]. This clinical condition may lead to the diagnosis of OSA in women. Men with OSA usually have more pronounced AHI and symptoms such as loud and strong snoring witnessed apnea, and daytime drowsiness. The consequences of OSA are also distinct: hypertension and depression are more common in women and diabetes and heart disease in men [28]. Women with OSA severity like those of men usually present impairments in quality of life and attend health services more intensively [29]. In the treatment of OSA with Continuous Positive Airway Pressure (CPAP), women tend to be less adherent to therapy, using alternative treatments [30]. In clinical practice, women report that they do not want to be seen by their spouse using the equipment during sleep.

Other sleep disorders present prevalence between genders and can be found in Table 2.

Table 2 Prevalence and relevance of sleep disorders between genders

Sleep disorder	Prevalence	Relevance
Circadian rhythm	♀	♀ are more prone to morning-type and increased wakefulness
Insomnia	♀	♀ are more prone to morning-type and increased wakefulness Risk of up to 40% more than ♂ Cognitive impairment is greater in women with sleep deprivation ♀ report unsatisfactory sleep during different stages of life Peri- and post-menopause accentuate risk factors ♀ double workday affects the quantity and quality of sleep
Obstructive sleep apnea	♂	Increased waist circumference is a risk factor for OSA severity in ♂ ♂ have more pronounced AHI ♀ are underdiagnosed, have nonspecific symptoms Depression is associated with OSA in ♀
Restless legs syndrome	♀	Associated with anemia, pregnancy, iron deficiency
Central sleep apnea	♂	Lower BMI and age above 65 years
REM behavioral sleep disorder	♂	♂ tend to have dreams of more violent content and with more explicit physical manifestations than ♀ Ratio ♂ /♀ of 1.62/1
Sleep-related eating disorders	♀	Associated with eating problems in childhood
Narcolepsy	♂	With or without cataplexy, ratio about ♂ /♀ of 1.4 / 1.8

AHI apnea-hypopnea index, *OSA* obstructive sleep apnea, *BMI* body mass index, ♂ man, ♀ woman

3.1 Sleep in Different Phases Across Women's Life

The sleep pattern is experienced in a unique way between women in different stages of life, either by physiological, cultural, or behavioral factors. There are changes that occur in the cycles of female life that influence and are influenced by sleep: menarche (which indicates the beginning of the reproductive phase) and monthly periods (also called pre-menopause); pregnancy (a fluctuation of hormones throughout 3 trimesters); peri-menopause (the phase that marks the end of a woman's reproductive life, with an approach to the last period, around the age of 50, which happens by the decrease in estrogen production and precedes menopause); menopause itself (the last first day of a period); and post-menopause (clinically recognized when there is amenorrhea (absence of menstruation) in the last 12 months, ruled out pathological causes) [31]. All these hormone-controlled phases physiologically impact the sleep pattern (Fig. 1) [16].

Menarche and the new infradian rhythm of the menstrual cycle tend to promote changes in the young woman's quality of life. From this time on, girls are prone to the development of mood disorders, twice as much as boys [16]. Symptoms of the perimenstrual syndrome, dysmenorrhea, and night bleeding are early associated with a compromised sleep pattern. In PSG examination there is an increase in EEG

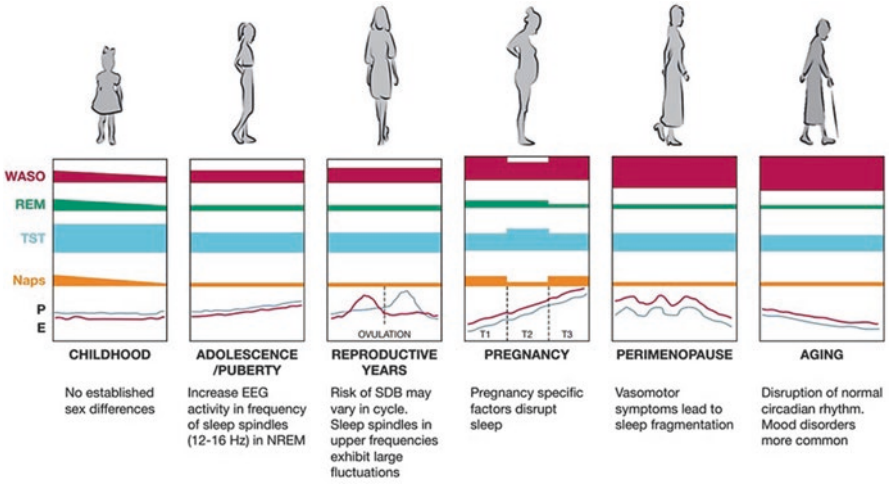

Fig. 1 Sleep in women across the life span. E estrogen, NREM non-rapid eye movement, P progesterone, REM rapid eye movement, SDB sleep-disordered breathing, T trimester, TST total sleep time, WASO wake after sleep onset. (Reprinted with permission from Pengo et al. [16])

activity, and N2 stage sleep spindles in the post-ovulatory luteal phase [32] already indicating a change in the sleep architecture. The menstrual cycle is divided into the pre-ovulatory follicular phase and post-ovulatory luteal phase, in which the onset of the period marks the beginning of a new cycle. Sleep complaints appear at the end of the luteal phase (pre-menstrual) and at the beginning of the follicular phase, as worsening in the quality of sleep and insomnia symptoms [33]. Additionally, women with irregular menstrual cycles had twice the chance of having sleep problems, compared to women with regular menstrual cycle patterns [34]. Premenstrual syndrome can be accompanied by complaints of insomnia, unpleasant dreams, poor sleep quality, daytime sleepiness, and fatigue [35]. Dysmenorrhea and lower sleep efficiency are negatively interlaced [36]. Instructing the patients to keep a three-month diary is a good opportunity to working out whether the sleep problems are related to the menstrual cycle and therefore seek help.

Pregnancy is a period of physical and psychological changes that modify the quality of life and contribute negatively to the duration and consolidation of sleep. Sleeping during pregnancy (for two or more!) is a challenge. As many as 97% of pregnant women say that their sleep is disturbed, especially in the third semester. Pregnant women have typical sleep disorders when compared to non-pregnant ones [37], and a poor quality sleep in the first months was associated with the development of gestational diabetes mellitus [38]. During pregnancy, the narrowing of the upper airway is a risk factor for the presence of rhinitis, nasal congestion, snoring, and even OSA. There is an even higher prevalence of restless leg syndrome due to iron deficiency and hormonal influences. In the first trimester, high levels of progesterone increase daytime and sleepiness and the need for sleep. Progesterone also increases urine production and can disturb sleep as the enlarged uterus presses on

the bladder, so disrupting sleep to go to the bathroom. In addition, nocturia and musculoskeletal discomfort usually disturb the pregnant woman's sleep. In the second trimester, fetal movement and uterine contractions are added to this picture. Restless sleep and sleep complaints increase toward the start of the third trimester. In the last trimester, leg cramps, heartburn, gastroesophageal reflux, frequent trips to the bathroom, and the difficulty of finding a comfortable position in bed promote a superficial and fragmented sleep, added to the anxiety of a mother to be [16]. In addition, oxytocin can add to more fragmented sleep. Also, the preparation for childbirth, financial planning, and future lifestyle changes caused by the new family member [37] also contribute to increased stress and anxiety that compromise the sleep pattern.

In the postpartum period, the sleep of the mother (in the free course! and so sleep deprived!) accompanies the polyphasic sleep of the baby, which means multiple awakenings, decreased sleep efficiency, and increased fatigue [39]. Baby care during the first few weeks is associated with mood swings such as anxiety and depression, and poor sleep is an important risk factor [37].

Another moment of physical and psychological changes in the transitional phase from reproductive to non-reproductive stages is called menopausal transition or perimenopause. Some women notice signs of progression toward menopause, such as menstrual irregularity, around their 40s, but some may notice changes as early as their mid-30s. In this phase, there are decreased follicles, increased follicle-stimulating hormone levels, and reduced estradiol levels. In this phase, the woman can experience the climacteric symptoms (hot flushes and sweating, musculoskeletal pain, vaginal dryness, osteoporosis, metabolic disorders, cognitive symptoms, genitourinary syndrome, and complaints of sleep disorders) [40].

Menopause is a milestone in a woman's life, representing the end of reproductive life, and it can have several implications, such as sleep disorders and musculoskeletal pain [41–43]. Post-menopause is defined retrospectively: after 12 consecutive months of amenorrhea, discarding other endocrinological causes [44]. It represents the end of the reproductive period and ovarian (physiological) failure. Thus, estrogen rapidly falls, which causes several physiological changes in the short and long term, highlighting the presence of vasomotor symptoms (night sweats, hot flushes), which occur in about 70% of women and interrupt sleep. There are indications that the most frequent sleep disorders in post-menopause are insomnia, obstructive sleep apnea, restless leg syndrome, and periodic limb movements [45].

4 Sleeping Together

In some cultures, couples sleep in the same bed. The couple is seen as a "system" that feeds itself through rules that maintain the pattern of interaction [46]. A change in one member inevitably affects the other. What can happen to the sleep of those who share the same bed? Can preference for waking up and going to sleep improve or impair the quality of individual sleep and the quality of the marital relationship?

Quality of sleep is associated with the functioning of the marital relationship reciprocally [47]. Fragmented or insufficient sleep resulted in cognitive impairment, irritability, as well as difficulties in social interaction, mainly in men. Conversely, women had low quality sleep as a consequence of what they experienced during the day. A recent investigation found that married persons have a significantly increased percentage of stage R sleep (within normal range) as compared to never-married persons [48]. Stage R sleep is vulnerable to psychosocial stress factors and thus represents an important mechanism through which partnerships impact sociability and (mental) health.

Using actigraphy as an objective instrument to evaluate the sleep-wake rhythm, the researchers found that discrepancies in time in bed were a predictor of marital conflicts the next day [47]. On the other hand, the process of sharing the bed with the spouse establishes a mutual regulation of sleep as the time to go to sleep and the time to wake up [49], co-regulating the wake-sleep cycle. In a recent study, it was also possible to verify beyond the synchronization of sleep that factors such as emotional support and relationship depth may be important in the change from individual to shared sleep [50]. According to the *Wake-Up Call: Global Sleep Satisfaction Trends Report* form 2020, 36% of participants reported sleeping separately from their partners/spouses occasionally to improve the quality of their own sleep [51].

Sleep disorders, such as OSA, can be considered a stressor for both the patient and the spouse [52, 53]. Generally, the man does not notice that snoring, but the woman standing next to him interrupts her sleep numerous times by the loud noise or frequent respiratory apneas caused by hypoxemia. This situation results in unsatisfactory sleep, feeling tired, fatigue, and symptoms of insomnia in the women, as well as irritability directed to the spouse. Sleep disorders may account for about 30% of the couple's conflicts [51], and marital relationship problems may interfere with the etiology, evolution, and treatment of a sleep disorder. Experts should evaluate the quality of the couple's relationship by identifying negative factors that may impair treatment and suggesting possible alternatives according to each couple. The clear and respectful communication between the couple about their sleep habits and their difficulty sleeping usually solves conflicts of this nature.

5 Final Words

So far it seems to be challenging to identify gender versus sex differences and how these factors can impact the quality of normal sleep and sleep disorders. Even today, these two domains (sex and gender) are poorly understood. The evaluation of psychological and socio-cultural factors demands more interest and clarification from researchers. Understanding the individual through the lens of sex and gender is the first step for the development of research directed to the subject and to personalize the clinical care of sleep difficulties.

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Sleep in Neurologic Diseases

Lúcio Huebra Pimentel Filho, Marcos Manoel Honorato, and Fernando Morgadinho Santos Coelho

Systemic diseases have a complex relationship with circadian rhythm, sleep, and sleep disorders. Many neurological diseases present intensification of their symptoms at a certain time of the day, right after waking up, close to bedtime, or even during sleep. Several conditions, especially neurological diseases, can present themselves as precipitating or perpetuating factors of sleep disorders. Also, sleep disorders can be aggravating factors of the symptoms of several diseases. The proper approach to sleep disorders in patients affected by neurologic diseases becomes important. It is necessary to know the main sleep symptoms related to the underlying neurological diseases, how to investigate them to enable treatment with consequent improvement in the quality of life. In this chapter, we will stick to the following neurological diseases, due to their higher prevalence and their association with sleep: stroke, epilepsy, Parkinson's disease, Alzheimer's disease, neuromuscular diseases, and headache.

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1 Stroke and Sleep

Cerebrovascular disease is highly prevalent in all regions of the world and is an important cause of morbidity and mortality [1].

Ischemic stroke is the most common type of stroke due to vessel obstruction, and it can have multiple etiologies. The most frequent causes are atherosclerosis, microangiopathy, and embolism of cardiac origin. Intraparenchymal hemorrhage is less prevalent and is generally linked to systemic arterial hypertension. Both kinds of stroke have a variable prognosis depending on the extent of the injury, age, and treatment offered. Rehabilitation through physiotherapy and speech therapy has a fundamental role in this outcome [2].

In addition to motor or sensitive weakness due to vascular injury, many patients develop sleep disorders after stroke. Previous sleep disorders may be a risk factor, and also worsen the patient outcome [3, 4]. The identification of these disturbances is essential for proper treatment to be instituted. This impacts an improved quality of life [5].

On the other hand, it is well established that patients with sleep apnea have a recognized increased risk for cerebrovascular disease [6–8].

Changes in sleep architecture are very common after stroke. Alteration in REM sleep is more frequent in infratentorial lesions, while in supratentorial lesions changes in spindles and slow-wave sleep. In this case, there is usually a decrease in non-REM sleep, overall sleep time, and sleep efficiency. There are regional differences in brain electrical activity. For example, in some patients with thalamic infarction occurs poverty of k complexes. Pontine injuries can cause complete disorganization in the formation of spindles and acute vertex waves [9].

Excessive sleepiness and obstructive sleep apnea are the most common sleep disorders in post-stroke patients [5].

Excessive daytime sleepiness can occur due to structural damage to the central nervous system after stroke, especially when there are lesions in regions of the upward activating reticular formation and bilateral stroke. The rationale for this is the compromise of structures responsible for the source of the sleep-wake cycle [10].

Systemic diseases such as decompensated diabetes and hypothyroidism are frequent comorbidities. Hydroelectrolytic disorders, especially hyponatremia or hypernatremia, are common in hospitalized patients and can contribute to sleepiness [11].

Obstructive sleep apnea syndrome is the most common sleep disorder in stroke patients. It affects more than half of the patients and is related to underlying cardiovascular or metabolic diseases, with an emphasis on obesity [12]. It consists of recurrent upper airway obstructions causing hypoxemia, hypercapnia, and low sleep efficiency, and consequent sleep fragmentation and excessive daytime sleepiness [13].

The diagnosis of obstructive sleep apnea can be difficult in critically ill patients, hospitalized, or with major sequelae, virtually unable to perform polysomnography. Current diagnostic criteria require events to occur at a frequency greater than or

equal to 15 per hour. The occurrence of 5–14.9 events associated with symptoms (fatigue, excessive daytime sleepiness, respiratory pauses) is also satisfactory for confirmation [14].

Obstructive sleep apnea has a bidirectional relationship with stroke. It is considered a modifiable risk factor and contributes to increased mortality [15]. The mechanism involved in this process can be indirect, through the worsening or deregulation of hypertension and underlying heart diseases. But it can also be direct, through inflammatory mediators, hypercoagulability, endothelial dysfunction [16].

The use of continuous positive airway pressure is recommended to treat obstructive sleep apnea in stroke patients. It decreases apneas and hypopneas and improved hemoglobin saturation. Intraoral devices and body positioning can help also. A multi-professional approach is needed to increase treatment adherence: physical therapists, dentists, and psychologists can be essential [5, 17].

There is a consensus in the literature that interventions benefit the quality of life, as well as reducing the risk of a new vascular event, and decreases mortality [18].

Restless legs syndrome and periodic limb movements of sleep have also been reported by some authors in the context of patients with cerebrovascular disease [19].

2 Epilepsy and Sleep

Epilepsy is one of the most common neurological diseases, characterized by being a brain disorder with a lasting predisposition to present epileptic seizures and triggering neurobiological, social, cognitive, and psychological consequences.

Epilepsy has a complex and reciprocal relationship with sleep. Poor quality of sleep can lead to greater difficulty in controlling epileptic seizures, and epileptic phenomena can harm sleep, as well as night seizures can simulate sleep disorders. The neurobiological basis of this relationship is still largely unknown, but a few studies suggest that hypersynchrony of neurons that occurs in some stages of sleep and epileptic seizures are related to the same mechanism [20].

Part of generalized genetic epilepsies are characterized by a crisis on waking; others are predominant during sleep [21]. Many patients have their crises precipitated by sleep deprivation. This phenomenon is even used as an activation method in preparation for the EEG, to increase the sensitivity of the exam [22]. Both characteristics occur particularly in patients with juvenile myoclonic epilepsy [23].

The sleep state can also influence electroencephalographic manifestations. West syndrome is severe epilepsy with a poor prognosis that starts in infants and has multiple etiologies. Child spasms usually occur during the transition between sleep and wakefulness. Pathognomonic electroencephalographic features constitute hypsarrhythmia and may not be fully observed if only wakefulness tracing is obtained [24].

People with familial frontal lobe epilepsy, virtually caused by specific genetic mutations, demonstrate seizures almost exclusively during sleep [20].

Another epilepsy that has an intimate relationship with sleep is encephalopathy with an epileptic status of slow-wave sleep (ESES). It may also have a genetic etiology. Persistent discharges are activated by slow-wave sleep [25].

Authors reported that epilepsy alone already changes the architecture of sleep, with low sleep efficiency and changes in the distribution of REM and non-REM stages being frequent [26].

Although the electroencephalogram (EEG) is the routine complementary exam in the evaluation of people with epilepsy, eventually epileptiform discharges may be observed during the recording of polysomnography [Fig. 1].

People with epilepsy are usually treated with anti-crisis medications. The mechanism of action is to block the sodium channels, which prevents the depolarization of hyperexcited neural networks. A common side effect of this class of drugs is excessive drowsiness, with emphasis on carbamazepine, oxcarbazepine, and pregabalin. Sleepiness also occurs after the use of GABAergic drugs such as phenobarbital and valproic acid [27]. Modern anti-crisis drugs such as lamotrigine also act on ion channels, but with a less sedative effect. Levetiracetam, an inhibitor of the release of synaptic vesicles, has a different profile and does not usually influence sleep [20, 27].

The ketogenic diet is an alternative treatment used for medication-refractory epilepsies in children and adolescents. It is rich in fats, suitable for proteins, and low in

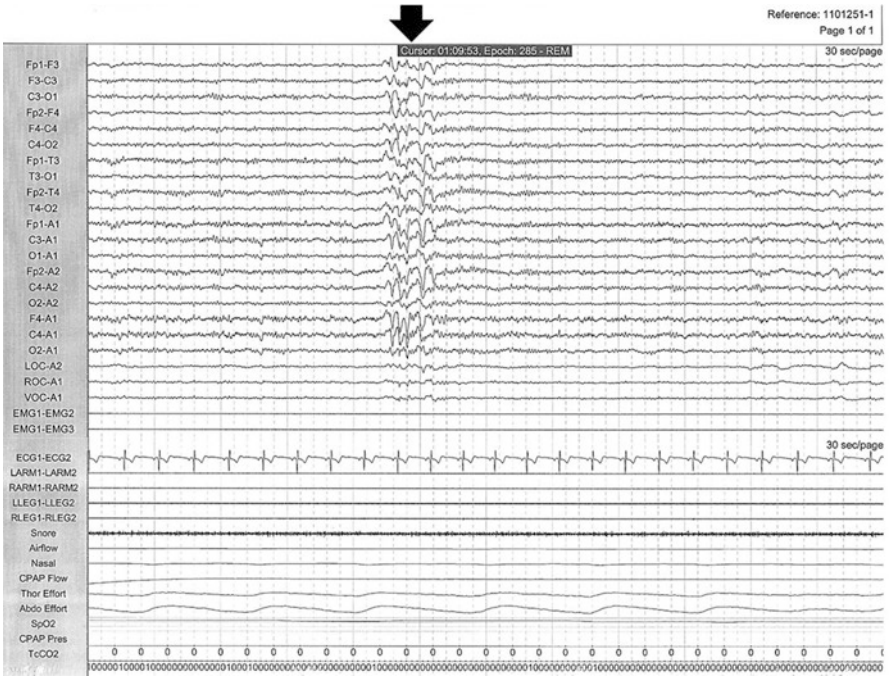

Fig. 1 Black arrow showing the epileptiform activity on the electroencephalogram, consisting of generalized high-voltage slow spike-wave patterns in this 30-second epoch of neurologic polysomnography. (Image courtesy from Dr. Fernando Morgadinho Santos Coelho)

carbohydrates [28]. Its effect on sleep was reported by some authors, who observed an increase in total sleep time and a reduction in non-REM sleep [28, 29].

Likewise, vagus nerve stimulation is useful in many cases of difficult-to-control epilepsy and can reduce excessive daytime sleepiness, minimizing the summative toxic effect of multiple drugs, but there are reports of increased occurrence and severity of sleep apnea in these patients [30, 31].

It is thought that some medications used for sleep disorders may have an anti-crisis effect, such as melatonin, used for disturbance of circadian rhythm. It was effective in reducing seizures in mice, but a meta-analysis was not effective in confirming these findings [32–34]. Modafinil, used to treat narcolepsy, also reduced epileptic seizures in experimental rat models. Pitolisant, which acts on the histamine H3 receptor, was effective in reducing the photo paroxysmal response in patients with photosensitive epilepsy, but the studied sample was small [35].

Understanding the biological basis of this relationship between epilepsy and sleep requires a brief review of the sleep-wake cycle regulation mechanism.

The ascending activator reticular system (ARDS) is a set of structures that regulates the sleep-wake cycle and consists of nuclei of the median raphe located in the brain stem that project into the cerebral cortex, with an activating effect. It is believed that this system is partly responsible for the fundamental rhythms observed in the normal electroencephalogram during surveillance [20].

Experimental models obtain synchronous neuronal activity and sleep induction after electrical stimulation of the thalamus, which suggests its participation as a primordial element in the synchronization of brain rhythms. In contrast, stimulation of ARDS causes sleep disruption and desynchronization of brain electrical activity, causing wakefulness [20].

These projection circuits to the cortex responsible for the wakefulness rhythm are largely excitatory, and the neurotransmitters most involved are acetylcholine and glutamate, which are also the neurotransmitters involved in epileptogenesis [20].

The inhibitory circuits are responsible for the synchronization and the sleep rhythm of slow waves and are mostly modulated by GABA (GABA-amino-butyric acid). The same structures seem to be responsible for the generation of generalized spike-slow-wave discharges [36].

As this circuit is involved in the control of cortical excitability, its dysfunction would be responsible in part for the hyper synchronization that would originate generalized epileptiform discharges [20]. Functional magnetic resonance and tractography studies reveal that thalamocortical connections are possibly involved in this process [37].

The suprachiasmatic nucleus functions as a relay that adjusts the sleep-wake cycle to the circadian rhythm. The routes related to it could explain the occurrence of crises in certain periods of the day. There is evidence that CLOCK gene expression may be reduced in patients with refractory epilepsy [38].

3 Parkinson's Disease and Sleep

Parkinson's disease is a neurodegenerative disease characterized primarily by bradykinesia associated with resting tremor, stiffness, and/or loss of postural reflexes. According to its pathophysiological characteristics, it is included in the group of neurodegenerative diseases known as synucleinopathies, which have similarities in their clinical presentation due to the presence of the motor symptoms already mentioned and the occurrence of non-motor symptoms, currently an important target of studies, such as changes in smell, loss of visual sensitivity to distinguish colors, constipation, and REM sleep behavior disorder.

Sleep disorders are seen in 50–60% of patients with Parkinson's disease and have an important impact on the quality of life. The disorders presented can be diverse, and the complaints presented vary from insomnia, excessive daytime sleepiness, non-restorative sleep, night fragmentation of sleep, or restless sleep [39].

Insomnia in patients with Parkinson's disease can occur for several reasons, from general conditions regardless of the underlying disease, such as poor sleep hygiene, inadequate environment, as well as the use of specific medications and disorders in this population. Selegiline (monoamine oxide B inhibitor) is metabolized to amphetamines and can generate alertness, causing difficulty in starting sleep according to the time of medication use [40]. The use of levodopa, amantadine, and trihexyphenidyl can also impair sleep quality. Patients with Parkinson's disease and insomnia should always be submitted to non-pharmacological treatment with guidance on sleep hygiene, specific cognitive-behavioral therapy for insomnia, the regularity of schedules, and the establishment of a routine of active activities during the day. Pharmacological treatment, when indicated, can be performed through non-benzodiazepine hypnotics such as zolpidem, zopiclone, zaleplon, or even the use of low doses of quetiapine [40].

In patients with difficulty falling asleep, symptoms of restless legs syndrome should always be actively questioned, since even when severely symptomatic patients may not directly complain about this condition. RLS has an increased prevalence among Parkinson's disease patients, affecting 10–20% of these patients. The first-line treatment is the use of dopaminergic agonists such as pramipexole and rotigotine. Gabapentin, opioids, and clonazepam can be used as a second-line or in case of augmentation syndrome with the use of the dopaminergic agonist [41].

Agitation at night can have an important social impact, generating fear and apprehension in family members and caregivers. Parkinson's disease patients commonly experience vivid dreams and nightmares arising from the use of dopaminergic therapy. The excessive rhythmic movement of the lower limbs can arise in the context of periodic limb movements of sleep (PLMS). If there is vocalization and complex movements suggestive of dream enhactment, REM sleep behavior disorder (RBD) should be remembered. RBD affects about 15–30% of Parkinson's disease patients and can precede the onset of motor symptoms of the disease and the moment of clinical diagnosis by decades [39]. During episodes of this parasomnia, patients show significant improvement in parkinsonian symptoms with increased voice

volume, greater agility of movement, and absence of tremor. The episodes tend to be aggressive and can generate trauma for the patient or partner, even with serious injuries. In the clinical suspicion of RBD, it should be investigated by performing basal polysomnography with 4-limb electromyography and video monitoring, looking for episodes of loss of atony during REM sleep and behavioral changes in dreams experience. Symptoms generally respond well to treatment with the use of low doses of clonazepam or melatonin [39].

Excessive daytime sleepiness is another important complaint of patients with Parkinson's disease, being most of the time multifactorial. The frequent and generally undervalued reason is night fragmentation of sleep due to parkinsonian symptoms during sleep. The presence of significant stiffness with difficulty in moving during the night or the presence of tremors can generate multiple awakenings.

Obstructive sleep apnea does not seem particularly characteristic of Parkinson's disease, but the literature remains conflicting. The majority of studies reveal that the prevalence of OSA in Parkinson's disease is similar to the general population or matched control subjects [42]. But OSA should be investigated whenever there are other suggestive signs and symptoms such as snoring, dry mouth, morning headache, nocturia, overweight, and non-restorative sleep.

Sleep attacks, characterized as sudden drowsiness, can occur in 5.3% of patients on monotherapy with dopaminergic agonists and 7.3% of patients on the combined use of levodopa and dopaminergic agonists [39].

Clinical studies show that circadian disturbances are frequent in patients with Parkinson's disease, probably related to blunted circadian melatonin secretion and reduced amplitude of melatonin rhythm. These alterations may also be related to both insufficient exposures to bright light and phase advances related to treatment with dopaminergic drugs [43].

Exercise rehabilitation influences positively objective sleep patterns, changing sleep structure and acting as a promising supportive treatment for Parkinson's disease patients [44]. Fatigue and sleepiness are frequent complaints; a short nap after each rehabilitation session may improve tiredness [45].

4 Alzheimer's Disease and Sleep

Alzheimer's disease is a neurodegenerative disorder characterized by progressive cognitive decline with impaired memory, language, temporospatial orientation, executive functions, and other domains. It is considered the main irreversible cause of dementia in the elderly.

Sleep changes are part of the normal aging process, with an increase in nocturnal sleep fragmentation, nocturnal awakenings, and a greater tendency to sleep during the day. The prevalence of sleep disorders in Alzheimer's disease is estimated at 25% in mild cases and up to 50% in moderate to severe cases. Sleep disorders can take different forms such as excessive sleepiness during the day, difficulty sleeping in the night, fragmentation of night sleep, and early awakening. Sleep disorders can

be common factors of stress and negative impact on the quality of life for patients and caregivers, in addition to being important risk factors for early institutionalization [46].

The origin of sleep disorders in patients with Alzheimer's disease appears to be multifactorial, through the combination of neurodegeneration mechanisms that regulate sleep mechanisms and somatic and psychiatric comorbidities.

The most common sleep disorder in patients with dementia is the sundowning phenomenon, which corresponds to an acute confusional state, with the appearance or exacerbation of neuropsychiatric symptoms, especially agitation, anxiety, confusion, and aggression at the end of the day and early evening [46].

Alterations in the circadian rhythm of sleep-wakefulness are frequent in these individuals, presenting difficulties in initiating night sleep, maintaining sleep, and daytime sleepiness. In extreme cases, there may be a complete inversion of the sleep-wake pattern with a longer sleep period during the day. A reduction in the amplitude of the circadian rhythm and a delay in the sleep phase can be observed. These changes in rhythm are possibly related to degeneration of the suprachiasmatic nucleus in the evolution of Alzheimer's disease. Although there is no involvement of the pineal gland in Alzheimer's disease, there is evidence of a reduction in the melatonin CSF level, which may be a contributory factor to this process [47].

Sleep deprivation and poor sleep quality are related to the accumulation of beta-amyloid protein and neurofibrillary tangles, pathophysiology similar to that of Alzheimer's disease. The most widely accepted theory is that a negative impact on sleep impairs the function of the glymphatic system in performing the brain clearance of these toxic proteins [48].

Other sleep disorders, which are usually more common in the elderly regardless of cognitive function, may appear comorbidly in patients with Alzheimer's disease. Obstructive sleep apnea, restless legs syndrome, and insomnia can lead to poor sleep quality in these patients and thereby impair memory consolidation during sleep, aggravating the cognitive impairment of this population.

The treatment of sleep disorders in patients with Alzheimer's disease should be directed to the predominant symptoms and generally requires pharmacological and non-pharmacological therapies. Sleep hygiene, exposure to sunlight, and use of melatonin can help patients with changes in circadian rhythm. Low doses of atypical antipsychotics, hypnotic antidepressants, or even non-benzodiazepine hypnotics can be used in case of insomnia.

5 Neuromuscular Diseases and Sleep

A neuromuscular disease is a heterogeneous group of chronic diseases in which affected patients may present different patterns of injury with varying degrees of muscle weakness, and may even affect respiratory muscle and ventilation. Depending on the underlying disease, age of the patient, time of evolution, and the type of muscle involvement, there may be different types and severity of

sleep-related respiratory diseases such as obstructive sleep apnea, increased upper airway resistance, hypoventilation, or central apnea.

The prevalence of sleep disorders in patients with neuromuscular disease is estimated at 27–62% of children and 36–53% of adults [49]. When untreated, they can contribute to increased cardiovascular risk, cognitive impairment, and reduced life span. Respiratory sleep disorders can precede respiratory failure by several years and therefore should be investigated before daytime signs of ventilatory impairment. Snoring, increased nighttime awakenings, excessive daytime sleepiness, and morning headache should be questioned, and when present, baseline polysomnography is used to investigate respiratory disorders during sleep.

Pulmonary function tests during wakefulness do not correlate with the severity of respiratory disorders during sleep; however, some findings indicate polysomnography: reduction in FEV1 below 40% of predicted, excess base greater than 4 mmol/l, PaCo2 greater than 54 mmHg, and hypoxemia [50].

Treatment will be directed according to the sleep-disordered breathing diagnosed, and it is usually necessary to use a non-invasive ventilation mechanism during sleep. The use of the ventilation device ensures improvement of nocturnal hypoxia, hypoventilation, respiratory distress index, number of awakenings, sleep architecture, blood pressure, daytime sleepiness, and other symptoms. The most common ventilatory modality in this patient profile is bilevel positive airway pressure ventilation.

6 Headache and Sleep

The bidirectional and dynamic relationship between sleep and pain has been already shown in another chapter of this book, but headaches have also a complex relationship with sleep.

The most important sleep symptom of patients with chronic tension headaches and chronic migraines is insomnia. Poor sleep quality or insufficient sleep can be the trigger for headache episodes and the risk factor for more frequent episodes and even for daily chronic headaches [51].

Patients with migraines have often difficulty sleep precipitating and during attacks. On the other hand, sleep has a good therapeutic role in terminating the pain of an acute migraine attack due to its serotoninergic tonus. It is also common that patients feel fatigued or somnolent in the postdrome phase [51].

Another sleep disorder comorbid with migraine is obstructive sleep apnea. Obstructive sleep apnea patients report often morning headaches or awakening headaches. Awakening headache may be a warning sign of the need for the patient to undergo polysomnography to investigate OSA, but other differential diagnoses must be remembered, such as bruxism and expanse intracranial lesions [52].

Evidence shows that there is an improvement in the control of headache crises and related sleep symptoms in patients suffering from comorbid tension headache and insomnia when they were submitted to cognitive-behavioral therapy for insomnia [50].

Cluster headache attacks follow a striking circadian rhythm with an intriguing influence on sleep. Sleep quality is reduced in both types of episodic and chronic cluster headache [53].

Regular physical activity, in addition to its benefit in the quality of sleep, has a beneficial prophylactic effect in the control of headaches and should be encouraged, especially in patients with sleep disorders and migraines [54].

Sleep quality should always be questioned during the follow-up of patients with neurological diseases. It is only through questioning about sleep-related symptoms such as difficulty in initiating or maintaining sleep, early awakening, snoring, breathing pauses, daytime sleepiness, restlessness during the night, and non-restorative sleep that we can hypothesize that there is an associated sleep disorder and from there search the diagnosis and further start treatment. The treatment of sleep disorders comorbid to chronic neurological disorders is important for better control of the symptoms of the underlying pathology, greater adherence to treatment, and even for an overall improvement in the quality of life.

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Sleep and Chronic Pain Interlaced Influences: Guidance to Physiotherapy Practice

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1 What Is Pain

Pain was recently redefined by the International Association for Study of Pain (IASP) with more precision since the 1979 definition [1]. Pain is an unpleasant, sensory, and emotional experience in which a difference is clearly made between pain, nociception, and the person who experienced it (Table 1).

The recent joint effort of the IASP and the World Health Organization (WHO) resulted in a classification system for chronic pain syndromes. Nowadays, chronic pain is recognized as a disease, namely "chronic primary pain." Thus, pain can be

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Table 1 Pain definition according to International Association for the Study of Pain 2020 [1]

Definition
An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage
Six keynotes and etymology
Pain is always a personal experience that is influenced to varying degrees by biological, psychological, and social factors
Pain and nociception are different phenomena. Pain cannot be inferred solely from activity in sensory neurons
Through their life experiences, individuals learn the concept of pain
A person's report of an experience as pain should be respected
Although pain usually serves an adaptive role, it may have adverse effects on function and social and psychological well-being
Verbal description is only one of several behaviors to express pain; inability to communicate does not negate the possibility that a human or a nonhuman animal

categorized as primary such as fibromyalgia, complex regional pain syndrome, chronic primary headache, orofacial pain (e.g., temporomandibular disorders), or other chronic musculoskeletal conditions such as osteoarthritis, rheumatoid arthritis, or ankylosing spondylitis, but also as secondary, if the pain is tributary to an underlying disease such as cancer-related pain, or secondary headache among others [2].

The understanding and comprehensive analyses of pain characteristics are essential to optimize treatment efficacy and promote the best prognosis for individuals with chronic pain. Nonetheless, the assessment of the pain patient should not be limited to pain. From a biopsychosocial perspective, different biological, psychological, and social factors can influence the origin, perpetuation, and progress of chronic pain [3]. A variety of aspects can significantly modulate the pain experience, such as higher psychological distress (anxiety and depression symptoms, fear, trauma, pain catastrophizing, kinesiophobia, negative emotionality, beliefs); lower social function (lower socioeconomic status and education, poor active coping, no acceptance, less social support, living alone, no self-efficacy); and general biological factors (female gender, sedentarism, obesity, genetic influence, age). One of these aspects is sleep (Fig. 1), which has been consistently associated with acute and chronic pain over the years in a wide variety of populations [4–9] and interacts directly with pain.

2 The Comorbidity Between Chronic Pain and Sleep Disturbances

In 2015, the National Sleep Foundation conducted the Sleep in America Poll and showed that poor sleep quality and sleep debt were related to increased pain complaints. People with acute pain slept an average of 14 minutes less than they needed, and people with chronic pain slept 42 minutes less per night than they felt they

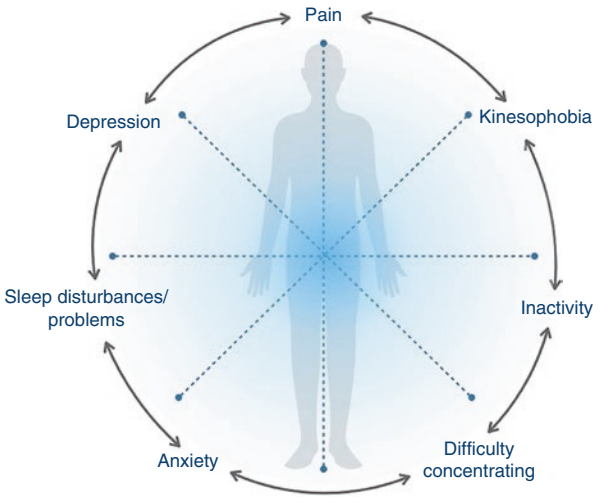

Fig. 1 Illustration of the interaction between biopsychosocial aspects and pain, including sleep

needed. Another interesting finding of this poll was that people with both acute and chronic pain reported sleep often was fragmented by environmental factors such as noise, light, temperature, and an unconformable mattress [10].

Regarding sleep duration, average adults require between 7 and 9 h sleep [11], with less than 6 h and more than 9 h correlating with increased pain the next day [12]. In addition, sleeping for 3 h or less was associated with an 81% increase in pain intensity compared to sleeping 6–9 h; and sleeping for more than 11 h was associated with a 137% increase in pain intensity [12]. In this sense, it is not only lack of sleep, sleep deprivation, and sleep disorders that affect pain perception, but surprisingly, an increased amount of sleep also can affect pain perception.

In chronic pain populations, evidence from clinical and epidemiological studies demonstrated that individuals have a variety of sleep disorders such as insomnia, sleep apnea, and restless legs syndrome [13–15]. A survey of 18,980 individuals from five different countries (the United Kingdom, Germany, Italy, Portugal, and Spain) demonstrated that significantly more individuals with chronic pain conditions (e.g., limb, joint or back pain, gastrointestinal pain, headache) experienced insomnia when compared to those without pain. In addition, again when compared individuals without chronic pain conditions with those with pain, this latter were 3 times more likely to experience difficulties with initiating or maintaining sleep, early morning awakenings, and nonrestorative sleep [16], indicating sleep difficulties.

Moreover, a recent large sample size review and meta-analysis from studies that used objective measures of sleep (i.e., polysomnography exam) or examined diagnosed sleep disorders (by a physician) in participants with chronic pain demonstrated that chronic pain was associated with reduced sleep duration, increased sleep onset, poorer sleep efficiency, and more time awake after initially falling asleep. In addition, the pooled prevalence of diagnosed sleep disorders in this sample of patients with chronic pain was 44%, being 72% with insomnia, 32% with restless

legs syndrome, and also 32% with obstructive sleep apnea (32%) [17]. Furthermore, patients with chronic pain experienced greater sleep fragmentation, more awakenings, and movement-related disruptions to sleep (apnea/hypopnea, PLMS) compared to pain-free individuals [17]. In this same investigation, sleep architecture seemed to be less affected by chronic pain, with only NREM 1 duration being longer. Remarkably, NREM 3 sleep, which has a restorative function [18], was not significantly shorter in chronic pain patients, though it did approach statistical significance, and might have been a finding with no statistical relevance but with clinical relevance. Reduction in NREM 3 sleep of chronic pain patients is presented in the literature with mixed results, with fibromyalgia reportedly being associated with reduced NREM 3 sleep [19], and rheumatoid arthritis associated with increased amounts, perhaps as a reparative response to inflammation [18].

2.1 Temporal Associations

On one hand, experimental models indicated that poor sleep, sleep disruption or deprivation, and sleep disturbances could contribute to an altered pain perception by triggering a hyperalgesic state/behaviors, with possible gender-specific effects [20]. On the other hand, it has been shown that besides delaying the onset of sleep and/or interrupting its stages [21], pain is able of causing frequent awakenings, thus disturbing the continuity of sleep [22]. However, the finding of pain disturbing sleep has been more inconsistent over the years [23, 24].

Regarding clinical populations, there are reports on changes of sleep architecture in patients with chronic musculoskeletal pain such as lower sleep efficiency, increased sleep onset, the lower density of slow-wave EEG activity, fewer sleep spindles in EEG activity, more frequent sleep stage shift and unstable deep sleep, and presence of more microarousals related to cyclic alternating patterns (changes in heart rate increase and increase in muscle tone) [25, 26]. In patients with fibromyalgia, for example, the intensity of chronic pain led to a sympathetic over-activity in both states, awake and asleep, due to possible autonomic nervous system dysfunction yet to be confirmed [26]. In longitudinal population studies (the ones that follow the subjects for many years to see if they develop any disease, symptoms, if they improve or not from a specific disease or condition), the severity of pain was related to the incidence or persistence of insomnia [27].

A representative study of the population of the United Kingdom with 4,236 participants over 50 years of age investigated the development of musculoskeletal pain over 10 years. After 10 years, 18.5% of the participants developed generalized chronic pain. Among these, 7.7% had no pain and 24.6% had “some pain” at baseline [28]. In the analysis, the authors found that anxiety and non-restorative sleep were predictors for the development of generalized chronic pain, the latter being the strongest predictor. An investigation of 12,350 women without musculoskeletal pain or physical disabilities demonstrated that after 10 years, almost 3% developed fibromyalgia [29]. The interesting fact lies in the dose-dependent association found

in this study between poor sleep quality and the risk for fibromyalgia. This same investigation followed by 18-year found an increased chance of developing chronic pain conditions between 1.5 and 2.2-fold [30]. Interestingly, non-disturbed sleep had a significant effect, reducing in almost fourfold the resolution of multi-site pain (to no pain) [31], indicating the relevance of sleep on predicting the onset and resolution of pain. A large population-based survey with a 17-year follow-up showed that disrupted sleep along with non-specific health complaints were risk factors for the onset of chronic pain and predictive factor for an unfavorable course of chronic pain in the female population [32]. Specifically, disrupted sleep was an independent risk factor (2-fold chance) for the development of chronic pain in initially pain-free women [32].

3 Sleep Disorders and Pain

A recent comprehensive review listed the most likely sleep disorders associated with chronic pain [15]. This included insomnia, sleep apnea, up to sleep bruxism, and rarely, narcolepsy.

Insomnia is another sleep disturbance considered a risk factor for the development of chronic painful conditions. Complaints of insomnia predicted 93% of the risk of new cases of chronic widespread pain in pain-free participants [33] and were considered a risk factor, increasing by 1.4-fold the chance of developing back pain, with no inverse association [34]. In addition, the treatment of insomnia complaints (symptoms) in participants with osteoarthritis and insomnia leads to improvements in pain severity and osteoarthritis symptoms [35]. Taken together this data points out to a uni-directionality of insomnia as a plausible risk factor for the development of chronic pain.

Obstructive sleep apnea (see chapter "Obstructive Sleep Apnea: An Overview" in this volume for more information) is also associated with chronic pain, both in increased prevalence and pain intensity, such as orofacial pain [36], psoriasis, an immune-mediated chronic inflammatory painful disease [37], or fibromyalgia (almost 50%) [38]. Indeed, clinical symptoms are increased, and prognosis and physical function is decreased when patients present both chronic pain and OSA, which may interfere in the rehabilitation of musculoskeletal diseases [39, 40].

Another sleep disorder that has been associated with chronic pain in the orofacial area is sleep bruxism (see chapter "Sleep Bruxism: An Overview" in this volume for more information). The association of awake and sleep bruxism to chronic pain is largely debated, and causality remains to be proven [41]. Indeed, sleep bruxism has been categorized as a risk or contributory factor to dental pain and/or temporomandibular disorders (TMD), although these reports are very variable depending on the subjective or objective nature of the bruxism reports [42]. Indeed, large polysomnographic studies have shown that the distribution of TMD between bruxers and non-bruxers is similar [43], and the occurrence of TMD pain is not associated with the intensity of sleep bruxism [44, 45]. Nevertheless, different subgroups of individuals

might present different characteristics that can make them more vulnerable to develop pain or any other comorbidity. For instance, a very recent study using recent machine learning in the general population of Sao Paulo showed that the association between insomnia and sleep bruxism was more prevalent among middle-aged females when compared to other sex and age groups [46]. Although the investigation of the association between sleep bruxism and sleep continuity and disturbances across different phenotypes is active and progressing [43, 47], given the important link between sleep and chronic pain, more studies accounting for chronic pain as well are needed.

Patients with narcolepsy types 1 and 2 (with and without cataplexy, respectively) had a high prevalence of chronic pain and fatigue, increased symptoms of comorbid depression and anxiety, and negatively impacted quality of life. Both types presented a higher frequency of chronic pain: 84.8% for type 1 and 75.7% for type 2; 42.4% of all patients presented daily pain compared to controls regardless of its type; and surprisingly increased risk factor for pain, such as almost 21-fold in type 1, and 12-fold in type 2, compared with controls [48].

In longitudinal investigations, poor sleep has also been found as a predictor for next-day pain. A sequential relationship between sleep and pain was found in an analysis of 30-day self-reported ratings of pain and sleep in participants with fibromyalgia: a night of poor sleep was followed by a painful day, and a more painful day preceded a night of poorer sleep [49]. In postmenopausal women, the co-existence of insomnia and chronic musculoskeletal pain resulted in greater pain intensity and alterations in sleep homeostasis [50]. In this sense, sleep disorders should be considered as possible risk factors for the onset and/or worsening of musculoskeletal pain and treated when treating a patient with pain.

In summary, individuals suffering from sleep disturbances are at elevated risk for the development of pain over time frames from 1 year to 28 years [51–53]. Together, all these investigations from different groups and countries suggest that sleep impairments contribute exponentially to the development of somatic symptoms such as chronic pain in some time-point.

4 Mechanisms Involved in Sleep and Pain Relation

There are many hypotheses on the mechanisms of sleep and pain interaction. One hypothesis is that brain structures involved in the generation and maintenance of sleep are also involved in pain modulation, thus providing a neurobiological substrate for this relationship. For example, animal studies have shown that the periaqueductal gray matter of the midbrain is responsible for the modulation of both sleeps [54] and pain [55, 56]. In humans, sleep and pain processing often share afferent circuits such as the parabrachial-amygdala and parabrachial hypothalamic pathways [57]. Likewise, the thalamus is associated with excitation and the processing of nociceptive stimuli sent to the cerebral cortex in animals [58].

Another hypothesis, derived from animal research, is the pain-on and pain-off neurons' concept. These neurons, which are situated in the *nucleus raphe Magnus*, respectively, facilitate and inhibit nociceptive impulses to thalamocortical pathways and are influenced by the wake-sleep cycle: inhibitory pain-off neurons are activated during NREM N3 sleep, while excitatory pain-on neurons are activated during wakefulness [22].

Moreover, recent human neuroimaging studies have shown that acute sleep deprivation amplifies pain reactivity in the primary somatosensory cortex and that the degree of this amplification predicts the expansion of experienced pain across individuals. However, sleep deprivation seems to blunt pain reactivity in higher-order valuation and decision-making regions of the striatum and insular cortex, which are brain areas also involved in pain modulation [59]. In addition, sleep disruption increased reward-related connectivity between the *nucleus accumbens* and the anterior midcingulate cortex at pain onset [60], suggesting among others that sleep disruption could affect pain via attention and reward mechanisms.

Other possible underpinnings of the interaction formed between sleep and pain problems are the increase in distinct inflammatory markers potentially leading to a generalized inflammatory state, the influence and mediation of mood disorders (e.g., anxiety, depression) and affect issues, and the alteration of endogenous substances apparently related with both sleep and pain processes such as dopamine, or perhaps melatonin, vitamin D, or orexin/hypocretin as recently summarized in a comprehensive review [7].

Other hypothesized mechanisms involved in sleep and pain relation described neuronal and non-neuronal components such as (i) the opioid system (inadequate sleep deteriorates the function of the opioid antinociceptive system); (ii) the monoaminergic system (serotonin is known to promote wakefulness and to inhibit REM sleep [61] and is involved in both sleep-wake and pain control); (iii) the orexinergic system (also known as hypocretin, orexin neurons are active during wake and nearly silent during sleep, and orexin deficiency is associated with narcolepsy, and are also involved in nociception, specifically pain transmission and modulation, found in spinal dorsal horn); (iv) the immune system (an upregulation of inflammatory mediators such as cytokines and prostaglandins is observed both in pain conditions and in sleep impairments); (v) the pineal melatonin system (having innumerable functions, including sleep promoting effect [62], anti-inflammatory and analgesic, improving endogenous pain inhibition); (vi) the endocannabinoid system (modulation of pain and sleep and a possible treatment which still needs more research); (vii) the hypothalamus-pituitary-adrenal axis (HPA, dysregulations of HPA axis responses can be a marker for comorbid pain and sleep deficiency); (viii) the adenosine signaling (which has sleep-regulatory and sleep-promoting properties, and its increased activity is related to increased pain); (ix) the nitric oxide signaling (contributes in the homeostatic regulation of sleep and wakefulness, as nitric oxide is increased during sleep deprivation (and followed by an increase in adenosine), and together, nitric oxide and adenosine regulate sleep pressure and also are an important mediator of pain in periaqueductal gray matter area), among others [24].

Based on the above literature on the interaction between pain and sleep impairments, it seems beneficial to target a de-activating approach on several systems and mediators and complex reciprocal interactions [23]. However, evidence regarding approaches based on physical therapy that can simultaneously target sleep and pain problems is limited [23]. Thus, this remains a stimulating challenge to better understand this complex and intrinsic relationship. In this sense, PTs are essential clinicians to assist patients in their search for better sleep and less pain. Personalized medicine using machine learning and artificial intelligence approaches from an interdisciplinary perspective could certainly help in the understanding and management of the sleep and pain interaction.

4.1 Menopause and Traumatic Brain Injury as Clinical Conditions Adding New Knowledge to the Chronic Pain and Sleep Interactions

Two interesting domains that can add in the comprehension of the interaction between sleep and pain issues are (physiologic) aging and traumatic brain injury. In postmenopausal women, increased sleep duration predicted higher pain intensity upon waking; higher pain intensity only at bedtime predicted more time in bed and increased sleep duration, contributing to the intrinsic and cyclic relationship of sleep-pain [50]. Furthermore, this population demonstrated that higher nighttime pain severity was associated with longer sleep duration and reduced sleep efficiency [63].

In patients after 1 month of mild posttraumatic brain injury with moderate to severe pain (acute pain), there were more naps (>3 naps/day) and longer sleep (>8 h/night) than patients with mild pain in the same time period, while after 1 year, same patients continue to sleep longer, despite the presence of chronic pain [64]. This information that pain could be associated with more pronounced sleep needs leads to speculation about the mechanisms happening during sleep while unrelieved pain. The need for increased sleep reveals the compensation of sleep, probably an adaptation strategy to cope with pain. The authors hypothesized that patients could be in a relative state of "arousal" even when asleep, interfering with sleep restorative function [64]. Another possibility is that longer sleep duration would reflect an increase in non-restorative sleep stages. Could this longer sleep after traumatic brain injury be related to the repair of damaged areas, or reduce the perception of pain (as we have no perception of pain when in a non-conscious state or in deep sleep)? The coexistence of pain and sleep (including naps) looks as if it generates a healing environment for an adaptive process in order that patients after traumatic brain injury may function maximally and create a necessary adjustment of new neural pathways not only for rehabilitation of the musculoskeletal system but also for other systems in the body [65]. In addition, other investigations found increases in β power frequency, mainly in the prefrontal and frontal derivations during NREM and

REM sleep compared to pain-free patients and controls [66]. Investigations involving acute painful states have shown that noxious stimuli in the sleeping brain appeared to be reduced in magnitude compared to that of the waking brain [67]. The evidence in chronic painful conditions is scarce, as experiments do not mimic chronic pain during sleep [67]. The occurrence of headache, another condition associated with the pain and sleep deleterious interaction, following a traumatic brain injury is a common finding although the assessment of risk factors and causative mechanisms are not yet fully understood [68–70].

5 Management Route in Presence of Chronic Pain and Sleep in Physical Therapy Practice

Physical therapists should assess sleep, for its quality and restorative perception and for concomitant disorders as described above, as carefully and completely as possible in chronic pain patients using both subjective and objective measures (see chapters "Subjective Assessment of Sleep", "Objective Assessment of Sleep", and "Actigraphy" in this book for more information). The suggestions below are mostly empirical, and more evidence-based research is needed to understand how physiotherapists can break the sleep-pain cycle.

PTs expertise is related to different pain conditions of various etiologies, but perhaps their focus is musculoskeletal pain (e.g., rheumatoid arthritis, fibromyalgia, neck and lower back pain, temporomandibular disorders) in acute, post-trauma or post-surgical settings, in sub-acute conditions, in the presence of other chronic diseases such as diabetes, stroke, heart, or lung diseases, cancer, or in the end-of-life period [71].

5.1 Plan Your Treatment

If a primary sleep disorder is suspected, such as sleep apnea or periodic limb movements, or if the patient complains of excessive daytime sleepiness/fatigue interfering with his daily routine, PT should refer the patient to a physician specializing in sleep medicine. A diagnostic sleep study will be probably performed according to the patient's needs. Physical therapists can help with screening, by using sleep diaries, questionnaires, and pain records that will provide circadian evidence of chronic pain and sleep disturbances, and explain to the patients the notion on this may interplay with their quality of life. Actigraphy is a technique that monitors activity over a quiet period; it can be performed to give more objective cues on the temporal association between sleep and pain and to help patients to understand their wake and sleep behavior (see chapter "Actigraphy" of this book). Importantly, although PT can help with the screening and treatment of sleep disorders when indicated, it

is essential to understand that their management should be conducted by the sleep physician.

Therefore, after adequate indications, the PT will proceed to individualized treatment of the pain condition. One important point to remember is that the first-line choice for chronic pain and sleep treatment is the *active* involvement of the patient, as a partner. To reach such, a variety of complementary approaches and techniques are available, including education and self-management (e.g., neuroscience pain education or cognitive behavior therapy for pain (CBT-P)); therapeutic exercise including strengthening-coordination-function, activities of daily living, use of proper body mechanics (motor control), physical activity, and exercise (choose type, duration, frequency, and intensity), knowing the effects of exercise on both sleep and pain to induce hypoalgesia (e.g., aerobic training, resistance exercise, stretching, isometric exercises, and mind-based exercises); passive techniques (manual therapy such as mobilizations, manipulations, soft tissue massage, muscle energy, traditional massage, and Rolfing; movement therapies such as Feldenkrais, proprioceptive neuromuscular facilitation, and global postural reeducation; *watsu* (a form of hydrotherapy which encompasses stretches, massages, and acupressure in warm water used for deep relaxation and passive exercises; and relaxation); and electrotherapeutic and dry needling modalities (Table 2). Note that all chronic pain conditions cited have sleep impairments such as non-refreshing sleep, fragmented sleep, or disturbances.

In addition, sleep hygiene tips and cognitive behavior therapy for insomnia and other sleep disturbances (please have a look at chapter "Optimizing Behavior Strategies for Sleep" of this book) can be added, in order to improve sleep and to make the patient have knowledge and action in the treatment. Sleep hygiene is always a subject that should be discussed in PTs treatment. Furthermore, sleep positioning should be addressed for any sort of musculoskeletal pain; the positioning can always be improved (see chapter "Sleep Ergonomics" of this book).

The restoration of adequate sleep is essential to avoid the exacerbation of painful symptoms. In this sense, we encourage PTs to look at sleep habits/routine and symptoms in patients who seek assistance.

This is complex work to be done and may take a longer time. In order to maximize efficiency and manage more comprehensively the patient with sleep disturbance and chronic pain, an interdisciplinary approach where PT collaborates with other health professionals such as psychologists, dentists, pharmacists, and physicians is essential [7, 72].

Of importance, we need to reiterate that adequate acute pain treatment can prevent the development of chronic pain, and poor sleep to insomnia and/or exacerbation of concomitant sleep disorders. Improving patient quality of life and satisfaction with care, as well as enhancing clinical resource management and reducing long-term costs, remains one of the major health decision-makers' objectives.

Table 2 Summary of physical therapy techniques in the management of chronic primary and secondary pain, including examples of pain condition, qualitative level of evidence and references. (Note that level of evidence is low to modest for most)

PT techniques		Chronic pain condition	Level of evidence	References
Education and self-management	Neuroscience pain education	Musculoskeletal pain	Strong	Watson et al. [73]
	Biopsychosocial approach	Chronic pain	Strong (short- and medium-term) Low (long-term)	Gianola et al. [74]
		Subacute low back pain	Very low–low	Marin et al. [75]
Physical activity and exercise	Aerobic training	Knee osteoarthritis	Strong	Loew et al. [76]
		Rheumatoid arthritis	Strong	Scarvel and Elkins [77]; Hurkmans et al. [78]
	Resistance exercise/ strengthening	Fibromyalgia	Strong	Busch et al. [79]
		Mechanical neck disorders	Low	Gross et al. [80]
		Nonspecific neck pain	Strong	Sihawong et al. [106]
		Nonspecific shoulder pain	Strong	van den Dolder et al. [90]
		Patelofemoral pain syndrome	Strong (short-term), low (long-term)	Searle et al. [109]
	Stabilization exercises	Nonspecific low back pain	Strong	Smith et al. [107]
	Isometric exercises	Mechanical neck disorders	Moderate	Gross et al. [80]
	Pilates	Nonspecific back pain	Strong	Patti et al. [81]
		Nonspecific low back pain	Very low–moderate	Yamato et al. [82]
	Meditative movement-based exercises (Yoga, Tai Chi, Qigong)	Fibromyalgia (yoga)	Strong	Langhorst et al. [83]
		Fibromyalgia (qigong)	Low	Lauche et al. [84]
		Nonspecific low back pain	Very low–moderate	Nascimento et al. [85]
	Aquatic exercises	Musculoskeletal conditions	Strong, but moderate effects	Barker et al. [86]
		Fibromyalgia	Low–moderate	Bidonde et al. [87]
		Knee and hip osteoarthritis	Strong	Bartels et al. [88]
	Motor control exercises	Nonspecific low back pain	Very low–moderate	Saragiotto et al. [89]

(continued)

Table 2 (continued)

PT techniques		Chronic pain condition	Level of evidence	References
Manual therapy	Soft tissue massage	Nonspecific shoulder pain	Strong	van den Dolder et al. [90]
		Post-operative cardiopulmonary surgery	Very low–moderate	Nerbass et al. [91]
	Manipulation or mobilization	Nonspecific low back pain	Very low–moderate	Nascimento et al. [85]
	Trigger point	Chronic non-cancer pain	Very low	Denneny et al. [92]
	McKenzie Method	Low back pain	Moderate–strong	Lam et al. [93]
Electrotherapeutic modalities	Ultrasound	Musculoskeletal pain conditions	Insufficient evidence	Wu et al. [94]
		Knee osteoarthritis	Strong	Wu et al. [94]
		Shoulder calcific tendinosis	Strong	Ebenbichler et al. [108]
	Phonophoresis	Musculoskeletal pain conditions	Low	Watson [97]
		Knee osteoarthritis	Low (not more effective than ultrasound alone)	Wu et al. [94)
	Photobiomodulation (Laser)	Joint pain	Strong	Bjordal et al. [95]
		Knee osteoarthritis	Strong	Bjordal et al. [96]
		Myofascial trigger points	Strong	Law et al. [98]
	Interferential current		Effective for a temporary decrease of pain	Fernando [99]
	Transcutaneous electrical nerve stimulation (TENS]	Low back pain	Inconclusive	Resende et al. [100]
		Central pain in multiple sclerosis	Moderate	Sawant et al. [101]
		Painful diabetic neuropathy	Strong	Stein et al. [102]
		Neuropathic pain	Very low–moderate	Jin et al. [103]
Needling modalities	Dry needling	Myofascial pain syndrome	Very low–moderate	Fogelman et al. [104]
	Acupuncture	Nonspecific low back pain	Very low–moderate	Nascimento et al. [85]
		Musculoskeletal pain	Very low–moderate	Kelly et al. [105]

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Part V
Physiotherapeutic Resources to Improve Sleep

Exercise and Sleep

Ozeas Lins-Filho, Maria Julia Lyra, and Christopher E. Kline

1 Exercise Training and Sleep

Although the underlying mechanisms of how it improves sleep are not completely understood, exercise training is a widely recommended strategy and an alternative to traditional forms of treatment for the management of sleep-related problems due to its low cost and easy access. Research conducted in the area of exercise and sleep attribute its positive effects to a variety of mechanisms such as thermoregulatory function, repair and restoration theories, and anxiolytic and antidepressant effects. However, these mechanisms are largely speculative, as few have been rigorously evaluated.

1.1 Thermoregulatory

The thermoregulatory theory suggests that the exercise-induced increase in body temperature is responsible for improving sleep, as during the 24 h period, changes in body temperature due to exercise are associated with a greater probability of staying asleep or awake. Body temperature tends to decrease near sleep onset,

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requiring vasodilation of the distal extremities and increasing peripheral blood flow [1, 2]. Thus, an exercised-induced increase in body temperature could promote sleep onset through the heat dissipation mechanism [3].

Research on the effect of aerobic exercise on body temperature has shown divergent results such as positive changes in slow-wave sleep or lack of changes, highlighting the time of day and the intensity of aerobic exercise as important factors that may lead to different effects on body temperature and, consequently, on sleep [4–6].

1.2 Repair and Restoration

Two theories regarding the purpose of sleep, the energy conservation and repair and restoration theories, postulate that sleep is a way to conserve or restore the metabolically active tissues that are impacted by exercise. Both of these theories assume that increases in energy expenditure would be related to increases in the duration of sleep and slow-wave sleep; therefore, the exercise would represent a stimulus for the depletion of energy reserves, playing a significant role in sleep [7]. These theories are based on homeostatic mechanisms of sleep regulation with adenosine being strongly related to sleep drive [8]. Studies [9, 10] with protocols of moderate- to high-intensity aerobic exercise have observed increases of 2.9% in slow-wave sleep duration in humans after high-intensity exercise and in adenosine concentrations measured after high-intensity exercise in animal models [9, 11].

1.3 Anxiolytic and Antidepressant Role of Exercise

Sleep disorders are closely associated with mental health conditions [12–14]. Anxiety and depression are commonly observed in patients with sleep problems and are risk factors for the development of insomnia; relatedly, insomnia is a risk factor for the development of anxiety and depression, highlighting the bidirectionality between insomnia and anxiety and depression [15]. Thus, considering the beneficial effect of exercise on anxiety and depression [16], the antidepressant and anxiolytic role of exercise may serve as a potential mechanism to reduce sleep disorder severity and improve sleep quality.

1.4 Changes in the Circadian System

Exercise performed at different times of day may influence the timing of the circadian system, advancing or delaying the sleep/wake cycle. Considering that several sleep disorders are related to circadian function, in this hypothesis, exercise could

modulate the timing of the circadian system, advancing when performed during the day or delaying when performed in the evening [17]. Thus, exercise could be an external facilitator of circadian adaptation in people who need to alter the timing of the sleep-wake cycle, such as travelers and night workers [18].

1.5 Impact of Exercise on Sleep Quality

Although sleep quality is an indicator widely used by the general population to assess sleep in clinical practice and in laboratory settings, its concept is quite broad and involves several parameters. There is still no consensus on what constitutes good sleep quality with its assessments generally occurring in a self-reported manner [19]. Some variables (e.g., latency, number of arousals, arousals after sleep onset, efficiency) can be considered indicators of sleep quality [20]. Although research reports that exercise improves sleep quality [21–23], there is a paucity of studies evaluating the isolated effect of interventions, with sleep quality often being assessed in conjunction with other sleep parameters in a variety of populations and conditions.

For example, a meta-analysis [24] with 6 studies and 305 adults examined the effect of interventions between 10 and 16 weeks with moderate-intensity aerobic exercise and/or strength training on sleep quality assessed with the Pittsburgh Sleep Quality Index (PSQI). In addition to an improvement in overall sleep quality, they observed decreases in sleep latency and sleeping pill usage.

Another systematic review [25] evaluated the acute and chronic effects of strength training alone and combined with aerobic training on the sleep quality of adults. The authors observed that combined training (aerobic training plus strength training) promoted better results in the subjective parameters of sleep quality, primarily assessed using the PSQI. Despite the interesting results, the methodological differences between studies included in this review do not allow us to indicate how combined training was superior in improving sleep quality when compared to aerobic or strength training performed alone.

The results of clinical trials similarly have demonstrated heterogeneity in findings according to the population studied. For example, in a sample of adolescents, 12 weeks of moderate-intensity aerobic and strength training improved sleep quality by 67%, sleep efficiency by 7.6%, and sleep duration by 64 minutes [23].

In a sample of inactive older adults, Jurado-Fasoli et al. [21] evaluated the effect of 12 weeks of exercise training on PSQI-assessed sleep quality. They observed sleep quality improvements in the group that practiced physical activity according to the recommendations of the World Health Organization (34% reduction in PSQI score), in the group that performed high-intensity interval training (34% reduction), and in the group that performed high-intensity interval training plus whole-body electrostimulation (40% reduction) [21]. In another study, strength training performed for 12 weeks significantly improved the sleep quality of patients with breast cancer [26]. On the other hand, in a sample of middle-aged women, improvements in PSQI after

4 months of practicing yoga and walking exercise were not observed [27]. Finally, in a robust review recently published by Kline and colleagues, it was observed that longer bouts of exercise training resulted in better sleep quality outcomes [28].

Thus, considering the findings presented, exercise training can be recommended as a tool for improving sleep quality. Despite this recommendation, due to the methodological limitations, it remains challenging to establish which type (e.g., aerobic or strength training), intensity (e.g., moderate, or high), or duration (e.g., 2, 6, or 12 weeks) would promote better responses in the sleep quality in various populations. Thus, the available evidence does not support the prerogative that evening exercise leads to poor sleep quality.

2 Exercise Timing

Although exercise performed in the evening is sometimes discouraged due to concerns that it may disrupt sleep, little evidence corroborates this assumption [29, 30]. Experimental studies have not found negative effects of exercising in the evening [10, 31]. Based on data from the National Sleep Foundation's "Sleep in America" poll, Buman et al. evaluated respondents' sleep according to the time of day of exercise; they found that most participants believed that their sleep was of equal or better quality (97%) and longer duration (98%) on the days they exercised in the evening (i.e., <4 h before bedtime) compared to the days they did not exercise [32]. The paucity of negative effects of evening exercise on sleep was also evidenced in a recent meta-analysis by Stutz et al. [33]; across 23 studies, exercise in the evening (i.e., <4 h before bedtime) promoted an increase of 7.7 minutes in rapid eye movement latency, an increase of 1.3% in slow-wave sleep, and a decrease of 1.0% in stage 1 sleep.

3 Effect of Exercise Training on Sleep Disorders

The most evident literature on the effect of exercise on sleep disorders has been observed among people with sleep-related breathing disorders, insomnia, or daytime sleepiness resulting from these conditions. Although the small evidence base does not provide an indication of the best type of exercise for each situation, current data suggest that there is an important role of exercise in the management of these disorders.

3.1 Obstructive Sleep Apnea

Among sleep-related breathing disorders, obstructive sleep apnea (OSA) is an important public health problem associated with hypersomnia, increased cardiovascular mortality, and metabolic dysfunction [34]. Characterized by recurrent

episodes of total or partial upper airway obstruction and influenced by genetic and environmental factors [35], the prevalence of OSA in Brazil is estimated at 33% of the adult population, with men showing higher prevalence than women (40.6% against 26.1%, respectively) [36].

In epidemiological research, the literature indicates that exercise has been associated with a lower risk of developing both mild and moderate to severe OSA [35, 37]. For example, in a study with more than 14,000 participants, Murillo et al. [38] observed in a cross-sectional study that 150 minutes per week of moderate- to vigorous-intensity physical activity was associated with 24% lower odds of having mild or moderate to severe OSA [38]. Corroborating these data, da Silva and colleagues [39] studied 5453 men and women and observed that adults who practiced structured exercise had 23% and 34% lower odds of having moderate or severe forms of OSA, respectively, while those who performed occupational activities (based on the employee's reported significant engagement in standing, walking, sitting, lifting, carrying, pushing, and pulling at work) did not show any reduction in the odds of having OSA [37]. Despite these suggestive findings, the methodological designs of these investigations did not allow the establishment of cause-and-effect relationships on the role of exercise training in the treatment of OSA.

Although no study has focused on the effect of an acute bout of exercise on OSA, several studies have investigated the effect of long-term exercise training [40–45]. Some systematic reviews [22, 46, 47] observed that exercise intervention lasting between 4 and 16 weeks with a frequency between 3 and 6 days a week and between 25 and 60 minutes per training session resulted in a reduction of approximately 30% in OSA severity despite no effect on total body weight. In addition, exercise training promoted a positive effect in aspects associated with daily functioning, such as a 13% improvement in quality of life and a 16.5% reduction in daytime sleepiness [22].

Aerobic exercise training [42, 44, 48–50] and combined training (i.e., aerobic exercise plus strength exercise) [40, 43, 45, 50] have been the most investigated types of exercise. For example, in a seminal work [48] of 6 months duration with moderate-intensity aerobic training, a 50% reduction in OSA severity was observed. Similar results were found in a study by Servantes et al. [50], in which an OSA severity reduction of 40% was observed with a 12-week aerobic training plus strength training intervention. On the other hand, increased exercise intensity does not seem to have additional effects in the improvement of OSA, as modest OSA severity reduction in the order of 24% was observed in adults with severe OSA after 12 weeks of high-intensity interval training [44].

On the other hand, combined training (i.e., when the intervention is composed of aerobic exercise plus strength exercise) has also had a positive impact on reducing OSA severity. For example, a 12-week trial that featured 150 minutes per week of moderate-intensity aerobic training and 2 days per week of moderate-intensity strength training [40] promoted a reduction in OSA severity of approximately 25% in adults with moderate OSA.

Although the results point to a clear benefit of exercise for reducing OSA severity, the underlying mechanisms of the relationship between OSA and exercise

remain unclear. Reduction in the severity of OSA with exercise training is frequently credited to weight reduction and the consequent reduction in mechanical compression in the upper airways caused by the fat accumulation in that region [51]. For example, the literature suggests that a 10% reduction in total body weight can promote reductions up to 30% in OSA severity [52, 53]. However clinical trials [40, 41, 49, 50] have observed reductions in OSA severity following exercise regardless of weight reduction. Thus, some alternative hypotheses are presented as potential mediators of this relationship.

For example, reducing the fluid accumulation in the cervical region during sleep is one such potential mechanism. A sedentary lifestyle and reduced ability to walk contribute to fluid accumulation in the lower limbs since the muscles in this region are primarily responsible for the dynamics of fluid return. Thus, during sleep, the horizontal position contributes to the fluid shift from the legs toward the cervical region, with consequent mechanical compression and reduction of patency of the upper airways [54]. This phenomenon can increase the severity of OSA and daytime sleepiness, contributing to a more sedentary lifestyle and thus promoting a vicious cycle. In this sense, an association between reduced fluid shift after aerobic exercise training and increased upper airway diameter has been observed [55, 56]. Despite this finding, a deeper understanding of the role of exercise in this dynamic remains to be clarified.

Despite the studies showing relevant preliminary results on the role of exercise as a therapeutic approach to sleep-related breathing disorders, the available findings still have some important limitations that should be considered when used in clinical practice. For example, the small sample size in several published experimental studies impacts the ability to extrapolate data. Another important point to be mentioned is the fact that several interventions have not investigated the isolated effect of exercise, as it has often been combined with other approaches such as continuous positive airway pressure or dietary modification. Finally, research in the area of exercise and sleep-related breathing disorders has not yet investigated the effect of different exercise protocols. For example, it remains unknown the effect of different intensities, durations, and doses of exercise or whether the type of exercise (aerobic or strength exercise) can have a distinct impact on the treatment of sleep-related breathing disorders.

3.2 Insomnia

Insomnia leads to both health and quality of life problems. Although hypnotic medication is the main treatment for insomnia, the most recent literature has pointed out that exercise training is a relevant adjuvant or alternative treatment, considering the several longitudinal studies and trials indicating the benefits of regular exercise for adults with insomnia [57–61].

In a longitudinal study of more than 1000 older adults, lower levels of physical activity as well as presenting some degree of depression were directly associated

with increased incidence of insomnia [57], with low levels of physical activity corresponding to 5.2 times greater odds of developing insomnia. This scenario was also observed in another investigation involving more than 3000 adults, where the lack of habitual exercise was associated with 30% greater odds of having insomnia [58].

Thus, even considering the influence of various psychosocial factors, habitual physical activity seems to play a protective role in the incidence of chronic insomnia, especially in older adults. In this context, several clinical studies have analyzed the effectiveness of exercise interventions for the management of insomnia. In a sample of adults with insomnia, Passos et al. [59] compared the effect of three different types of acute exercise bouts: moderate-intensity aerobic, high-intensity aerobic, and moderate-intensity strength exercise [59]. They identified a 55% decrease in sleep onset latency, an 18% increase in total sleep time, and a 13% increase in sleep efficiency, in addition to a 15% reduction in anxiety before sleeping, in the adults that performed a bout of moderate-intensity aerobic exercise.

Clinical data with aerobic exercise training in samples of adults with insomnia seem to point in a direction similar to the results from studies that examined the impact of a single exercise session [60]. In inactive adults with insomnia, improvements in overall sleep quality (as assessed by the PSQI), sleep latency, sleep duration, sleep efficiency, and depressive symptoms in addition to significant reductions in insomnia severity occurred after 16 [60] and 24 [62] weeks of exercise training, respectively.

Despite the aforementioned beneficial effects, the studies mentioned have small sample sizes and different measures of sleep quality and insomnia, preventing broad conclusions about these findings. Moreover, the impact of exercise-related factors such as type, duration, and intensity remains unknown.

4 Final Considerations

Multiple forms of exercise (i.e., aerobic, strength, and combined) improve several sleep parameters, including dimensions such as quality, OSA severity, daytime sleepiness, and insomnia. However, due to the methods used in the various studies, it is not possible to establish how the different variables of an exercise program such as intensity, duration, type, and the number of exercises can impact sleep and its associated disorders (Fig. 1). There are probable mechanisms that seek to explain how exercise improves sleep parameters; however, there is no predominant one, and the available probable mechanisms remain largely speculative. Finally, we can state that exercise training is a promising tool for the management of sleep and its disorders, promoting well-being and impacting factors that go beyond those that are objectively assessed including aspects of daily function such as sleepiness, sleep quality, and quality of life.

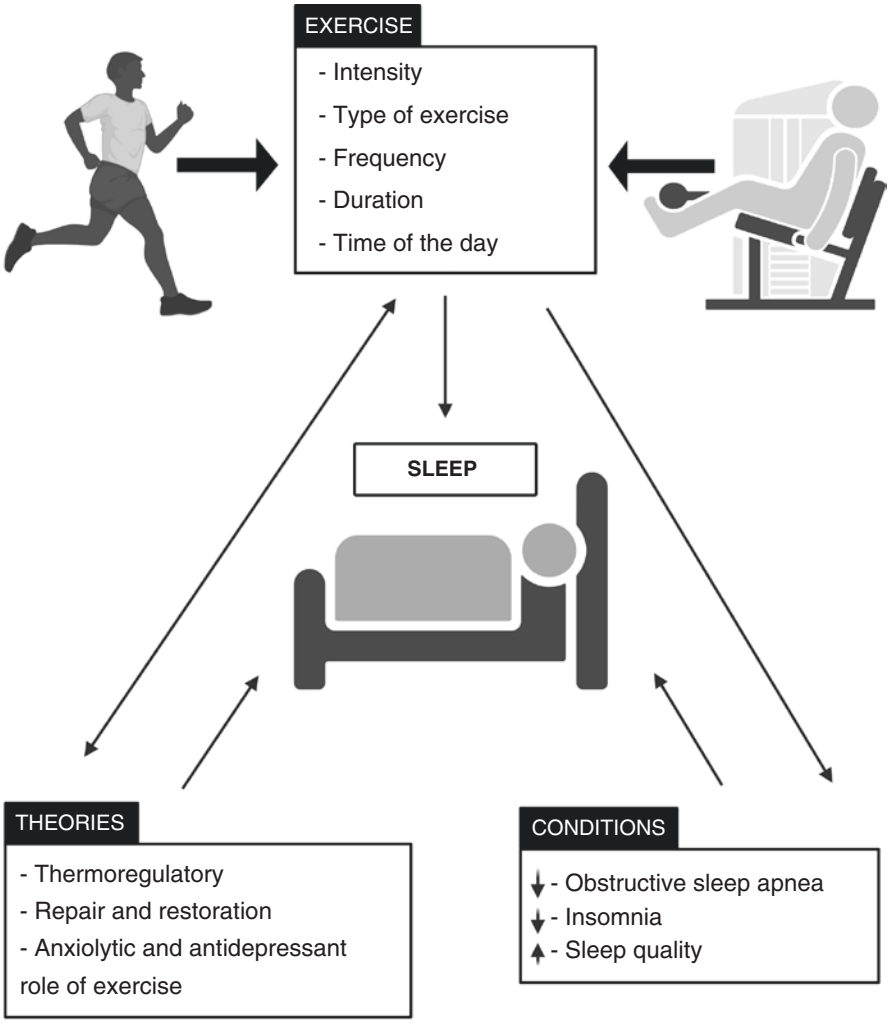

Fig. 1 Exercise training impacts sleep in those with and without sleep problems. In addition, it is known that conditions such as obstructive sleep apnea, insomnia, and poor sleep quality can be improved by exercise. Many different mechanisms could potentially explain how exercise promotes sleep. However, considering that there are several factors involved in the prescription of exercise (e.g., intensity, duration, frequency, mode, timing), it remains unclear how these various factors influence the effect of exercise on sleep

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Hydrotherapeutic Resources for Sleep Management

Sandra Souza de Queiroz

The use of water, as a resource for treating several clinical conditions, is probably as old as humanity and can be used in its three forms: solid, liquid, and gaseous [1]. This technique is related to naturopathic intervention [2], and it receives several denominations, such as cryotherapy, hydrotherapy, hot bath, inhalation, sauna, swimming, balneotherapy, aquatic therapy, aquatic physiotherapy, and thalassotherapy, among others. More important than knowing and mastering hydrotherapeutic techniques available on the market, it is necessary the knowledge of the physical properties of water [3], the physiological and therapeutic effects of water, and the influence of such effects on the different body systems existing [1]. This chapter aims to improve the physiotherapist's skills in how water can be used to aid sleep complaints and disorders, both as an adjunct treatment to other therapies and as a treatment per se.

With the millennial fascination for water [4] and the development of science, we currently have many papers involving water as a non-pharmacological strategy for the treatment and prevention of several clinical conditions, and with a focus on maintaining physical and mental health for both genders, from newborns to elderlies. The sleep outcome is introduced in some of these papers [1, 5–10].

Hydrotherapeutic intervention proposals are based on the physical and therapeutic properties of water: density, hydrostatic pressure, fluctuation, viscosity, and heat, and their respective physiological and therapeutic influences on the immersed body [1, 3, 4, 11, 12]. The therapeutic utility of water depends on its abilities to retain heat and transfer thermal energy. Water can, therapeutically, be used in a wide range of temperatures depending on treatment objectives. For example, intense exercise on the water will be more effective if performed at a temperature between 28 °C and 30 °C; as well as therapeutic exercise or aquatic relaxation needs the temperature to

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be in between 33 °C and 35 °C to produce therapeutic effects without cooling or overheating, being more pleasant and inducing to more relaxed muscles and joints [3].

The use of heated water, as a bath, near bedtime and having total or partial immersion of the body, has been proven to promote muscle relaxation with a consequent decrease of muscle tone, and increase of peripheral blood flow and heat dissipation through peripheral vasodilation [13]. These events result in a decrease in the activation of the sympathetic autonomic nervous system [13], thus facilitating quietness behavior with consequent decrease of sleep onset latency, and also ensuring the restorative sleep [1, 3, 12, 14–16].

The control of central body temperature is performed by the diencephalic structure (i.e., hypothalamus), in association with the suprachiasmatic nucleus [17]. Except for a fever, the central body temperature remains virtually constant varying around 0.6 °C. Thus, the average central body temperature usually ranges from 36.5 °C to 37 °C [18]. The circadian rhythm of thermoregulation is influenced by the balance between heat loss and production throughout the day, closely related to the waking and sleep phases, and to the change of behavior from higher to lower physical and mental activity [14, 19]. The temperature of the skin, also called peripheral temperature, has a wider range ranging from 24 °C to 33 °C, being 29 °C considered a thermoneutral temperature. However, the temperature of the skin surface varies between the regions of the body and does not have, therefore, a fixed value, as it depends on individual vasomotor variability, ambient temperature, and blood flow redistribution [19–22]. With that information in mind, it is possible to think about the effects that immersion in water can cause in the body: relaxation, decrease of the sympathetic nervous system tonus, change of body temperature, and muscle fatigue. These effects induce sleep [1], in addition to all the effects, on sleep, related to the practice of physical exercise (see chapter "Exercise and Sleep").

Chronic pain, which usually is related to muscle tension and insomnia, is a clinical condition that commonly alters the autonomic nervous system, as it keeps its sympathetic division predominantly activated at the expense of the activation of the parasympathetic division. This scenario affects, negatively, the onset and maintenance of sleep [23]. Body and mental relaxation are attainable goals with hydrotherapy. However, it is noteworthy that these conditions often require multidisciplinary intervention and, when necessary, a combination of non-pharmacological and pharmacological treatment modalities [24–26].

It should be noted that healthy people also present difficulty to initiate sleep sometimes and that some strategies, as the use of heated water in the feet, are able to favor the beginning of sleep by promoting the dilation of peripheral blood vessels. This dilation increases the temperature and heat loss in the body ends, favoring the loss of central body heat. This mechanism figures as the best physiological predictor for the quick onset of sleep [15].

A structured and appropriate hydrotherapeutic program requires the identification of the biological and social rhythm of the patient, in order to establish the best time for the practice, the water temperature that is pleasant and capable of promoting peripheral vasodilation, and whether the immersion will be partial or total, in addition to establishing the aquatic activity and the duration of the intervention [3].

Horne, one of the pioneers in considering the effects of passive body heating on sleep, conducted a pilot study back in 1987 to verify whether passive body heating would influence the amount of slow-wave sleep (SWS, N3 stage). Six healthy men with no sleep complaints underwent immersion in a bath heated at 41 °C for 30 minutes, 3 times a week for 2 weeks. Immersion occurred at 2 scheduled hours: 17 h and 21 h. Each intervention happened with a 3-day range. The polysomnography exam (PSG) and the Stanford Sleepiness Scale were the instruments used, each day of the intervention, to evaluate the objective sleep pattern and sleepiness. The researchers found that in the days of immersion at 21 h there was an increase of 15.4 minutes in SWS [27]. This finding demystifies the statement that taking a warm bath around bedtime can be harmful to sleep. It is worth noting that 21 h, except for night workers or shift workers, is a favorable time to decrease body temperature, as it is also the average time when the individual is more prone to quietness. With passive body heating, by means of peripheral vasodilation, there will be an exchange of heat with the environment (water), which will induce the decrease of the core body temperature, in addition to greater muscle relaxation – being these two crucial factors for a good night's sleep.

An investigation with older women, with an average age between 60 and 72 years old and with insomnia diagnosis, addressed the sleep changes caused by passive body heating (immersion in hot water in a bathtub). The participants underwent two baths with different controlled water temperatures: first, ranging between 40 °C and 40.5 °C, and second ranging from 37.5 °C to 38.5 °C, during 2 consecutive nights, for 30 minutes immersed until the level of the chest [28]. The baths took place 90 minutes before the usual time of sleeping. The sleep period was then monitored by PSG, and the participants also answered specific questionnaires on sleep quality. After bathing with water temperature between 40 °C and 40.5 °C, there was a significant decrease in the number of awakenings after the sleep onset (WASO), and an increase in the amount of SWS [28]. In both temperature ranges, the participants reported an improvement in the perception of sleep quality. Correspondingly, when they answered the post-sleep questionnaire, they considered that the sleep was deeper and restorative and felt more willing to wake up in the morning [28]. Regardless of the specific mechanism that explains the effects of passive body heating, this can be considered an effective non-pharmacological method, which improved the sleep of older women with insomnia, further suggesting that a passive body heating routine is beneficial for both the sleep and waking phases, for deep and restorative sleep favoring better performance of activities in the waking phase.

Using a milder temperature of 36.1 °C, postmenopausal women diagnosed with fibromyalgia were submitted to 15 sessions (5×/week for 3 weeks) of passive immersion in a temperature-controlled bathtub. The participants were comfortably positioned in dorsal decubitus with water up to the level of the sternal manubrium and stayed there for 30 minutes. This protocol was performed between 18 h and 20 h for 15 days. The PSG was performed in the following moments: 1st PSG, adaptation aiming at familiarization with team and equipment; 2nd PSG, baseline, in order to determine the sleep pattern; 3rd PSG, acute, after the 1st intervention; 4th PSG, chronic, performed on the 15th day; and the follow-up PSG, performed after 15 days of the 4th PSG. As a result, the chronic and follow-up evaluations

showed a decrease in WASO, sleep latency, and REM sleep, as well as an increase in sleep efficiency. The increase of SWS was observed only at the chronic assessment [29]. This finding demonstrates that the establishment of a heated bath routine prior to bedtime may be beneficial for a restorative sleep night with consequent relief of pain and improvement in quality of sleep and, therefore, quality of life.

In addition to the proposals of passive body heating without the direct intervention of the physiotherapist, there is a well-known technique in the literature, called Watsu, in which the physiotherapist takes the patient in his arms and leads him, passively, by the heated pool combining muscle and mental relaxation, stretching, joint mobilization, and Shiatsu. The Watsu method is recommended for people of any age with acute or chronic pain complaints, and is also indicated for people with sleep complaints [30].

Sleep and wakefulness regulation is well synchronized by two processes called circadian and homeostatic [31]. The sleep pressure imposed by the homeostatic process depends on the energy expenditure throughout the day, and, most often, people who cannot enjoy restorative sleep cannot have enough energy to perform regular physical activity, becoming increasingly sedentary and susceptible to increased body weight and other unfavorable clinical conditions that will negatively impact their sleep quality. The incentive to exercise in the aquatic environment is generally well accepted because it is more pleasant to perform intense exercises than in the ground, whether focused on muscle strength gain, cardiovascular, individual, or group fitness. Thus, with greater energy expenditure, there will certainly be greater pressure on sleep. It is important to emphasize that group activities promote the socialization of people with a tendency to social isolation, impacting positively on anxiety and depression symptoms. Aquatic exercise supports body weight and reduces stress in the musculoskeletal, aspects that are very important for the elderly because it decreases the risk of falls, which is commonly a barrier to perform ground exercises [32–34].

A hydrotherapeutic method used to gain muscle strength and improve body perception is named Bad Ragaz ring method [35]. A recent study, while not directly investigating the sleep variable, found that by proposing and performing hydrotherapeutic intervention via Bad Ragaz and Ai Chi aquatic methods for participants with low back pain, pain complaints decreased after 4 weeks of treatment using these methods [36].

1 Final Words

Although there are several hydrotherapeutic techniques, it is worth noting that the most important is to have knowledge about the physical properties of water, selecting the appropriate and pleasant temperature for the patients in an individualized way, and proposing an intervention that meets the specific needs and objectives of the patient. This can be through hydro kinesiotherapy [37], referring to specific approaches aimed at mitigating the consequences of clinical conditions (e.g.,

fibromyalgia, fatigue, anxiety, stress, sleep disorders). In this way, physiotherapists will be assertive in promoting a good night's sleep, with consequent positive effects in the waking period.

Although in clinical practice we realize that hydrotherapy presents promising results mainly for sleep disorders that require prior relaxation (e.g., insomnia), there are no consensus and guidelines, or research into the theme that calls for 100% of this practice. Thus, further scientific research is needed using population-representative samples, disease-specific, focusing on the use of water resources specifically related to the improvement of sleep.

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Optimizing Behavior Strategies for Sleep

Luciane Bizari Coin de Carvalho

Good sleepers start and maintain sleep in a natural process, developing a lifestyle and habits that promote sleep. These habits and behaviors have positive effects before, during, and after bedtime. The act of sleeping is associated with the loss of control over the body, "surrendering to sleep." For this to happen, the individual needs to be fully rested, not anxious, relaxed, and confident in himself and the place he will sleep [1, 2].

Changing some behaviors may be enough to improve sleep. Several behavioral therapies have been specifically developed for sleep treatment (for insomnia, sleep apnea, narcolepsy), and a few alternatives and complementary approaches (e.g., acupuncture, mindfulness, dietary supplements) have also been used. The nature and focus of these treatments differ substantially, but they were all intended to reduce or eliminate one or more of the putative factors that prolong sleep disturbances, including sleep disruptive arousal and/or habits and conditioning factors that sustain the disorder over time. Among these therapies are a variety of single-component therapies (i.e., stimulus control, sleep restriction therapy, relaxation therapy, cognitive therapy, biofeedback, paradoxical intention, intensive sleep retraining, sleep hygiene), delivered in isolation. In addition, there exists second-generation therapies that advanced from the several single-component therapies and combined many treatments to constitute a more comprehensive, multi-component intervention approach (i.e., cognitive behavior therapy (CBT) and brief therapies), as specified in a systematic review and meta-analysis by the American Academy of Sleep Medicine [3].

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1 Sleep Hygiene

One of these single-component therapies is sleep hygiene. Sleep hygiene is a set of rules, a guide, to adopt behaviors that are hindering sleep. Sleep hygiene was described as:

> (…) education is intended to provide information about lifestyle (diet, exercise, substance use) and environmental factors (light, noise, temperature) that may interfere with or promote better sleep. Sleep hygiene also may include general sleep-facilitating recommendations, such as allowing enough time to relax before bedtime and information about benefits of maintaining a regular sleep schedule. [4]

Sleep hygiene aims to eliminate anxiety generated by the anticipated fear of not sleeping, negative thoughts related to sleep, or that bedtime will be stressful [5–7]. Sleeping and waking up at the same time every day, including weekends and holidays, helps the rhythm required for melatonin production and other factors that depend on circadian rhythm. In normal circumstances, daytime naps are unnecessary and hinder nighttime sleep. Unless you need a scheduled nap for a specific reason (i.e., narcolepsy) and they are part of the routine, following time and duration. The regularity of meals is also important, as its regularity during the day and the choice of food at dinner and dinner time are all related to sleep, as they are external cues for entrainment of the circadian system. The room environment should be quite suitable and comfortable for the promotion of sleep: good support from the mattress and the pillow, room temperature (slightly cooler is optimal), no noises, blackout curtains, or light control should be suitable. Attention to stimulating screens, such as television, tablets, smartphones, computer, games, etc., as they emit a blue light that can interrupt the melatonin release and therefore disrupt sleep. The balance between work and leisure should also be observed. Many activities accumulate tiredness (increase sleep pressure) and delay bedtime. The routine for sleeping well includes a period for rest and shutdown of thoughts, especially problems, worries, and work for the next day.

Sleep hygiene is used to teach the individual healthy habits and behaviors that can disrupt sleep (Table 1). There are no contraindications, as sleep hygiene is a benign intervention.

Sleep hygiene is one of the multicomponent approaches of the CBT, and not CBT solely. There is a need for the physical therapist to explain the rationale and the relevance for each of the instructions, emphasizing that they are not casual and scientific-based and that they may also contribute to the development of insomnia. Also, the individual's willingness to change habits is fundamental to the success of CBT. Other problems that affect behavior change include the place where the individual lives (if there is noise, light, danger, or neighbors that disturb), the help of the family (if there are sick, alcoholic, aggressive individuals), the type of work/study (time, distance, stressful activities), and if there is a possibility of leisure (children, relaxing activities, physical activity), among others.

Using a sleep diary can help the patient to be aware of his sleeping habits, and the PT to understand the routine or lack of it, and to what extent, to change and

Table 1 Sleep hygiene education for patients and rationale. (Adapted with permission from: Siengsukon et al. [8])

Sleep hygiene rule		Rationale
Routine	Go to sleep and wake up at the same time every day. This will help set your natural biological clock. Exposure to bright natural light when you first wake up is also helpful to set your natural biological clock	This regularity and the exposure to sunlight will allow the biological clock to be synchronized, indicating to the brain that it's time to wake up. On the other hand, avoiding exposure to light in the early evening will be key to favoring the release of melatonin which is a sleep-inducing hormone
Bed = sleep	Use your bed for only sleep and sexual activity to help train your brain that if you are in your bed, you should be sleeping. Do not eat, work, or watch TV in bed. Do these activities outside of the bedroom. Leave bed if unable to fall asleep within 20 minutes and return when sleepy. If unable to leave the bed due to limited mobility or safety concerns, do something relaxing (i.e., relaxation techniques) until sleepy and able to fall to sleep	To promote better circadian cycling, set an alarm to go to sleep and to wake up every day at the same time
Relaxing routine prior to sleep	Develop a relaxing bedtime routine. This may include taking a warm bath, reading a book, meditation, or stretching. Avoid stimulating activities right before bedtime, including watching TV or discussing a stressful topic	The heating promoted by the bath, for example, can cause a downregulation of the central temperature and facilitate the onset of sleep and the deepen of sleep
Physical exercises	Avoid moderate to vigorous exercise at least 2–3 hours before bedtime. Exercising immediately before bedtime stimulates your body and brain making it hard to fall asleep. There is evidence however that doing regular (preferably moderate to vigorous) exercise improves your sleep at night. Talk to your physical therapist about an appropriate exercise program	Doing intense physical exercises close to bedtime can stimulate the body and brain making it difficult to lower body temperature, necessary for the onset of sleep. On the other hand, there is evidence that regular physical exercise helps reduce pre-sleep anxiety, facilitating the onset of sleep and helps synchronize the wakefulness cycle-sleep. In addition, regular practice of physical exercises has antidepressant and anxiolytic effect, associating the improvement of sleep quality. Aerobic exercise can deepen sleep. Deeper sleep is more restorative and protect against noise, pain, and hot flashes. Unclear whether exercise can help sleep a greater amount and more quickly

(continued)

Table 1 (continued)

Sleep hygiene rule		Rationale
Caffeine	Avoid caffeinated foods and drinks at least 4 hours before bedtime (includes most tea, coffee, chocolate, and soft drinks). Check the presence of caffeine in your drink or food by reading the label. Caffeine can cause difficulty falling asleep and increase the number of times you wake up during the night	Scientific evidence indicates that caffeine is antagonistic to adenosine receptors, in addition to delaying the rhythm of melatonin, and thus hinders the onset of sleep and dysregulate our biological clock
Alcohol and cigarettes	Refrain from drinking alcohol or smoking at least 3–4 hours before bedtime. Although people may think drinking alcohol causes relaxation before bedtime, it can increase the number of times you wake up during the night and can cause you to wake up early. Nicotine in cigarettes can cause difficulty falling asleep	Alcohol consumption can cause relaxation before bedtime; however, alcohol directly interferes with sleep, especially in REM sleep, decreasing its amount, and increases the nocturnal awakenings and wake earlier in the morning. Nicotine in turn is a stimulant that impairs asleep
Sleeping pills	Do not take un-prescribed or over-the-counter sleeping pills	
Naps	Avoid daytime napping so that you are tired at night and can fall asleep easily. If you feel you need to take a nap, limit the nap to 30 minutes and avoid napping in the evening	If you choose this habit, take this nap preferably after lunch (when we have a slight fall in body temperature). Avoid napping at other times and for an extended time. This will impair night sleep in quantity and quality
Sleep environment	Make your sleeping environment comfortable and relaxing. This includes avoiding too much light and disturbing noises. Stop using light-emitting electronics (i.e., television, computer, smartphone) at least 30 minutes before bedtime, as the blue light that is emitted can disrupt sleep by suppressing melatonin production. Use ear plugs, light-blocking curtains, or an eye mask if needed. Also, keep the temperature comfortable. Being too warm or cold may disturb your sleep. Also, use a comfortable and supportive pillow and mattress	The wavelength of blue light emitted by these devices impairs sleep induction by suppressing melatonin production and informing the brain that it is daytime. Another fundamental point is to seek a comfortable and preferably well-aligned posture. Choose the mattress and pillows well – not only the one that will support the head, but others of support that can assist in the optimal adjustment of posture
Food and liquids	Avoid eating a large meal or spicy food 2–3 hours before going to bed. Your digestive system slows down while you are sleeping which can stimulate acid secretions that cause heart burn. A light snack may be helpful if you are hungry. Avoid excessive liquid 2–3 hours before bedtime. Remember: it's not only *what* you eat, but also *when* you eat	The digestion of large or very caloric meals impairs so much sleep, as the digestive system slows down at night and can stimulate the secretion of acids that cause heartburn and reflux Avoid liquids before going to sleep so you don't have to wake up at night to go to the bathroom
Help	Talk to your doctor or health professional if you still have trouble sleeping	

improve sleep [9]. The sleep diary is explained in chapter "Subjective Assessment of Sleep" of this book. Sleep diary provides information about sleep duration, the number of awakenings during the night, sleep efficiency, sleep latency period, whether there is regularity in bedtime and waking up during the week and on weekends, naps during the day.

In the 1980s, the first CBT protocols for insomnia emerged, combining cognitive and behavioral techniques for changes in sleep habits. CBT has been indicated in clinical guidelines as an evidence-based treatment of choice for chronic insomnia, but can be used for sleep disorders, aiming to increase sleep time and improve sleep efficiency [10–15]. When used alone, cognitive, and behavioral techniques have a clinical effect, proved to be more efficient and lasting, together with other treatments. As a single treatment, it does not present scientific evidence in all sleep disorders, except for insomnia, but within subjective parameters, not objective ones [1].

2 Cognitive Behavioral Therapy

CBT aims to reduce sleep-related negative behavioral symptoms and reduce anxiety-related cognitive symptoms related to sleep. CBT requires customized forms of application [10] (internet, group, individual, self-application, etc.); a different number of sessions (from 4 to 8); duration of the sessions (60–120 minutes); and techniques applied according to the needs of each individual [16].

The CBT applied in person or at a distance can count on the aid of ready texts or pamphlets, and its effectiveness has proven both individually and in groups [10, 16]. In many countries, it can be applied by any health professional qualified in CBT, such as a psychologist, physician, nurse, occupational therapist, speech therapist, and/or social worker, and by the physiotherapist [10].

CBT uses a commonly employed multi-component package that combines sleep restriction therapy, stimulus control therapy, relaxation, paradoxical stimulation, and cognitive therapy [3].

3 Sleep Restriction Therapy

Sleep restriction (or time-in-bed restriction, a more accurate name) aims to increase sleep efficiency, which is the relationship between how much time is spent sleeping in the time that the individual set out to sleep (sleep time/time in bed × 100%) [10, 12]. Many individuals stay in bed too long trying to sleep or waiting for sleep to come, thus causing an increase in anxiety, usually leading to irritability in the absence of sleep, spending much more energy trying to sleep than effectively sleeping. Sleep restriction therapy consists of reducing the time in bed which can result in consolidation of sleep without interruptions and reduction of anticipatory sleep anxiety. This therapy is indicated for those who have sleep difficulties, in which sleep efficiency is less than 85%, indicated by a 1- or 2-week (preferably with

weekdays and weekends) sleep log or retrospective report. In this technique the individual is invited to reduce the time spent in bed, adjusting this time to the time in which he effectively sleeps.

For example, a man goes to bed at 22 h and refers to many problems when going to sleep. He feels he takes too long to fall asleep, thinking about work, how was the day, and how is going to be the next day. He stays in bed, turning from one side to another and with ruminating thoughts. He sleeps around midnight, and his alarm clock rings at 06 h every day, when he wakes up and shower. His 1-week sleep diary reveals:

Average bedtime to rise time	22 h to 06 h
Average time in bed	8 h
Average sleep latency	2 h
Average sleep duration	6 h
Sleep efficiency	75% = (6 h/8 h) ×100

In our example, the sleep efficiency was 75%. If he goes to sleep later, closer to midnight, the sleep efficiency will become 100%. The goal can be ≥85% of sleep efficiency. As he presents with no complaints in waking up time, the decision is made to adjust the time of going to bed. Then he is asked to go to bed closer to midnight and to keep a diary for one more week in this new schedule. This increased his sleep efficiency. To prevent excessive daytime sleepiness, time in bed should not be reduced to ≤5 hours per night, so there should be a precaution for sleep restriction. In addition, the physical therapist might consider how the patient's sleep is impacted by his/her condition or disease, which might warrant less strict sleep restriction and use of sleep compression instead.

4 Stimulus Control

The stimulus control technique consists of identifying the environmental stimuli related to eliminate the association between the bed/bedroom and wakefulness in order to restore the association of bed/bedroom with sleep. Falling asleep is conceptualized as an instrumental act produced to harvest reinforcement (i.e., sleep). This is possible by monitoring behaviors and habits performed at bedtime. As new habits and behaviors are created with a proper sleep routine, the room and its environment are associated with the rapid stimulation of falling asleep [10, 12]. The stimulus control therapy is centered on the notion of reinforcing the cues of the bed and bedroom for sleep and weakening the cues for activities that influence the falling asleep and developing a consistent sleep-wake schedule to sustain progress. The stimulus control technique directions are created to be effective for sleep onset problems, whether they occur at the beginning or middle of the night. For example, if not asleep in 15–20 min or if feeling anxious, get out of bed and try to relax. For physiotherapists, might want to provide modifications for the patient to get out of bed safely.

It is understood that the individual who has difficulty recognizing the sleep signal has difficulty establishing a sleep routine. Before going to bed it is necessary to rest and to prepare for sleep, to have habits to reinforce the link between bedroom and sleep. Good sleepers, or people without sleep disorders, often perform several activities before going to bed, such as having an environment with dim lights, a shower, lavender scents, etc.

The therapy starts with an inventory about all behaviors performed at bedtime, especially those already in bed: reading/studying, eating, watching TV, listening to music, looking at the clock, performing manual work, drinking (coffee, tea, alcohol, chocolate), smoking, calling friends/boyfriend, reviewing and planning the day, doing accounts and checking bank, reviewing concerns, and thinking about diseases and problems in the family, among others. Next are carried out guidance on the stimulus control, which should be followed every day (weekdays and weekends): going to bed with the intention of sleeping; not using the bed or bedroom for an activity other than sleep (do not read, watch tv, eat, worry, check e-mails of messages), with the exception of sexual activity; establishing a routine to go to bed, so that these activities will serve as a sign to fall asleep; not to remain in bed awake, and if the individual is unable to fall asleep in a short period of time, the individual should get out of bed and go to another room to perform the activity proposed as a sign of sleep, and when the individual perceives this sign should again go to the bedroom/bed; if the individual return to the bedroom/bed and do not fall asleep in a short time, should again repeat the previous instruction until he is able to fall asleep quickly. The goal is to associate the bed with sleeping quickly.

5 Relaxation

For individuals who present anxiety at bedtime, a muscle relaxation technique can be beneficial for taking tension out of the body and reducing excitation levels, and not as a sleep induction technique [10, 12]. The relaxation technique should be chosen with the individual: progressive muscle relaxation, Biofeedback, Mindfulness, meditation, guided imaginary training, autogenic training, Jacobson technique, or any other technique that helps in relaxation. Relaxation techniques are used when enhanced somatic and or cognitive arousal interferes within sleep.

For instance, autogenous or self-induced relaxation is performed passively, through the suggestion of sensations such as weight, heat, and cardiac and respiratory rhythmicity. Edmund Jacobson described, in the 1960s, the effectiveness of progressive muscle relaxation, which involves tensing and relaxing different muscle groups [17]. The patients are trained to focus on and to compare feelings of relaxation with tension that was present before the relaxation procedure. Homework includes practicing daily, before bedtime, and sometimes during the nighttime awakenings. During the day, it can be performed in the bedroom, to facilitate classical conditioning. *In the* biofeedback technique, there is sensory feedback, which can be auditory or visual, or mechanically, with computers and amplifiers. The aim

is to help patients to learn how to control physiological parameters such as muscle tension and finger temperature, for example, to reduce somatic arousal [18]. In other words, biofeedback actively involves the patient in the therapeutic process and provides the awareness of the patient's own sensations and response to stressors. The individual is trained to use his own body signals to relax. Monitoring physiological reactions, especially those related to anxiety and stress, helps the person to perceive the changes that occur in his body during relaxation. Biofeedback is also used as a form of cognitive restructuring, in pain control, in the elimination of organic symptoms, and in the rehabilitation of muscle functions.

6 Paradoxical Intention Therapy

Paradoxical intention aims to eliminate the anxiety that inhibits falling asleep [10, 12] and the maladaptive relationship between effort to sleep and ability to sleep. This technique has shed light on investigations that participants with insomnia had more success falling asleep when they tried to remain awake when they had to try to fall asleep [19]. The individual should be prepared to spend the whole night awake performing an activity compatible with your sleep routine (e.g., watching a movie), without going to sleep. It is about taking a different perspective of sleep and sleep habits, beliefs, and fears. The instruction for the patient to stay awake as long as possible after getting into bed, to persistently involve in the feared action (staying awake) to reduce anxiety and conscious intent to sleep that misperceives associated goal-directed performance (falling asleep). This method eases the patient's disproportionate focus on sleep and anxiety over not sleeping; as a result, sleep becomes less difficult to initiate. There are elements of paradoxical intention incorporated into CBT techniques (Table 2).

7 Cognitive Therapy for Dysfunctional Beliefs About Sleep

Cognitive Therapy aims to identify beliefs (dysfunctional thoughts), attitudes, and knowledge of the individual in relation to sleep, in order to replace them with more appropriate/adapted thoughts and behaviors [10, 12]. Cognitive restructuring should help the individual understand what normal sleep is, how many hours of sleep are needed, what hours one should sleep, what are the bodily signs of sleep, how to distract unwanted thoughts, causes the individual to be aware, to recognize and review his expectations about sleep. For the AASM, cognitive therapy is "[…] a set of strategies including structured psychoeducation, Socratic questioning, use of thought records, and behavioral experiments designed to identify and modify unhelpful beliefs about sleep that may support sleep-disruptive habits and/or raise performance anxiety about sleeping" [3].

Table 2 Paradoxical aspects of other Cognitive Behavioral Therapy methods. (Reprinted with permission from Espie [20])

CBT method	Patient concern	Therapeutic response
Sleep restriction therapy	*I have got insomnia. I feel I am not getting enough sleep.*	*What are going to do is to reduce the time you spend in bed, so you need to stay awake for longer…*
Stimulus control	*I keep awakening up during the night and can't get back to sleep.*	*Get up out of your bed, and get out of your bedroom, and go and read a book instead.*
Progressive muscle relaxation	*I feel wound up and unable to let go.*	*Tense up muscles in your fingers and your hands to make a fist, keep the tension going at a steady rate, …*
Cognitive therapy	*I feel that if I don't sleep soon, then I am going to be completely useless tomorrow.*	*So what's the worst that could happen if you don't sleep? You could try that as an experiment.*
Keeping a sleep diary	*I just can't stop thinking about my sleep. How I sleep and how I feel the next day is constantly in my mind.*	*I would like you to start keeping a detailed and careful note of your sleep pattern and sleep quality in a diary. Now every day you need to fill this in accurately…*

Education about sleep, circadian rhythm (internal clock, effect of hormones), on the influence of age and gender, and the effects of sleep deprivation promote decreased anxiety and reformulation of sleep. The control of concerns can be done through guidance to put on paper everything that is thought, as well as the tasks that were performed that day and the planning of the next day, in the late afternoon or early evening, in a different place from the bedroom. Listing problems and possible solutions have proven to be an efficient resource to reduce sleep time concerns. Relaxation techniques and mental training also help to avoid this schedule.

The repetition of new habits turns them into routines in 4 weeks. As the problems of everyday life do not end and life is a succession of them, some nights of insomnia may reappear. But using the trained techniques, the patient can sleep the next night and recreate the good sleeping conditions and beliefs. This is the educational character of cognitive therapy.

8 Final Words

Sleep education considers appropriate habits and personal needs to make up a good sleep routine. Proper eating, physical activity, sleeping environment, regularity of bedtime, and waking up influence good sleep habits. Having positive experiences with sleep too. Resting and turning off thoughts are important behaviors in preparing for sleep. The presented techniques aim to reduce sleep-related behavioral symptoms that make the patient sleep poorly and reduce anxiety-related cognitive symptoms to fall asleep.

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Sleep Ergonomics

Silmara Bueno and Cristina Frange

It is during sleep that the whole body recomposes and prepares itself for the next day. Being asleep is a state of physical and mental restoration, essential to the body, where the plasticity of the entire organism occurs. Thus, body supporting during sleep is of major importance. The human spine must be supported by the combination of a mattress, a bed base, and a pillow to adopt its natural position. The acquisition of a non-neutral position may influence painful processes, and in particular, musculoskeletal system pathologies.

Sleep quality and comfort are frequent questions of patients in the daily practice of physiotherapists, as the number of hours and the quality of sleep is well established to affect overall health – and to acquire that one must sleep on a proper surface. The posture adopted during sleep influences the physical health of the individual and may be correlated with musculoskeletal disorders in the shoulders, neck, lumbar region, as well as headaches, for example, that can, in turn, predispose to sleep fragmentation, poor quality, and quantity, leading to sleep disturbances.

A proper sleep system (i.e., mattress and support structure, and head pillow) can align the spine to some extent in its neutral posture which is the same as the spine alignment in the upright position [1]. A non-neutral posture can affect lateral bending and unbalanced loading on intervertebral disks and facet joints. For the intervertebral disks, growth and restoration depend on the amount of pressure and its

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manner of application on them, as to hydrate the soft tissues. During sleep, there is a change of the direction of the gravity vector; the intervertebral disks are unloaded and can rehydrate to restore their elasticity [2]. Supplying a patient/client with proper surfaces upon which to relax is also the focus of physical therapy.

The causes of pain in the axial skeletal muscle system may be due to mechanical disorder, postural and ergonomic factors, or excessive overload of the upper or lower limbs. Mechanical factors can be attributed to resting postures such as deviations in the position of the head, static or repetitive contractions of the neck muscles [3, 4]. For instance, sleeping with an incorrect height of the pillow: high, low, or no pillow (too low), or even sleeping in an incorrect posture may lead to frequent awakenings, to pain during the night and following day, or even to chronic pain in a course of time.

1 What Is a Good Posture for Sleep?

How is the correct body alignment during sleep? Having a good posture can increase body awareness and injury prevention. Posture can be defined as the distribution of body masses in space, this distribution being harmonious, involving a minimum amount of effort and overload and leading to what we call "good posture." The alignment of body mass and joints is one of the fundamental characteristics to acquire the "good posture". However, maintaining alignment does not depend on our voluntary control; the movement is often carried out involuntary during the recumbent posture that we adopt when asleep, and also via reflexes. There are several factors that influence and configure posture during sleep.

Proper maintenance of postures, body parts with the centerline of gravity, is associated with lower energy expenditure due to lower demand for antigravity muscles [5–7]. The muscular effort spent to maintain the different postures adopted is based on the position of the different parts of the body according to their relative weight, that is, head 6–8%; trunk, 40–46%; upper limbs, 11–14%; and lower limbs, 33–40% of the total body weight [8]. According to the assumed posture, there is a change in the internal pressure of the intervertebral discs [9].

Changes in body posture are one of the problems often faced by young people, adults, and older ones. In this context, the prophylactic approach of a postural reeducation with an intervention in the posture aims to minimize the effects of the degenerative process and the mechanical overload caused by the continued bad posture in all day and also night periods [10].

A posture is called "bad, poor" when it is ineffective, when it does not reach its intended purpose or when a great muscular force is used to maintain it, consuming more energy than it should [5]. A poor posture can result in pain due to mechanical overload for a prolonged period (i.e., sleep), adaptive shortening of soft tissues, and consequent muscle weakness [11]. Mechanical stresses, such as those imposed by postures outside the anatomical alignment for a prolonged period, lead to an increase in the production of fibroblasts and collagen, with the loss of the need for tissues such as muscles and soft tissues [12]. When the posture is maintained statically for

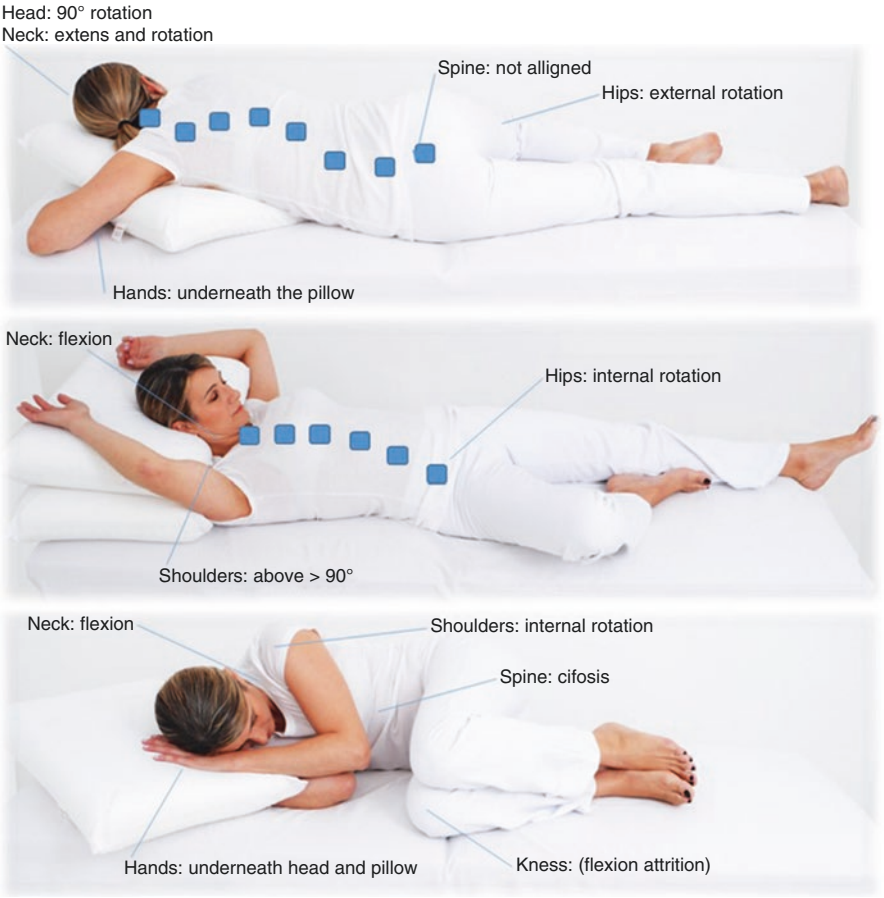

Fig. 1 Illustration of ineffective postures, with a mechanical overload of joints and muscles. (Image courtesy from Dr. Silmara Bueno.)

a long time, that is, with isometric and repetitive contractions, the phases of muscle relaxation become noticeably short, promoting muscle fatigue that can translate into a sensation of discomfort or pain [13] (Fig. 1).

In the biomechanics of the spine, aspects such as length, strength, endurance, and muscle coordination are involved, maintaining the balance between them. The lack of application of healthy biomechanics to the spine during sleep is associated with a decrease in range of motion, changes in alignment, and normal control in kinesthetic perception due to inadequate postural habits, maintained for a prolonged period. Among the lengths associated with postural dysfunctions, the decrease in range of motion due to changes in flexibility, pain, and increased muscle tension due to overload stands out. In addition, there is a decrease in strength and resistance leading to muscle fatigue due to the postures adopted or due to disuse and inadequate trunk stabilization [11, 14]. The increase in static, repetitive, and excessive

resistance increases the risk of inflammatory or degenerative processes that affect the skeletal muscle system [14].

Postural assessment at bedtime makes it possible to assess imbalances to restructure posture through ideal support for the entire skeletal muscle system. The pelvic area of the human body is broader and heavier than other body parts. The thoracic area, because of the presence of the lungs is wider but not heavier. When lying in a lateral decubitus for sleep, on a very firm mattress, there is unsuitable spinal support, as only the broader areas of the body are supported (e.g. pelvis and shoulder). When these forces are not respected, ischemia may appear in body regions that are in contact with the surface. Ischemia generates metabolic substances (which will stimulate the nerve extremities and lead to discomfort and pain in lumbar and neck regions. The continuity of this factor can cause chronic muscular pain in the neck spine [15, 16]. Postural discomfort due to continuous muscle contraction can decrease blood supply, increase tension (stretching tight), or ligament compression, usually leading the individual to change the posture. Different studies have shown the association of microtrauma with pain and functional disability caused by poor posture during sleep [14, 17–19], highlighting the importance to have ideal support for the body and a correct and aligned posture.

The adopted posture for sleeping is something incredibly unique and particular. We move more than 10 times during sleep, this tends to decrease with age, and most of the time we are unable to remember the position in which we fall asleep or wake up. The body requires a position according to the degree of comfort and habit, so the body tends to adapt during a change in the musculoskeletal system.

2 Mattress: Alignment of the Body

In comparison about the mattress, custom-made surface, firm, and soft matters showed that the custom-made matters have maintained the natural alignment of the spine, arranged with different stiffness zones (Fig. 2a).

In the firm matters, the spine has bent down in the lumbar area, as only the shoulder and pelvis received good support on these surfaces (Fig. 2b). The softness of the soft mattress caused the pelvic area to sag more into the mattress, while the position of the vertebra C7 on soft surfaces is higher than that of the pelvis, due to the relatively lower mass of the upper part of the body (Fig. 2c) [20]. Therefore, the

Fig. 2 Alignment of the spine on custom-made (**a**), firm (**b**), and soft (**c**), surfaces. (Reprinted with permission from Leilnahari et al. [20])

Fig. 3 Supine position with roll under the knees to protect the lumbar region, hips, and knees; and lateral decubitus with supported contour-shaped body pillow. (Image courtesy from Dr. Silmara Bueno.)

custom-made mattress allowed the neutral alignment of the spine, close to the natural standing position.

In the supine position, the center of gravity is a result of all segmental centers of gravity in relation to weight, having as many centers of gravity as there are positions to be adopted. The individual is in stable balance in the supine position when the line drawn from their centers of gravity coincides with the base of support [21].

The most common sleeping position in adults is the lateral decubitus (57%) [22], most likely due to the increased support of the spinal structures [23], followed by the supine position (17%) and the prone position (11%), despite this last one not being indicated for sleep. The other postures are variations of the positions in which the individual lies down to sleep [24]. The supine and the lateral decubitus are the sleeping postures most indicated, as they allow greater comfort and efficiency [25]. Yet, both positions require the use of two pillows (or a bigger one): one supporting the head and the other, below or between the knees (Fig. 3). The supine position allows the alignment of the spine with the use of pillows, cushions, and supports. For this case, it is recommended to use a pillow for the head and another pillow under the knees to align the pelvis.

3 Pillows: Neck Support

When sleeping in the prone position, the head is usually turned to the side, which increases the rotation of the neck. This rotation is up to 90° and flexion of 10°–20° of the neck, with negative repercussions on muscular structures, nerves, vessels, ligaments, and other segments. This posture constitutes a potential source of neck pain, fatigue, muscle tension, tension headache, and pain in the temporomandibular joint [11]. Consequently, there is an increase in spinal load, because several facet joints of the most cranial vertebra are compressed on the ipsilateral side, while the contralateral ligaments will be under tension and stretching. Blood vessels can also be compressed, causing headaches, dizziness, and other disorders [1]. Despite all the disadvantages, many people prefer the prone position. It is therefore advisable to improve the alignment of the spine by placing a pillow, under the shoulder and the ribcage next to which the head is facing, or by raising your arm from that side, or even by placing a pillow under the belly to restore lumbar lordosis. The same alignment of an eventual hyperlordosis can be achieved by raising the knee and the hip next to which the head is rotated, or by placing a pillow under the hip and knee on this side. In fact, most of the aforementioned corrections implement a slight change of position to an almost lateral position [1].

Inadequate posture of the head when sleeping imposes a considerable consumption of muscle energy in the neck region. Poor neck posture during sleep, increase biomechanical stresses on neck spine structures, producing neck pain and stiffness, headache, and scapular or arm pain, resulting in low-quality sleep [26]. A suitable pillow is a proper support for neck lordosis [27]. Choosing an adequate pillow can

Fig. 4 Different materials with different supports for pillows. (Image courtesy from Dr. Silmara Bueno.)

reduce pain and improve sleep quality [28]. The big question is: "How is the suitable pillow? How do I chose one? Where do we have it on the market?" There is still no consensus regarding the best type of material for pillows, or their shapes and heights, which are still under debate in the literature (Fig. 4).

The main role of a pillow during sleep is to support the neck spine in a neutral position. A neutral position of the spine prevents loss of neck spine curvature and neck waking symptoms by minimizing end-range positioning of spinal segments [23, 29]. In addition, proper support can increase the contact area between the neck and the pillow so the pressure exerted upon the muscles can be evenly distributed [30]. Modifications of the neck inclination from 10 to 15 degrees alter muscle activity and blood supply in the region [31]. During the neck flexion, the horizontal distance between the center of gravity of the head and the axis joint at the atlanto-occipital joint increases considerably. The contraction of the scapular elevator muscles, with repercussions on the brachial plexus, is expressed by symptoms of pain, tingling, and decreased strength of the upper limbs [31]. Likewise, such manifestations can be observed when lying down, maintaining the prolonged positioning of the neck in semi-flexion.

Neck and spine pain as a whole has been described as one of the factors that can interfere with sleep quality. Pain and discomfort were related to higher and longer electromyographic (EMG) activities of trapezius in participants who have neck and shoulder pain. However, the relation of comfort and EMG activity of the neck and upper trunk during lateral sleeping position in different pillow heights is still a gap in the literature [32].

We already know that many people might not fall asleep when the neck was stiff and shoulder muscles were not relaxed. In addition, we should use props to relax the joints and loosen stiff muscles having proper support [33].

Pillow temperature must also be taken into consideration. A pillow that helps reduce core and head temperatures during nighttime sleep has been shown to be important for deep sleep (slow wave sleep) [34]. The reason individuals using a pillow made of a material that helps the pillow surface stay cool could fall asleep more easily and sleep well is strongly related to the lowered core and head temperatures and slowed heart rate [35]. Moreover, a pillow designed to reduce the temperature of the head can reduce sweating and whole-body temperature, and indirectly improve sleep quality [36].

An investigation on the effects of three types of pillows with different contents on neck lordosis, pillow temperature, and pillow comfort was conducted [37]. The three pillows were made of different materials: the orthopedic pillow (a roll-shaped pillow containing multiple polypropylene capsules), the memory foam pillow (contoured pillow consisting of polyurethane foam), and the feather pillow (regularly shaped pillow filled with 100% goose feathers). The Cobb angle from C2-C7 of the participants was measured from a radiograph, and when comparing the pre-Cobb angle in a standing position and the post-Cobb angle in a supine position with the use of the three different pillows, the researches found that the angle was significantly increased with the orthopedic pillow, from −3.83° at baseline to 7.70° (Fig. 5). The memory foam pillow increased the Cobb angle from −3.83° to −0.33°,

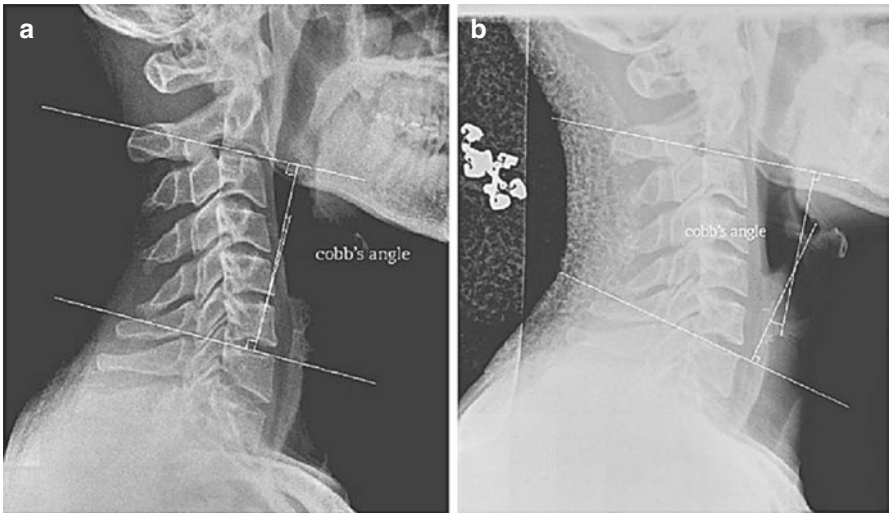

Fig. 5 Measurement of the Cobb angle in a standing position (**a**) and a supine position with an orthopedic pillow (**b**). (Reprinted with permission from Jeon et al. [37])

and the feather pillow decreased the Cobb angle from −3.83° to −6.20°, but with no statistically significant differences (that might be because of the small sample size). The variations in pillow temperature were measured using an infrared thermometer, and the temperatures of each of the three pillows increased significantly after 20 minutes of lying on the pillows. However, the degree of temperature increase was significantly lower for the orthopedic pillow (1.53 °C) than for the memory foam (3.13 °C) and feather pillows. The orthopedic pillow was also considered the most comfortable one by the participants [37].

In another investigation, neck pain and quality of sleep were tested with six different pillows [38]. The participants tested all the pillows in a random order over the course of 3 weeks. Pillows with firm support for neck lordosis could be recommended for the management of neck pain and improvement of sleep quality [38].

The use of the wrong type of pillow can compromise pain-sensitive structures and produce waking symptoms, such as neck pain and stiffness, headache, and arm pain leading to low sleep quality. The height of the pillow affects the comfort and quality of sleep and was identified as one of the factors that influence the alignment of the neck spine [39, 40]. It is believed that using an "ideal" pillow for adequate neck support to maintain neck lordosis while sleeping can lead to high-quality sleep [30]. However, many people make poor choices of pillows, which leads to the adoption of bad postures of the neck during sleep, resulting in biomechanical stress [26]. The pillow intends to avoid the discomfort caused by the posture adopted when sleeping, promoting the alignment of the axial skeleton in any decubitus, and supports the skeletal muscle system, being considered compensating support [41].

The traditional dimension of the pillow used in many countries is 50 × 70cm, with a height of 10–18 cm. In order to make them soft and comfortable, they can be made in different materials, (e.g., feathers, polyurethane flakes, polyester fiber, viscoelastic, latex, and others), and in different formats (e.g., the traditional rectangular ones, format of soap, triangular and ergonomic ones). The pillow should adjust to the different decubitus positions adopted during sleep. For instance, in the supine position, if the height of the pillow is too high, it will cause flexion of the neck. Similarly, if the height of the pillow is too low, there is hyperextension of the neck. Both can impair respiratory function during sleep, increase muscle activity, and generate pain.

The EMG activity of the neck and mid-upper back of asymptomatic adults using foam pillows of three different heights (5, 10, and 14 cm) was evaluated by a group of Brazilian researchers [42]. The 10 cm pillow foam elicited the lowest EMG activity of the middle trapezius in lateral decubitus and was considered by the participants the most comfortable one [42]. A study conducted with participants with a high variation in height, from 155 to 180 cm, found the intermediate pillow height of 10 cm as an ideal [34], as other investigations also have proposed [30]. Indeed, the ideal height for each person is a fundamental aspect of pillow use. This is a product that needs to be designed specifically for a population according to their anthropometry.

4 Positional Therapy for Sleep Apnea

A sleep-positioning pillow can heltp to resolve or resolve positional obstructive sleep apnea (OSA) in some cases. It is a simple accessory, many times used toghether with PAP therapy, deserving consideration as an alternative or complementary treatment. Please refer to Chapter “Obstructive Sleep Apnea: Physiotherapeutic Approach” for more on sleep position for OSA, and for pictures of devices for positional therapy, such as chest belts, inflatable dampers and tennis ball technique.

Only four studies up to now investigated the use of different sleep positioning pillows in patients with OSA, two of them using objective parameters. The effect of the positional pillow (Fig. 6a) was investigated using objective measures derived from polysomnography on both respiratory variables and sleep architecture (baseline, consecutive treatment response at 1 and 6 months, and follow-up polysomnography) along with questionnaires to identify sleepiness, fatigue, and sleep quality [43]. The satisfaction of both participants and bed partnerers was assessed. The use of the positional pillow statistically significantly reduced supine position, sleep fragmentation, apnea-hypopnea index, respiratory disturbance index, and oxygen desaturation, both at 1 and 6 months. Sleepiness and fatigue also showed reductions and sleep quality improved in all-time points [43].

There was a significant reduction in respiratory disturbance index, hypoxemia, and snoring after one night with a triangular pillow in participants with mild to moderate OSA (Fig. 6b) [44]. Therefore, we must be aware of shoulder pain when using this pillow. One night of positional therapy with a head-positioning pillow

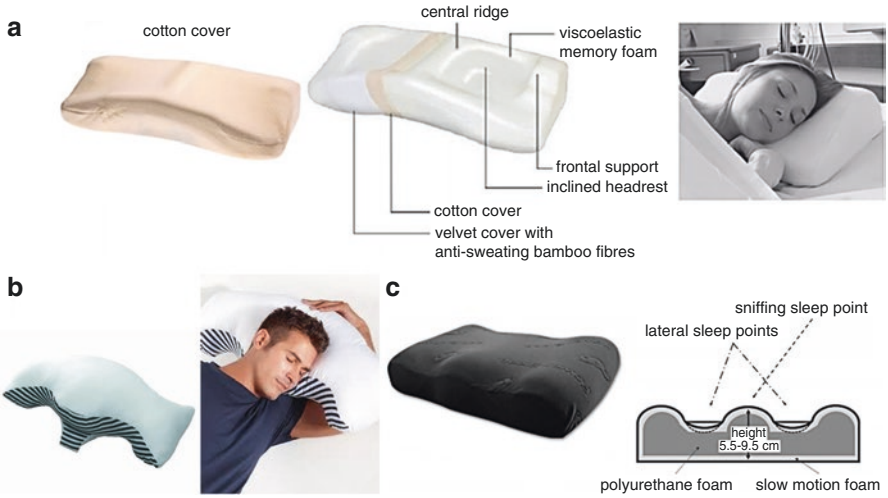

Fig. 6 Different types of sleep positioning pillows for obstructive sleep apnea. (**a**) Visual aspect of the pillow's external cotton cover; observable underlying foam structure beneath illustrated velvet cover; subject's head and neck placement in lateral position; (**b**) pillow that only adjusts the head and neck in lateral decubitus with an arm space; (**c**) polyurethane head positioning pillow. (Modified with permission from Newell et al. [43])

(Fig. 6c) in a sample of post-stroke patients showed a significant reduction of supine position and AHI, having an acceptable adherence following 3 months [45].

In addition, the head positioning pillow for 2 consecutive nights in mild to moderate positional OSA patients showed significant reductions of subjective and objective snoring severity in normal-weight patients, in contrast to overweight patients where only a reduction in subjective snoring was shown [46].

Positional therapy may therefore present as a valuable first-time intervention in positional OSA. Individualized care for positional OSA treatment by determining who will benefit from positional therapy alone or as an adjunct therapy is still needed, as well as guidelines on the theme.

5 Final Words

Material properties of a sleep system should be adjusted to personal needs in an objective way and preferences, for the reason that they are the underlying determinants of most physical ergonomic features (e.g., spine support). For example, obese patients need a firmer mattress in order to prevent the pelvic girdle from dropping too deep into the mattress. Materials therefore must be developed and combined to optimize general sleep system characteristics. Here, we point out a new avenue for research and increase the interest for the physical therapist to be evolved in positioning for better sleep.

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Part VI
Evidence from Basic Science and Its Contribution to Physical Therapy in Sleep Medicine

Basic Research for Sleep Physiotherapy

Monica Levy Andersen and Sergio Tufik

1 Ethics in the Use of Animals for Research

Animal models are used in Science to emulate physiological and pathological conditions present in human beings, which allows the investigation of biological phenomena and diseases. This has led to major scientific and medical advances since the advent of modern science, ultimately helping us save millions of lives and extend life expectancy.

The use of animals in research has long been a controversial subject, given that experimental conditions can be distressful or even painful. This has prompted segments of society to advocate for the more humane treatment of laboratory animals, which has led to changes in legislation in many countries. Modern regulations in respect of the use of laboratory animals follow the basic principles of minimizing unnecessary suffering and guaranteeing animal well-being [1–3].

One of the most influential books published on this subject was The Principles of Humane Experimental Technique by Russel and Burch, which introduced the concept of the 3 R's, Replacement, Reduction, and Refinement, into animal experimentation [4]. Replacement refers to substituting, whenever possible, the use of animals for "insentient material," such as cell cultures or computer models. Reduction refers to minimizing the number of animals used in each experiment. And Refinement refers to improvements in animal welfare and the Reduction of discomfort through measures, such as the use of anesthetics and better housing of animals.

The use of the 3 R's and the principles of minimizing animal suffering have governed the use of animals in research since the twentieth century, and started to become widely adopted in the 1990s. This is an important topic that must be

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constantly considered and updated; and of which scientists, health professionals, and the general population must be aware.

2 Animal Models for Sleep Research

Animals are used in sleep research as analogs for human sleep or sleep disorders. The use of animals in research presents practical and scientific advantages as they are easily manageable, which makes for better control of experimental conditions and helps avoid experimental biases. Further, the use of standardized species across experiments and in multiple laboratories ensures the replicability of results.

The use of animals, however, also presents obstacles, since there are no species that perfectly emulate the physiology of human sleep. For this reason, animal models are treated as mere approximations and do not fully replace the use of humans in sleep research. In practice, scientists choose very carefully which animal model to use depending on the phenomenon under investigation. In some cases, a species or strain is chosen for its biology, while in other settings scientists use clever experimental designs to mimic human sleep disorders that would otherwise not be present in animals.

Human sleep presents typical events that must be at least partially represented by a model for it to be useful in research. These events include the release of hormones, the occurrence of sleep phases, specific electroencephalographical (EEG) patterns, and other phenomena [5]. The animals most commonly used in sleep science are rats, mice, cats, and dogs [6, 7], all of which carry some level of similarity to human sleep.

A defining trait in human sleep is the intercalation of rapid eye movement (REM) sleep with non-REM (NREM) sleep, two different phases that can be detected by EEG. REM sleep presents desynchronized, low-amplitude EEG wave patterns that resemble those observed when an individual is awake, which also gives it the name "paradoxical sleep." Human NREM sleep presents synchronized, high-amplitude wave patterns and can be subdivided into stages 1, 2, and 3, each with progressively deeper sleep and slower waves.

In 1970, it was found that rats show sleep stages analogous to those found in humans [8], which eventually made them the most widely used animal model in sleep science. The most commonly used species of rat are *R. rattus* (the house rat) and *Rattus norvegicus albinus* (an albino variation of the brown rat bred specifically for scientific purposes). Unlike humans, rats sleep in a polyphasic manner, that is, they sleep multiple times a day in short sections of about 12 minutes each, averaging a total of 13 hours of sleep per day [6, 9]. Rats are nocturnal animals, meaning they explore, eat, interact, reproduce, and carry out other activities mostly during the dark phase of the 24-hour cycle.

As stated previously, the architecture of sleep in rats is remarkably similar to that of humans. Rats alternate between REM and NREM sleep, and their NREM sleep is subdivided into three stages, SS_I, SS_{II}, and SS_{III}, which, like humans, present increasingly slow and synchronous wave patterns as sleep gets deeper [8]. The order

of sleep stages in rats is not constant, meaning that, after any given state, either the previous one may resume, or a new stage may begin.

Another valuable model species is the mouse (*M. musculus*). This species has a long history of use in science [6, 10], and there are currently over 11,000 strains being used in research [11]. Sleep varies between strains, but, on average, mice sleep for between 11 and 15 hours every day. Similar to rats, mice have polyphasic sleep, presenting sleep bouts of 2–4 minutes each. Characteristics such as the ratio between light and dark phase sleep, the percentage of R and NREM stages, the presence or absence of sleep disorders, and others vary between strains, which must be considered when choosing a strain for research.

Cats (*F. catus*) and dogs (*C. familiaris*) are also prominent models utilized in sleep research. Cats were used in the first study to ever describe REM sleep in a non-human animal [12] and have been used to this day to study neuroanatomy, physiology, and mechanisms of REM sleep. Dogs have been utilized since the nineteenth century in sleep research [13] and are currently used to model sleep disorders. Narcolepsy naturally occurs in many domestic animals, including cats, dogs, and mice, which led to the discovery of a mutation in the orexin/hypocretin receptor II gene as one of the main causes of the disease. Interestingly, this discovery was made independently by two different groups, one studying dogs and one studying mice, both of which published their results in August 1999 [14, 15].

Restless leg syndrome (RLS) studies point to two probable underlying causes in patients: abnormalities in the dopaminergic system and iron deficiency in the cerebrospinal fluid [7], and animals with these abnormalities are used as models for RLS. Rats with induced depletion of the diencephalic A11 dopaminergic nuclei showed improvements after treatment consistent with clinical results in humans, although subjective measures, such as the sensation of discomfort in the legs, cannot be evaluated [16]. Mice with iron deficiency showed increases in wake time prior to light-phase onset, which, since mice are nocturnal animals, corresponded to the time of day when RLS is most severe in humans, pointing to iron deficiency as a possible model for RLS in mice [17].

Obstructive sleep apnea (OSA) is the most common sleep disorder in humans, affecting nearly 1/3 of the adult population [18]. For this reason, many animal models have been developed in an attempt to study and combat it. English bulldogs are suitable for this due to their upper airway anatomy, which hinders airflow to the lungs during their sleep, mimicking many of the symptoms observed in humans [19]. A few other species naturally present OSA symptoms, including minipigs and a few strains of rats and mice [20].

3 Sleep Interventions

Sleep interventions provide means for the development of models for sleep disorders in animals that do not present them naturally. Interventions usually come in the form of mechanisms that interfere with sleep, or bioactive molecules that influence

the molecular pathways of sleep. Sleep deprivation is a frequently used intervention that allows the measurement of the consequences of the lack of sleep in animals. Experimental designs usually mimic patterns of sleep deprivation present in humans, such as insomnia or chronic sleep restriction, and measure effects linked to the lack of sleep, including worsening of attention, reflexes, and pain [21, 22].

To induce sleep deprivation, a technique called "gentle handling" is often employed, in which a technician actively keeps an animal awake for a set period of time. When the animal shows signs of sleep onset, the researcher may introduce or remove objects from the cage, generate acoustic stimuli, or even touch the animal to keep it awake. This technique must be performed in such a way that avoids acoustic or physical pain while generating the minimum amount of stress possible, as it is known that stress hormones, such as corticosterone and adrenocorticotropic hormone, interfere with sleep patterns and may bias the experimental [23].

The correct performance of gentle handling depends heavily on the experience of each technician, which makes it difficult to standardize and replicate. To avoid this and to keep stress levels to a minimum, a number of devices have been developed that completely automate the process, thus eliminating the need for a technician. These mechanisms detect when an animal is falling asleep via computerized systems, and gently move the cage in order to wake them up [24, 25]. Alternatively, when the experimental design requires sleep fragmentation without complete sleep deprivation, a specialized cage coupled with an automated sweeping bar can be employed. The bar moves across the cage floor at a constant speed, touching the animals whenever they are asleep, thus waking them up for a brief period of time at regular intervals [26].

In some instances, the experimental design requires deprivation of the R stage exclusively, in which case the most popular strategy is the "platform method" [27]. In this method, the animals are placed in a tank containing small platforms (usually five) surrounded by water for a set period. When REM sleep initiates, the accompanying muscular atonia makes them fall into the water, thus waking them up. This method has been improved over the years to reduce the stress caused by REM sleep deprivation. A modern variation is the multiple platform method [28], which uses a greater number of platforms (usually ten), allowing the animals to swim between them during the experiment.

It is possible to mimic OSA symptoms in models that do not present them naturally by inducing an anesthetic state, leptin hormone deficiency, or obesity [20]. Another common strategy is to induce the symptoms mechanically. OSA patients suffer from collapses of the upper airway during sleep, which usually causes snoring and cessation of airflow into the lungs. This results in a periodic lack of oxygen in the blood and tissues in a process known as "intermittent hypoxia," which results in short and frequent awakenings during the night that is not perceived by the patient but induces sleep fragmentation [18].

It is possible to induce intermittent hypoxia in animals with the use of a "hypoxia chamber." This device consists of a sealed chamber that does not allow gas exchange with the exterior. Gas cylinders are attached to a computerized system that discharges pre-set concentrations of oxygen, carbon dioxide, and nitrogen at regular

intervals. By alternating between atmospheric and infra-atmospheric saturation levels of oxygen, this system induces intermittent hypoxia in the animals placed inside the chamber. This condition simulates, and allows assessment of, the gas imbalances present in naturally occurring OSA, including oxygen desaturation and hypercapnia [7].

An important aspect of sleep interventions is the ability to influence the circadian rhythm. Sleep is mainly regulated by two mechanisms: the endogenous biological clock, which consists of a set of genes expressed at regular intervals throughout the light-dark cycle that synchronize most bodily functions, and by environmental cues captured by sensorial organs. Light plays an important role in modulating both the circadian clock and sleep [29]. In the laboratory, scientists use light to artificially influence sleep for experimental purposes. In this setting, lighting variables, such as spectral composition, intensity, and the duration of the photoperiod are carefully controlled to produce effects in the studied animals. The complete absence of light removes the environment as a modulator of the circadian rhythm, leaving only the biological clock as a regulator of physiological functions, a process known as "free-running."

4 Pharmaceutical Interventions

Drugs that modulate particular neurophysiological states can be employed to induce or alter sleep. Animal models have been widely used to study and discover these drugs, and, conversely, these drugs have been used to study the sleep process in animals and humans.

An important class of drugs consists of hypnotics, molecules capable of inducing sleep that is usually employed to treat insomnia. Benzodiazepines and Z-drugs are examples of hypnotics that target the GABAergic system of receptors, as GABA (gamma-aminobutyric acid) is a major inhibitory neurotransmitter in mammals [30], although other molecules may be used to modulate different receptor families. The use of hypnotics in sleep science and for treatment must be carefully considered, as each pharmaceutical may influence different stages of sleep, and many are involved with unrelated neuronal circuits [30].

Stimulant drugs have the opposite effect, inducing alertness and arousal, and delaying the onset of sleep. Examples include modafinil and dextroamphetamine, but the most common stimulant molecule consumed by humans is caffeine [31]. This drug acts by inhibiting the adenosine receptors associated with the accumulation of sleepiness after extended periods of the vigil, thus prolonging wakefulness. Stimulants are widely used to instill alertness and enhance attention, but they may have other uses, such as in the treatment for attention deficit and hyperactivity disorder [31].

There are classes of molecules capable of modulating the circadian rhythm, which is known as chronobiotics [32]. These molecules act by delaying or advancing the circadian clock, which, in turn, affects the onset of sleep. The most

well-known chronobiotic is the hormone melatonin, which is closely involved with the initial phases of sleep. It is possible to induce artificial circadian rhythms in animals by regularly administering melatonin while simultaneously controlling lighting conditions. This combination is used to model disorders specific to the circadian rhythm in animals, e.g., advanced or delayed sleep-wake phase disorders [33].

5 Final Words

Animal models are extremely valuable tools in the study of sleep. The similarities between animal sleep, particularly in mammals, such as rats, mice, cats, and dogs, and human sleep make it possible to employ complex experimental designs in sleep science and extrapolate the results to humans. By intervening or modulating animal sleep with mechanical devices or drugs, scientists are able to study sleep disorders to an extent that would not be possible otherwise, thereby helping treat millions of patients worldwide.

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Sleep and Musculoskeletal System

Helton de Sá Souza, Ana Claudia Pelissari Kravchychyn, and Sara Quaglia de Campos Giampá

What is the relationship between sleep and skeletal muscle? Before answering this question, it is important to note that understanding sleep alone is not an easy task. Sleep is a physiological phenomenon that remains a scientific enigma. However, it is recognized due to its importance and its impacts on health when it becomes inadequate [1]. Adequate sleep functions are attributed to health; on the other hand, the sleep debt generates significant negative organic changes, with emphasis on metabolic, hormonal, immunological, and cognitive functions. Collectively these changes can disrupt skeletal muscle homeostasis and compromise the normal functioning of this tissue.

There is a "popular knowledge" that skeletal muscle "grows" and recovers during sleep. Nevertheless, many questions remain without answers about the role of sleep in muscle recovery, as well as its influence on muscle physiology. In mid-2011, studies on the subject were published and gained notoriety by demonstrating the possible mechanisms underlying the sleep-skeletal muscle binomial [2]. However, there are still gaps to be filled. This chapter aims to discuss the complex and bidirectional relationship between sleep and skeletal muscle.

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1 Skeletal Muscle

Skeletal muscle is one of the most dynamic and plastic tissues of the human body; representing about 40% of the total body weight, they can store between 50 and 75% of all body proteins and are responsible for 30–50% of the whole body's protein "turnover" (balance *between* synthesis and degradation). Muscles are composed mainly of water (75%), protein (20%), and other substances (5%) (i.e., inorganic salts, minerals, fats, and carbohydrates) [3]. There are more than 600 muscles distributed throughout the human body, and these tissues have several functions, including mechanical, structural, metabolic, and endocrine [3, 4].

In this context, skeletal muscles have been seen as much more than effectors of muscle actions or structure for skeletal support. The literature is concise in showing that skeletal muscles are able to synthesize, store, and secrete substances (myokines) that can signal the muscle itself (autocrine function), neighboring tissues (paracrine function), or modulate the activity of various other body systems (endocrine function). In addition to these functions, it is known that skeletal muscles contribute to weight loss, together with the immune system activity and endocrine function, highlighted in recent years [5].

Therefore, understanding the factors that can influence skeletal muscle tissue, such as sleep or its damage, becomes essential to develop effective intervention strategies to promote and maintain population health.

2 Sleep and Skeletal Muscle: What Is the Relationship?

In 2005, Siegel proposed that sleep is a highly complex, active, and dynamic behavior that modulates cognitive activity, mood, and immune, endocrine, cardiovascular, and neuromuscular systems [6]. The main theories related to sleep functions are allocated into three categories: energy metabolism; related to modulation of the immune system and inflammatory processes, and, finally, the key role of sleep in the process of physical restoration [6, 7].

These categories of sleep functions are directly related to the physiology of skeletal muscle tissue, making it possible to establish the relationship between them. Furthermore, sleep seems to modulate factors related to memory and mood. Thus, while REM sleep is often associated with processes of maintaining cognitive aspects and mood, NREM sleep, especially slow-wave sleep (SWS or NREM N3), has been pointed out as one of the main responsible for modulating the immune system, energy conservation, and physical restoration [7].

Precisely to physical restoration, it is known that N3 stage plays an important role in the modulation of hormone secretion that has fundamental functions for skeletal muscle tissue, such as insulin and growth hormone (GH) [8, 9]. In contrast, global impairments in the sleep pattern of young adults were associated with a decrease in the secretion of testosterone, GH, insulin, and an increase in cortisol

levels, which represents catabolic signals, [10, 11] as well as inflammatory markers, such as Interleukin 6 (IL-6), Interleukin 1 (IL-1), and tumor necrosis factor-alpha (TNF-α), which can also negatively influence the integrity of skeletal muscle tissue [10, 12–17].

The first study that proposed the pathway by which sleep (adequate or inadequate) could influence skeletal muscle was done in 2011 [2]. Later, the same group demonstrated in animal models that this hypothesis could, in fact, be true. Therefore, it was observed that rats deprived of sleep for 96 hours presented reduction of muscle volume with a concomitant increase in corticosterone concentrations and testosterone reduction [18]. These initial results stimulated the development of a series of other studies that proposed to investigate intervention strategies that could minimize the deleterious effects of sleep debt on skeletal muscle tissue and biochemical pathways by which this phenomenon could be explained. To understand these paths, it is necessary, first, to remember how the protein turnover occurs.

2.1 Muscle Metabolism

In general, regardless of the type of stimulus, skeletal muscle tissue morphological adaptations are pervaded by changes in protein turnover. Strictly speaking, when there are higher signals of synthesis than of protein degradation, there are an accumulation of muscle mass (hypertrophy/hyperplasia), while when there are higher rates of protein degradation there is a reduction in the amount of this tissue (muscular atrophy).

As previously mentioned, protein turnover is regulated by different factors, among which are anabolic hormones testosterone, GH, and insulin-like growth factor 1 (IGF-1) [19].

In this perspective, it is necessary to consider that skeletal muscle tissue integrity is associated with the nutritional status of the person, i.e., in situations where there is prolonged fasting or poor distribution of macronutrients, the reduction of muscle mass can occur. On the other hand, when the diet is adjusted, especially related to protein supply, it favors stimulation of protein synthesis. Moreover, active lifestyle maintenance is also associated with increased or maintenance of function and amount of muscle mass.

The main intracellular mechanism involved in these processes is related to a cascade of biochemical signals that modulate the activity of the phosphatidylinositol-3-kinase pathway/protein kinase B/rapamycin target (PI3K/AKT/mTOR pathway) as shown in Fig. 1. In general, insulin and IGF-1, for example, promote the initial stimulation of this pathway. Testosterone and some intermediaries produced by exercise can directly activate AKT [21]. Some nutrients such as amino acids, for example, can directly activate mTOR, the main controller of protein synthesis. mTOR has the function of stimulating the assembly of the ribosomal complex through the 70 kilodaltons (p70s6k) ribosomal protein, incite protein transcription through 4E-BP1 activity, and the new proteins translation [21].

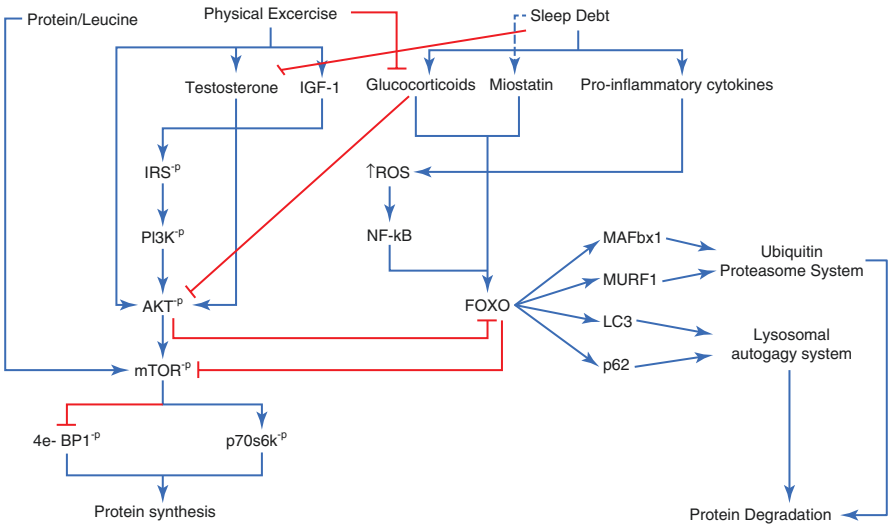

Fig. 1 Pathways for protein synthesis and degradation of skeletal muscles. Sleep deprivation/restriction causes a catabolic state, characterized mainly by the reduction of anabolic hormones, an increase of glucocorticoids, and pro-inflammatory cytokines, which favor the activation of FOXO protein and suppression of mTOR, stimulating the ubiquitin-system proteasome and/or lysosomal autophagy, hence protein degradation. Resistance exercise, on the other hand, promotes the creation of an anabolic environment through the increase of hormones such as GH, IGF-1, and testosterone, which activate the PI3K/Akt/mTOR pathway, in parallel with the inhibition of myostatin, increasing protein synthesis. The hyperactivity of the PI3K/Akt/mTOR pathway, per se, leads to higher phosphorylation of the FOXO protein making it inactive and, consequently, inhibiting the ubiquitin-proteasome system and lysosomal autophagy, thus protein degradation. In addition, the mechanical stimulus of resistance exercise, through the AKT/mTOR pathway, followed by activation of p70S6K protein and inhibition of 4E-BP1 protein, leads to increased protein synthesis. This integrated sequence of events caused by resistance exercise makes it a potential non-pharmacological intervention for skeletal muscle health in the face to stress of sleep debt. Leucine activates mTOR protein, which stimulates phosphorylation of p70S6K and 4EBP-1 proteins. The latter – when phosphorylated – enables the activation of eIF4G, which is also under mTOR control. Together, these processes lead to increased muscle protein synthesis. IGF-1 insulin-like growth factor-1, GH growth hormone, PI3K phosphatidylinositol 3 kinases, Akt kinase protein B, mTOR rapamycin target in mammals, p70S6K 70 kDa ribosomal protein S6 kinase, 4E-BP1 eukaryotic initiation factor binding protein 4E-1, FOXO forkhead box O, MAFbx Muscle atrophy F-box, MuRF-1 Muscle RING-finger protein 1. ↓ activation; ⊥ inhibition. (Adapted with permission from Mônico-Neto et al. [20])

In contrast, the AKT inhibition, whether by cortisol, pro-inflammatory cytokines, or proteins that control cell growth (myostatin), will paralyze the signs of protein synthesis and stimulate the degradation of muscle proteins. This process has signaling mediated by the transcription factor Forkhead Box O (FOXO), which will increase the degradation of structural muscle proteins (myosin, actin, Titin, tropomyosin) through the ubiquitin-proteasome system, and the degradation of functional proteins (ribosome, mitochondria) by the autophagy-lysosomal system [12].

In view of all the mechanisms and regulations that involve protein turnover, it is postulated that the sleep debt, through its influence on molecules, hormones, and cytokines, could influence this process, favoring the activity of protein degradation pathways and harming the activity of protein synthesis pathways.

3 Sleep Debt and Skeletal Muscle

Inadequate sleep may occur as a result of sleep deprivation (i.e., a sustained state of wakefulness and absence of sleep), or sleep restriction (i.e., chronically reduced sleep duration). Both conditions represent stress to the organism, with a strong influence on the breakdown of homeostasis. This situation increases the sympathetic autonomic nervous system and the neuroendocrine axes activation – hypothalamic-pituitary-adrenal axis (HPA) [18, 22].

The activation of both stress response systems favors a catabolic scenario, characterized by the reduction of anabolic hormone [23, 24]. Studies involving animal models exhibited that 96 hours of sleep deprivation reduced IGF-1 and testosterone concentrations and increased catecholamine and corticosterone concentrations, thus contributing to the installation and/or maintenance of the catabolic state [25]. All this hormonal panorama observed in animal models submitted to acute sleep deprivation protocols is also verified in chronic conditions of sleep restriction. In animal models, 6 hours of sleep restriction during 21 days also presented high levels of corticosterone and catecholamines, denoting catabolic status even in the long term [26].

Inadequate sleep is a determining condition for the imbalance of the anabolism/catabolism ratio, which may generate consequences for skeletal muscle tissue regeneration [18, 27, 28].

Although there is strong evidence demonstrating the deleterious effects of sleep deprivation on skeletal muscle of animal models, specifically rats, few studies analyzed this relationship in humans. Initial data demonstrate that only one night of partial sleep deprivation impairs the recovery of cyclists after a single exercise session [29, 30], but the possible mechanisms for this phenomenon were not explored. In this context, Dáttilo et al. (2020) investigated whether sleep deprivation after eccentric exercise-induced muscle injury could be modified the hormone and cytokine profiles in humans [31].

A randomized crossover clinical trial was performed by Dáttilo et al. (2020) with 10 men. Participants underwent the protocol of unilateral eccentric exercise-induced muscle damage, which comprised 240 eccentric contractions of the knee extensor muscles using an isokinetic dynamometer, having isometric muscle voluntary contraction tests and blood collected serially throughout the protocol. The protocol was tested under two different conditions. In one condition, it was performed after 48 hours of total sleep deprivation followed by 12 hours of normal sleep; in the other, it was performed followed by 3 nights of regular sleep.

Muscle voluntary contraction and serum creatine kinase levels (a diagnostic marker of skeletal muscle injury) increased equally in both conditions. Regarding hormones and cytokines, no difference was detected in testosterone levels between conditions, but IGF-1, cortisol, total cortisol/testosterone ratio, and IL-6 increased in total sleep deprivation condition. Thus, it was postulated that total sleep deprivation after eccentric exercise-induced muscle damage did not delay the recovery of muscle strength, but modifies inflammatory and hormonal responses [31].

Taken this information together, it is speculated about possible strategies that could minimize and/or even reverse the deleterious effects of sleep debt in skeletal muscle tissue. However, what are these strategies?

3.1 Sleep Debt and Skeletal Muscle: The Role of Physical Exercise and Protein Supplementation

Physical exercise and protein supplementation are non-pharmacological strategies that have gained notoriety in the field of skeletal muscle tissue health in sleep debt conditions [32, 33].

In the context of physical exercise, more specifically to the resistance model, it is the main choice to be adopted when aiming at skeletal muscle health. The mechanical load, hormonal, metabolic changes, and several intracellular events resulting from the practice of resistance exercise contribute to the improvement of strength and increase muscle protein synthesis [34].

Resistance exercise generates acute hormonal responses, especially the increase of IGF-1 levels, which plays an important role in the remodeling of skeletal muscle tissue [35]. The anabolic effects of IGF-1 involve activation of the PI3K/AKT/mTOR pathway and stimulation for proliferation, survival and differentiation of satellite cells [36], which collectively favor protein synthesis, resulting in muscle growth [37]. In addition, the mechanical deformation of muscle fibers (contraction and/or stretching) is already able to stimulate the AKT/mTOR pathway, independently of hormonal changes and immune/inflammatory responses [38].

In parallel, molecular pathways involved with protein degradation and consequent muscular atrophy, such as the ubiquitin-proteasome system, present a reduction of their activity by resistance exercise stimulating. This occurs because of the increased activity of the PI3K/ AKT/ mTOR pathway, which promotes higher phosphorylation of the FOXO, becoming inactive [13, 39].

Against this scenario, some researchers hypothesized [40] these physiological adaptations caused by resistance exercise could minimize or even delete the harmful effects of sleep debt on skeletal muscle (Fig. 1). In an experimental investigation to test this hypothesis, 50 adult male rats were allocated into 5 groups: (1) control group; (2) resistance training group; (3) the SHAM group; (4) 96-hour sleep deprivation group (PSP96); and (5) resistance training group subsequently subjected to 96-hour sleep deprivation (TR/PSP96). The resistance training protocol adopted

was of high intensity, with a duration of 8 weeks, performed 5x/week. Resistance training performed prior to sleep deprivation exerted a protective effect on skeletal muscle, minimizing the reduction of IGF-1 and testosterone levels, increasing the expression of proteins involved in protein synthesis (mTOR and p70S6K), and attenuating those involved in degradation pathways [33, 40].

Another potential intervention to minimize sleep deprivation-induced muscle atrophy was amino acid supplementation, more specifically leucine supplementation. Leucine is an essential branched-chain amino acid known to exert anabolic effects through its ability to stimulate protein synthesis and inhibit protein degradation [32]. The mechanisms involved include activation of the mTOR direct signaling pathway and, consequently, phosphorylation of p70S6K and 4E-BP1 proteins, resulting in increased protein synthesis (Fig. 1) [27, 32, 41, 42].

In conditions that lead to muscular atrophy, such as cancer-induced cachexia [43], aging [44], and limb immobilization [27], leucine supplementation has promoted the maintenance of muscle trophism. But what about the sleep debt condition? In this way, De Sá Souza et al. submitted rats to 7 consecutive days of leucine supplementation, whose last 4 days coincided with the protocol of sleep deprivation for 96 hours. The daily dose of leucine supplementation used was 1.35 g/kg of body mass of each animal. At the end of the study, the authors came across an interesting finding. Muscle atrophy caused by sleep deprivation preferentially affected muscles composed of muscle fibers of glycolytic predominance (type II), compared to muscles composed of muscle fibers of oxidative predominance (type I). In relation to leucine supplementation, it was able to attenuate part of the observed muscular atrophy, but only in the type IIb muscle fibers [32].

Although there is no certainty, there is evidence pointing out to humans experiencing the same phenomena supporting these hypotheses [18, 33, 45].

4 Sleep and Skeletal Muscle in the Aging Process and Its Interface with Sarcopenia

The relationship between sleep and skeletal muscle has been explored in the context of adequate sleep and, mainly, in specific conditions of inadequate sleep. Nevertheless, how does this relationship happen in less acute conditions or during health-disease processes?

First, it is necessary to understand that the aging process is a *continuum* and is associated with quantitative and qualitative changes of several body systems. Among these changes, it is possible to mention sleep (see chapter "Sleep and Aging") and skeletal muscle tissue itself. Specifically, on skeletal muscle, some older people (about 10%) may experience an important change until they develop sarcopenia.

Sarcopenia is a disease characterized by the reduction or deterioration of muscle mass and function, commonly related to the aging process [46]. Its pathophysiology

is multifactorial and comprises genetic, neuroendocrine, inflammatory factors, nutritional status, and level of physical activity [47, 48].

There exists a scenario in which skeletal muscle is influenced by healthy aging process, added with the changes in sleep pattern across aging [49]. In this sense, the aging process, similar to the condition of sleep debt, is recognized by the imbalance of the anabolism/catabolism relationship. Anabolic hormone pathways deteriorate with advancing age [50, 51] while catabolic pathways are enhanced. Hypercortisolemia is related to muscle catabolism in aging, muscle weakness, and weight loss [52].

In older people, there is a "U" form association between the prevalence of sarcopenia and sleep duration. Elderly individuals with short or long sleep duration have a higher prevalence of sarcopenia compared to those with normal sleep duration [47].

Among the most plausible pathophysiological hypotheses that relate sarcopenia to inadequate sleep, hormonal dysregulation and the pro-inflammatory scenario play an imperative role. The first refers to the increase in cortisol levels in contrast to the decrease in IGF-1 and testosterone levels; creating a catabolic environment, which promotes muscle degradation and thus the loss of muscle mass [53]. The latter concerns the increase of pro-inflammatory cytokines such as C-reactive protein, which appears to be involved in the process of muscle atrophy [54].

In this context, the practice of physical exercise combined with a good diet gains notoriety, by promoting benefits to muscle health, playing an important role in the prevention and/or attenuation of sarcopenia, as well as improving the quality of sleep.

5 Final Words

Adequate sleep plays a key role in maintaining and recovering the physiology of skeletal muscle. Maintaining the integrity of skeletal muscle depends on the balance between protein synthesis and degradation, both processes sensitive to several factors, including sleep, adequate nutrition, and physical exercise. In the same way, the evidence points out that the skeletal muscle healthy seems to positively influence sleep quality.

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Part VII
Sleep Assessment for Physical Therapy Clinical Practice

Subjective Assessment of Sleep

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The intention of sleep assessment is to provide sufficient and accurate data to determine treatment. Accurate sleep assessment is the first step in effective sleep management by the physiotherapist. Information on the nature of sleep disturbance, physiologic, behavioral, and emotional aspects, as previous experiences with sleep, are crucial for the beginning of the treatment and also for managing treatment. Valid and reliable measurements of sleep are needed to identify patients who require intervention and to evaluate the effectiveness of an intervention.

A detailed anamnesis includes an assessment of numerous variables that may interfere with sleep and may play crucial roles in sleep management. Patient characteristics such as age, gender, ethnicity, profession, and marital status should never be missed in the assessment. It is interesting to have height, weight (to calculate body

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mass index, BMI), and measures of the neck and abdominal circumference. Listed below are samples of key questions regarding sleep-related issues and disorders:

- Sleep routine: time of going to bed and waking up
- Quality of sleep: nonrestorative or unrefreshing?
- Difficulties falling asleep, staying awake during the night
- Number of hours that sleep refreshes vs. number of hours that really sleeps
- Adequate opportunity to sleep
- Somnolence during the day: tendency to nap easily during the day?
- How and when sleep disturbance/complaint started?
- Fragmented seep? How many awakenings?
- Tendency to snort or choke during sleep
- Tendency to stop breathing during sleep
- Witnessed apnea, lack of breathing or choking
- Grind teeth during sleep?
- Wake up during the night due to which reason?
- In which position do you sleep?
- Tendency to go to the bathroom/toilette during the night? How many times? Nocturia?
- Do you move a lot during the night?
- Environmental questions: How is your bedroom? Cozy? Warm? Blackout curtains? Loud disruptive snoring?
- Medications (that can interfere within sleep)
- History of appearing to "act out one's dreams" such as punching or flailing arms in the air, shouting, or screaming
- Tendency to experience unpleasant, nervous, creepy-crawly sensations in the legs/feet, primarily at night or when sitting at rest, an urge to move the legs, and the tendency for the unpleasant sensations to temporarily be relieved by moving the legs or walking
- A propensity for the legs to periodically jerk during sleep
- Propensity to experience cramps prior to or during sleep
- Tendency to struggle falling asleep before 1 h and 3 h (AM), and then tendency to awaken after 8 h in the morning
- Propensity to struggle to maintain wakefulness prior to 8 h in the evening, and then tendency to awaken earlier than 6 h in the morning

If in the anamnesis the physiotherapist suspects of any symptom or disease, questionnaires to evaluate them should be included, aiming to help within the clinical picture, as the diagnosis is performed by the sleep specialized physician and to monitor treatment.

Some scales are helpful for tracking a patient's progress. Some sleep diseases might need objective examinations prescribed by the physician or need the video recording of the sleep (e.g., REM sleep behavior disorder or sleep bruxism) to get to a defined diagnosis. Depending on the questionnaire, it is translated, validated, and adapted into many languages, including Brazilian Portuguese, English, Portuguese, French, German, Italian, Japanese, Korean, Spanish, Thai, and Turkish. Please do check the status of available translations within the preferred language.

Table 1 Questionnaires used to assess sleep quality, sleepiness, insomnia, risk for apnea, narcolepsy, restless leg syndrome, pain, and circadian preference

Condition	Questionnaire	Characteristics	Purpose + Score + Cut off values
Quality of sleep	Pittsburgh Sleep Quality Index Buysse et al. 1989 [1] www.sleep.pitt.edu/instruments	Evaluates last 1-month 7 subscales: subjective quality of sleep, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction 19 questions, grouped into 10 questions to answer from 0 (easy) to 3 (severe difficulty) on Likert scale	Assessment of overall sleep quality discrimination between good and poor sleepers assessment of multiple sleep disturbance Overall score: from 0 to 21 points Scores >5 indicate poor sleep, <5 good sleep
	Jenkins Sleep Evaluation Jenkins et al., 1988 [2]	Evaluates last 1-month 4 items: difficulty to fall asleep, wake up at night, difficult to stay asleep and wake up exhausted in the morning instead of sleeping as usual Likert scale from 0 to 5, where 0 is never, 1 is 1–3 days, 2 is 4–7 days, 3 is 8–14 days, 4 is 15–21 days, and 5 is 22–28 days 3–4 question	Sleep disturbance scores Overall score: 0–20 points Score from 1–11 defines a little of sleep deprivation Score ≥ 12 identifies a high frequency of sleep deprivation
	Sleep Scale from Medical Outcomes Study https://www.rand.org/health-care/surveys_tools/mos/sleep-scale.html [3]	Evaluates last 1-month 6 subscales: initiation (time to fall asleep), quantity (hours of sleep each night), maintenance, respiratory problems, perceived adequacy, somnolence (the last 4 items reported using a 6-item Likert scale ranging from "All of the time" to "None of the time") 12 items	Overall score: 12–71 points No formal cutoff scores are provided
Sleepiness	Epworth Sleepiness Scale Johns, 1991 [4] https://epworthsleepinessscale.com	Evaluates last 1-month respondents are asked to rate, on a 4-point scale (0–3), their usual chances of dozing off or falling asleep while engaged in 8 different activities: sitting and reading, watching TV, sitting inactive in a public place, as a passenger in a car for an hour of travel, sitting and talking with somebody, lying down and relaxing in the evening, sitting after having lunch without alcohol or in a car during a traffic jam item-scores are intended to be integers (0–3)	Excessive daytime sleepiness Overall score: 0–24 points scores 0–5 lower normal daytime sleepiness 6–10 higher normal daytime sleepiness 11–12 mild excessive daytime sleepiness 13–15 moderate excessive daytime sleepiness 16–24 severe excessive daytime sleepiness
	Stanford Sleepiness Scale Hoddes et al. 1972 [5]	7-point Likert-type scale has descriptors ranging from "feeling active, vital alert, or wide awake" (score = 1) to "no longer fighting sleep, sleep onset soon and having dream-like thoughts" 1. Single question	Quantify progressive steps in sleepiness at a certain point in timeOverall score: 7
	Karolinska Sleepiness Scale Åkerstedt & Gillberg 1990 [6]	The particular time during the day, a measure of situational sleepiness 9-point scale1 = extremely alert, 3 = alert, 5 = neither alert nor sleepy, 7 = sleepy – but no difficulty remaining awake, and 9 = extremely sleepy – fighting sleep	

(continued)

Table 1 (continued)

Condition	Questionnaire	Characteristics	Purpose + Score + Cut off values
Insomnia	Insomnia Severity Index Bastien et al., 2001 [7]	Evaluates last 1-month measures: severity of sleep-onset, sleep maintenance, early morning awakening problems, satisfaction with current sleep, interference with daily functioning, impairment attributed to the sleep problem, level of distress caused by a sleep problem 7 questions Likert scale of 5 points: 0–4 Recently, it has been described in three sub-domains: nocturnal sleep difficulties, the sum of questions 1 + 2 + 3, the impact of insomnia during the day, the sum of questions 5 + 6 + 7, and dissatisfaction sleep with the sum of questions 1 + 4 + 7	Cognitive-behavioral (b) Insomnia screening (c) Assessment of treatment response Overall score: 0–28 Scores 0–7: no clinically significant insomnia; 8–14: sub-threshold insomnia; 15–21: moderate insomnia; and 22–28: severe insomnia
	Athens Insomnia Scale Soldatos et al., 1999 [8]	Evaluates last 1-month The 8-item questionnaire evaluates sleep onset, night and early-morning waking, sleep time, sleep quality, frequency and duration of complaints, distress caused by the experience of insomnia, and interference with daily functioning Each question could be rated from 0 (no problem) to 3 (very serious problem), leaving two intermediate scores	The severity of insomnia using diagnostic criteria set forth by the International Classification of Diseases (ICD-10) Overall score: 0–24 Cutoff >6 define the presence of insomnia
	Insomnia Symptom Questionnaire Okun et al., 2009 [9]	Weeks, months, or years 13 questions Questions 1–5 are multiple choices on an ordinal scale to assess the presence, frequency, and/or severity of the complaint For example, the "During the past month have you had difficulty falling asleep?" item includes choices ranging from 0 = never to 5 = always (5–7 days per week), and a follow-up contingency question asks about the problem's duration Questions 6–13 assess the extent to which the individual's endorsed sleep complaints affect daytime activities, with response choices ranging from 0 = not at all to 4 = extremely	Designed to identify insomnia

Obstructive sleep apnea	STOP-Bang Chung et al. 2012 [10] http://www.stopbang.ca/osa/screening.php	Easy-to-use 8 yes" or "no" questions + anthropometric measures such as BMI, age, neck circumference, and male sex	Screen for symptoms of obstructive sleep apnea Cutoff ≥3 define having a risk for OSA
	Berlin Netzer et al. 1999 [11] www.sleepapnea.org/wp-content/uploads/2017/02/berlin-questionn	Focuses on 3 categories of apnea signs and symptoms: snoring, daytime sleepiness, and obesity/high blood pressure 11 questions	To identify individuals at high risk for sleep apnea 3 categories related to the risk of having sleep apnea Classification: High risk (≥2 positive answers) or low risk (<2 positive answers)
	NoSAS Score Marti-Soler et al., 2016 [12]	5 items: neck circumference, BMI, snoring, age >55 years, and male sex	Prescreening for sleep-disordered breathing Maximum score = 19 a score of ≥8 indicates an increased probability of sleep-disordered breathing
Narcolepsy	Narcolepsy Severity Scale Dauvilliers et al., 2017 [13]	15 questions to evaluate the frequency and severity of sleepiness, cataplexy, hypnagogic hallucinations, paralysis of sleep, and fragmentation of sleep	Maximum total score = 57 Higher total scores indicate greater severity of narcolepsy at the time of the evaluation
Restless legs syndrome	IRLSSG Restless Legs Syndrome Rating Scale for Severity The International Restless Legs Syndrome Study Group, 2002 [14] http://irlssg.org/RLS-Ratings	Evaluates last week 10 item scale: 5 addressing symptom frequency and intensity +5 addressing the impact of them Likert scale from 0–4, 1 is	Classifies the intensity of the symptoms Overall score: 0–40 points Scores: 0–10 mild; 11–20, moderate; 21–30, severe; and 31–40 very severe
	Johns Hopkins Restless Legs Severity Scale Allen et al., 2001 [15]	Based on the time of day at which symptoms begin to appear 1. Single question	RLS severity

(continued)

Table 1 (continued)

Condition	Questionnaire	Characteristics	Purpose + Score + Cut off values
Pain	Pain and Sleep Questionnaire Three-Item Index (PSQ-3) Ayearst et al., 2012 [16]	Direct measure of the impact of chronic pain on sleep 8 questions: 6 are scored on a 100 mm VAS (ranging from 0 [“never”] to 100 [“always”]) and asks respondents to rate how often they have trouble falling asleep; how often they need pain medication to fall asleep; how often they need sleeping medication to fall asleep; how often they are awakened by pain during the night and in the morning; and how often their partner is awakened. The seventh item is also scored using a VAS; however, it uses different anchor points (0 [“very poor”], 100 [“excellent”]) and asks individuals to rate the overall quality of their sleep. The final item asks individuals to indicate, using a number that can range from 1 to 24, the average number of hours of sleep they get each night	Impact of pain on sleep in chronic pain patients
	Chronic Pain Sleep Inventory (CPSI) https://cpsi-sleep.com [17]	5-item tool measured on a 100 mm VAS assessing: Trouble falling asleep because of pain, needed sleep medication to help you fall asleep, awakened by pain during the night, awakened by pain in the morning, rate overall quality of your sleep	Impact of pain on sleep quality
	Sleep assessment instrument for older adults with pain (SAIOAP) Santana et al., 2021 [18]	Simple and practical tool Sleep dimensions, namely, sleep onset and maintenance, physical discomfort, diurnal repercussions of sleep such as excessive daytime sleepiness, self-perception of health status and medication used for sleep 7 questions: yes and no +4 questions on time to go to bed and wake up, sleep latency, and sleep duration	Score: 1 point for each “yes” answer to produce the total score
Circadian preference	Morningness-Eveningness Questionnaire Horn & Osteberg, 1976 [19] www.cet.org	19 multiple-choice questions, each having 4 or 5 response options	Overall score: 16–86 points Scores: ≤41 indicate “evening types,” ≥59 indicate “morning types,” between 42 and 58 indicate “intermediate types”
	Munich Chronotype Questionnaire Roenneberg et al., 2015 [20] www.thewep.org/documentations/mctq	Evaluates past 4 weeks 4 subscales: work schedule, workday sleep schedule, free day sleep schedule, self-assessment of chronotype 17 questions	Assess individual phase of entrainment on work and work-free days Scored electronically by the website
Sleep Diary	www.thensf.org/nsf-sleep-diary www.sleepfoundation.org/sleep-diary	A simple and practical tool evaluates how many days desired (suggested to evaluate weekdays and weekends) routine	Detailed information on morning and evening pre-sleep and post-sleep collects data overtime on self-reported sleep

There are several questionnaires for sleep assessment, which are easy, costless, and very manageable at the physiotherapist clinic. Here we present questionnaires that have reliability and validity against objective measures and can be incorporated into physical therapists' (PTs) anamnesis and treatment outcomes evaluation (Table 1). These are subjective measures that assess self-perception of quality and quantity of sleep and can assist in the diagnosis of sleep disorders. Just a reminder that the questionnaires are not designed to provide clinical diagnoses by themselves.

For the evaluation of general sleep, the Pittsburgh Sleep Quality Index (PSQI) [1] is one of the most used in research and clinical practice, assessing sleep quality

THE EPWORTH SLEEPINESS SCALE

Name: _____

Today's date: _____ Your age (years): _____

Your sex (male = M; female = F): _____

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

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

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

Thank you for your cooperation

Fig. 1 Epworth sleepiness scale. (Reprinted with permission from Johns. Publisher: Oxford University Press [4])

Name: _____ **Date:** _____

1. Please rate the current (i.e., last 2 weeks) **SEVERITY** of your insomnia problems(s).

	None	Mild	Moderate	Severe	Very
Difficulty falling asleep:	0	1	2	3	4
Difficulty staying asleep:	0	1	2	3	4
Problem waking up too early:	0	1	2	3	4

2. How **SATISFIED**/dissatisfied are you with your current sleep pattern?

Very Satisfied				Very Dissatisfied
0	1	2	3	4

3. To what extent do you consider your sleep problem to **INTERFERE** with your daily functioning (e.g. daytime fatigue, ability to function at work/daily chores, concentration, memory, mood, etc.).

Not at all Interfering	A Little	Somewhat	Much	Very Much Interfering
0	1	2	3	4

4. How **NOTICEABLE** to others do you think your sleeping problem is in terms of impairing the quality of your life?

Not at all Noticeable	Barely	Somewhat	Much	Very Much Noticeable
0	1	2	3	4

5. How **WORRIED**/distressed are you about your current sleep problem?

Not at all	A Little	Somewhat	Much	Very Much
0	1	2	3	4

Fig. 2 Insomnia severity index. (Reprinted with permission from Bastien et al. Elsevier Science [7])

in a 1-month interval. PSQI is an extensive questionnaire on the behavior of sleeping times and problems. In addition, there are the Jenkins Sleep Evaluation Questionnaire (JSEQ) [2] and the Sleep Scale from the Medical Outcomes Study (MOS-Sleep) [3], which are also well used.

In respect of disease-specific instruments, there are many designed to assess specific conditions of the disease itself. For the sleepiness evaluation, there are some assessment tools such as the Epworth Sleepiness Scale (ESS) [4] (Fig. 1), the Stanford Sleepiness Scale (SSS) [5], and the Karolinska Sleepiness Scale (KSS) [6], which help to assess the impact of sleepiness on the ability to conduct daily activities.

For insomnia, the Insomnia Severity Index (ISI) [7](Fig. 2), the Athens Insomnia Scale [8], and the Insomnia Symptom Questionnaire (ISQ) [9] are among the most used questionnaires, designed to establish a clinically relevant case definition of insomnia consistent with widely used insomnia classification criteria.

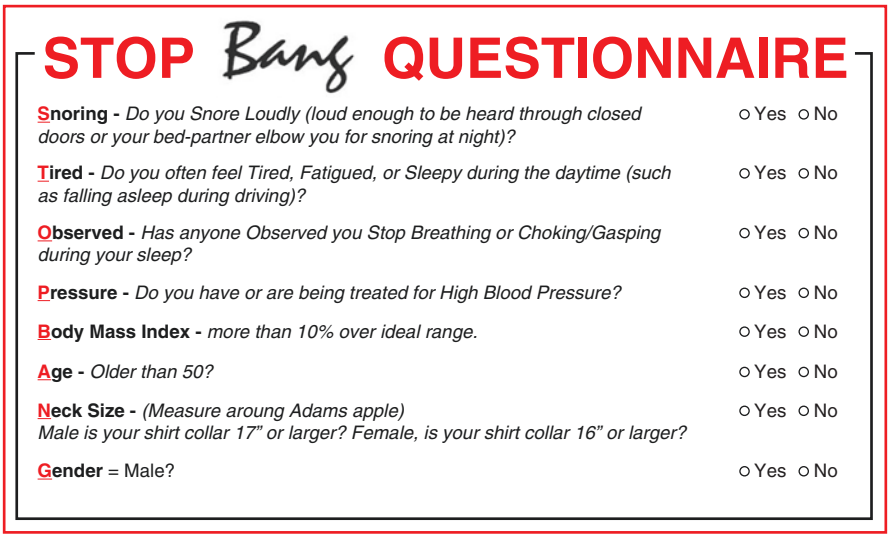


Fig. 3 STOP-Bang questionnaire. (Reprinted with permission from Chung et al. [10])

Population-based studies evaluating the accuracy of screening questionnaires for OSA against PSG were Berlin questionnaire [11], STOP-Bang Questionnaire [10] (Fig. 3), and NoSAS Score [12]. Regarding OSA, mouth and jaw can also be analyzed by a visual inspection, using the modified Mallampati Classification, which visually classifies the amount of mouth opening to the size of the tongue, and provides an estimate of space available for oral intubation by direct laryngoscopy (Fig. 4). A high Mallampati score (class 3 or 4) is associated with a higher incidence of sleep apnea [21, 22]. It is important at this moment to evaluate the patency of the oropharynx, and to measure neck circumference, and also the development of the maxilla (hypoplasia) and mandible (mandibular retro position) because retrognathia is a risk factor and, when added to other elements, can worsen obstructive sleep apnea [23, 24].

The Narcolepsy Severity Scale is a measurement tool for quantitative evaluation of narcolepsy symptoms, useful for monitoring and optimizing the management of narcolepsy [13]. As a new assessment tool, it is only available in French [13, 25], Brazilian Portuguese [26], and Chinese [27].

The International Restless Legs Syndrome Rating Scale (IRLSRS) was developed by the International Restless Legs Syndrome Study Group to assess the severity of a patient's RLS symptoms [14] (Fig. 5).

As we have presented in a separate chapter (chapter "Sleep and Chronic Pain Interlaced Influences: Guidance to Physiotherapy Practice"), there is a relationship between sleep and pain. Both can be evaluated together, by the Pain and Sleep Questionnaire Three-Item Index (PSQ-3), a direct measure of the impact of chronic pain on sleep [16]; and by the Chronic Pain Sleep Inventory (CPSI), a 5-item tool using a 100 mm visual analog scale [17]. A new measurement tool specifically

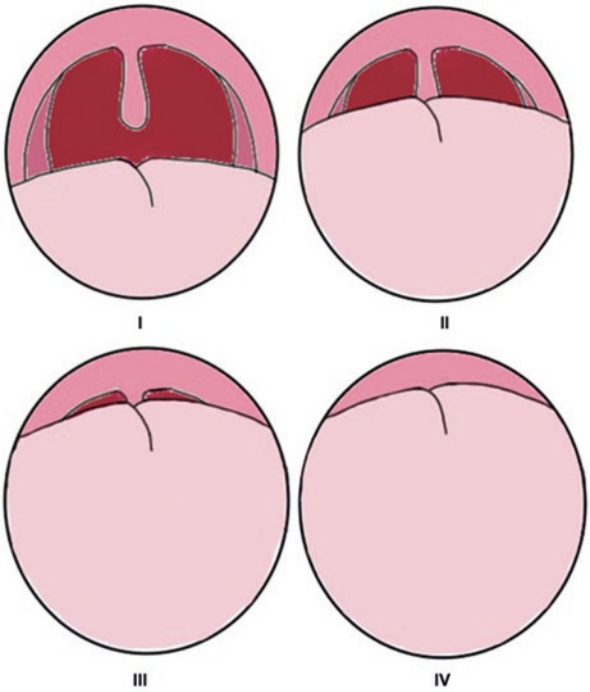


Fig. 4 Modified Mallampati Classification, classes I to IV. Mallampati classes: Class I corresponds to all structures visible (soft palate, uvula, fauces, and pillars); Class II, pillars are no more visible (soft palate, major part of uvula, and fauces visible); Class III, fauces are no more visible (soft palate and base of the uvula visible); finally, class IV, only the hard palate is visible. (Image courtesy from Dr. Maria Júlia Figueiró Reis. Original figure)

designed and validated for the older ones is the Sleep Assessment Instrument for Older Person with Pain (SAIOAP) [18](Fig. 6).

To assess circadian preferences (i.e., whether a person's circadian rhythm or biological clock produces peak alertness in the morning, in the evening, or in between) the Morningness Eveningness Questionnaire (MEQ) [19], which helps to determine individual differences in sleep-wake patterns, and the time-of-day people feel and perform best can be used (Fig. 7). Munich Chronotype Questionnaire (MCTQ) can assess individuals' chronotypes – diurnal preferences that manifest in personal sleep-wake rhythms [20].

The sleep diary is a record of an individual's routine of sleeping and waking times. It can be fulfilled by the proper patient, by a caregiver, or by the parents. The sleep diary records the subjective perception of the sleep period (Fig. 8) and can be recorded for at least 10 days, in order to include weekdays and weekends, or more, depending on the case. Often patients record information such as the time the patient

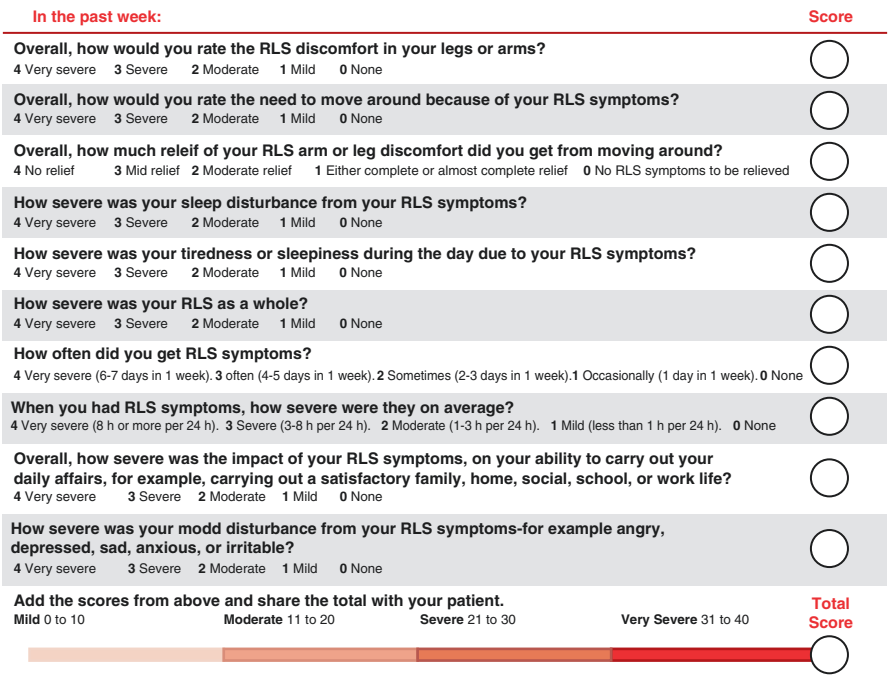


Fig. 5 Restless legs syndrome rating scale for severity. (Reprinted with permission from Walters et al. [14])

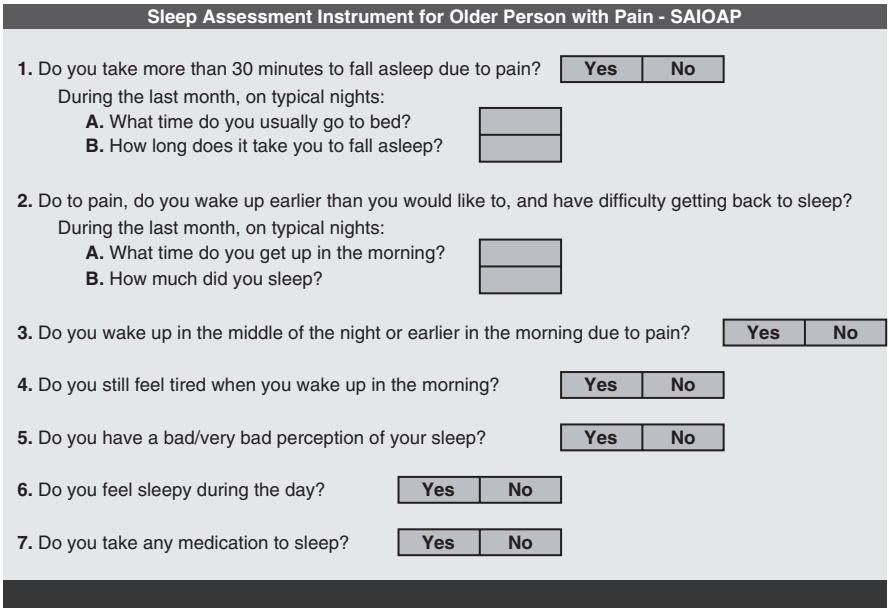


Fig. 6 Sleep assessment instrument for older person with pain. (Reprinted with permission from Santana et al. [18])

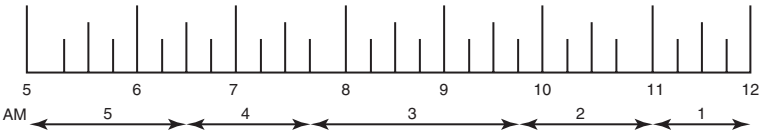
Morningness-Eveningness Questionnaire

Instructions:

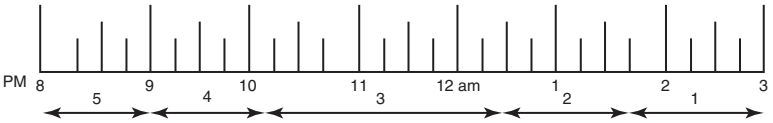
1. Please read each question very carefully before answering.
2. Answer ALL questions
3. Answer questions in numerical oeder.
4. Each question should be answered independently of others. Do NOT go back and cheek your answers.
5. All questions have a selection of answers. For each question place a cross alongside ONE answer only. Some questions have a scale instead of a selection of answers. Place a cross at the appropriate point along the scale.
6. Please answer each question as honestly as possible. Both your answers and the results will be kept, in strict confidence.
7. Please feel free to make any comments in the section provided below each question.

The Questionnaire with scores for each choice

1. Considering only your own "feeling best" rhythm, at what time would you get up if you were entirely free to plan your day?



2. Considering only your own "feeling best" rhythm, at what time would you get to bed if you were entirely free to plan your evening?



3. If there is a specific time at which you have to get up in the morning, to what extent are you dependent on bring woken up by an alarm clock?

Not at all dependent ☐ 4
Slightly dependent ☐ 3
Fairly dependent ☐ 2
Very dependent ☐ 1

4. Assuming adequate environmental conditions, how easy do you find getting up in the mornings?

Not at all easy ☐ 1
Not very easy ☐ 2
Fairly easy ☐ 3
Very easy ☐ 4

5. How alert do you feel during the first half hour after having woken in the mornings?

Not at all alert ☐ 1
Slightly alert ☐ 2
Fairly alert ☐ 3
Very alert ☐ 4

6. How is your appetite during the first half-hour after having woken in the mornings?

Very poor ☐ 1
Fairly poor ☐ 2
Fairly good ☐ 3
Very good ☐ 4

Fig. 7 Morningness eveningness questionnaire. (Reprinted with permission from Terman et al. [28])

7. During the first half-hour after having woken in the morning, how tired do you feel?

Very tired	☐ 1
Fairly tired	☐ 2
Fairly refreshed	☐ 3
Very refreshed	☐ 4

8. When you have no commitments the next day, at what time do you go to bed compared to you usual bedtime?

Seldom or never later	☐ 4
Less than one hour later	☐ 3
1-2 hours later	☐ 2
More than two hours later	☐ 1

9. You have decided to engage in some physical exercise. A friend suggests that you do this one hour twice a week and the best time for him is between 7:00-8:00 a.m. Bearing in mind nothing else but your own "feeling best" rhythm, how do you think you would perform?

Would be on good form	☐ 4
Would be on reasonable form	☐ 3
Would find it difficult	☐ 2
Would find it very difficult	☐ 1

10. At what time in the evening do you feel tired and as a result in need of sleep?

11. You wish to be at your peak performance for a test which you know is going to be mentally exhausting and lasting for two hours. You are entirely free to plan your day and considering only your own "feeling best" rhythm which ONE of the four testing times would you choose?

8:00-10:00 a.m.	☐ 6
11:00 a.m.-1:00 p.m.	☐ 4
3:00-5:00 p.m.	☐ 2
7:00-9:00 p.m.	☐ 0

12. If you went to bed at 11 p.m. at what level of tiredness would you be?

Not at all tired	☐ 0
A little tired	☐ 2
Fairly tired	☐ 3
Very tired	☐ 5

13. For some reason you have gone to bed several hours later than usual, but there is no need to get up at any particular time the next morning. Which ONE of the following events are you most likely to experience?

Will wake up at usual time and will NOT fall asleep	☐ 4
Will wake up at usual time and will doze thereafter	☐ 3
Will wake up at usual time but will fall asleep again	☐ 2
Will NOT wake up until later than usual	☐ 1

14. One night you have to remain awake between 4-6 a.m. in order to carry out a night watch. You have no commitments the next day, Which ONE of the following alternatives will suit you best?

Would NOT go to bed until watch was over	☐ 1
Would take a nap before and sleep after	☐ 2
Would take a good sleep before and nap after	☐ 3
Would take ALL sleep before watch	☐ 4

Fig. 7 (continued)

15. You have to do two hours of hard physical work. You are entirely free to plan your day and considering only your own “feeling best” rhythm which ONE of the following times would you choose?

8:00-10:00 a.m. ☐ 4
11:00 a.m.-1:00 p.m. ☐ 3
3:00-5:00 p.m. ☐ 2
7:00-9:00 p.m. ☐ 1

16. You have decide to engage in hand physical exercise. A friend suggests that you do this for one hour twice a week and the best time for him is between 10-11 p.m. Bearing in mind nothing else but your own “feeling best” rhythm how well do you think you would perform?

Would be on good form ☐ 1
Would be on reasonable form ☐ 2
Would find it difficult ☐ 3
Would find it very difficult ☐ 4

17. Suppose that you can choose your work hours. Assume that you worked a FIVE hour day (including breaks) and that your job was interesting and paid by results. Which FIVE CONSECUTIVE HOURS would you select?

12 1 2 3 4 5 6 7 8 9 10 11 12 1 2 3 4 5 6 7 8 9 10 11 12
Midnight Noon Midnight
1 5 4 3 2 1

18. At what time of the day do you think that you reach your “feeling best” peak?

12 1 2 3 4 5 6 7 8 9 10 11 12 1 2 3 4 5 6 7 8 9 10 11 12
Midnight Noon Midnight
1 5 4 3 2 1

19. One hears about “morning” and evening” types of people. Which ONE of these types do you consider yourself to be?

Definitely a “morning” type ☐ 6
Rather more a “morning” than an evening type ☐ 4
Rather more an “evening” than a morning type ☐ 2
Definitely an “evening” type ☐ 0

Fig. 7 (continued)

Consensus Sleep Diary - E (Please Complete Upon Awakening) **ID/NAME:** ____________

Sample

Today’s Date	4/5/11							
1. What time did you get into bed?	10:15 p.m.							
2. What time did you try to go to sleep?	11:30 p.m.							
3. How long did it take you to fail asleep?	55 min.							
4. How many times did you wake up, not counting your final awakening?	6 times							
5. In total, how long did these awakenings last?	2 hours 5 min.							
6a. What time was your final awakening?	6:35 a.m.							
6b. After your final awakening. how long did you spend in bed trying to sleep?	45 min.							
6c. Did you wake up earlier than you planned?	☒Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐ No
6d. If yes, how much earlier?	1 hour							
7. What time did you get out of bed for the day?	7:20 a.m.							
8. In total, how long did you sleep?	4 hours 10 min.							
9. How would you rate the quality of your sleep?	☐Very poor ☒Poor ☐Fair ☐Good ☐Very Good	☐Very poor ☒Poor ☐Fair ☐Good ☐Very Good	☐Very poor ☐Poor ☐Fair ☐Good ☐Very Good	☐Very poor ☐Poor ☐Fair ☐Good ☐Very Good	☐Very poor ☐Poor ☐Fair ☐Good ☐Very Good	☐Very poor ☐Poor ☐Fair ☐Good ☐Very Good	☐Very poor ☐Poor ☐Fair ☐Good ☐Very Good	☐Very poor ☐Poor ☐Fair ☐Good ☐Very Good
10. How rested or refreshed did you feel when you woke-up for the day?	☐Not at all rested ☒Slightly rested ☐Somewhat rested ☐Well-rested ☐Very well-rested	☐Not at all rested ☐Slightly rested ☐Somewhat rested ☐Well-rested ☐Very well-rested	☐Not at all rested ☐Slightly rested ☐Somewhat rested ☐Well-rested ☐Very well-rested	☐Not at all rested ☐Slightly rested ☐Somewhat rested ☐Well-rested ☐Very well-rested	☐Not at all rested ☐Slightly rested ☐Somewhat rested ☐Well-rested ☐Very well-rested	☐Not at all rested ☐Slightly rested ☐Somewhat rested ☐Well-rested ☐Very well-rested	☐Not at all rested ☐Slightly rested ☐Somewhat rested ☐Well-rested ☐Very well-rested	☐Not at all rested ☐Slightly rested ☐Somewhat rested ☐Well-rested ☐Very well-rested

Fig. 8 Consensus sleep diary with instructions. (Reprinted with permission from Carney et al. [30])

Consensus Sleep Diary - E (Please Complete Before Bed) **ID/NAME:** _____

	Sample							
Today's Date	4/4/11							
11a. How many times did you nap or doze? 11b. In total, how long did you nap or doze?	2 times 1 hour 10 min.							
12a. How many drinks containing have? 12b. What time was your last drink?	3 drinks 9 :20 p.m.							
13a. How many Caffeinated drinks (coffee, tea, soda, you have? 13b. What time was your last drink?	2 drinks 3 :00 p.m.							
14a. Did you take any over-the-counter or prescription medication(s) to help you sleep? If so, list medication(s), dose, and time taken	☑Yes ☐No Medication(s): Relaxo-Herb Dose: 50 mg Time(s) taken: 11 pm	☐Yes ☐No Medication(s): Dose: Time(s) taken:	☐Yes ☐No Medication(s): Dose: Time(s) taken:	☐Yes ☐No Medication(s): Dose: Time(s) taken:	☐Yes ☐No Medication(s): Dose: Time(s) taken:	☐Yes ☐No Medication(s): Dose: Time(s) taken:	☐Yes ☐No Medication(s): Dose: Time(s) taken:	☐Yes ☐No Medication(s): Dose: Time(s) taken:
15. Comments (if applicable)	I have a cold							

Fig. 8 (continued)

went to bed, the amount of time it took to fall asleep, time the patient left the bed in the morning, number of times patient awoke during the night, how refreshing overall sleep was, what may have disturbed patient's sleep (breathing troubles, leg movements, insomnia, etc.), number and time of caffeinated and alcoholic beverages consumed throughout the day, medications taken during the day, time spent exercising and period of the day, activities performed prior to bed [29, 30]. The National Sleep Foundation has a good example of a sleep diary (www.sleepfoundation.org). Sleep diaries are typically used in addition to or in place of objective measures (i.e., polysomnography or actigraphy) and can be completed over multiple time points. It is a self-report measure in which patients and participants record their sleep patterns and answer other questions related to their sleep on a daily basis (e.g., sleep quality, daytime sleepiness, medication use). Sleep diaries capture night-to-night variability in sleep. It is a particularly important tool for assessing sleep routine for the physiotherapist and the patient, as they can have a better idea of the patient's sleep patterns and habits, can help the physician with a diagnosis, and also can monitor the effectiveness of treatment. In addition, the sleep diary may help the patient to get more proactive about their sleep, knowing it better. Henceforth, we conclude best practice is to include both subjective and objective measures when examining sleep.

General Instructions

What is a Sleep Diary? A sleep diary is designed to gather information about your daily sleep pattern.

How often and when do I fill out the sleep diary? It is necessary for you to complete your sleep diary every day. If possible, the sleep diary should be completed within one hour of getting out of bed in the morning. The Nighttime Sleep Diary questions can be completed before you go to bed at night.

What should I do if I miss a day? If you forget to fill in the diary or are unable to finish it, leave the diary blank for that day.

What if something unusual affects my sleep or how I feel in the daytime? If your sleep or daytime functioning is affected by some unusual event (such as an illness, or an emergency), you may make brief notes on your diary.

What do the words "bed" and "day" mean in the diary? This diary can be used for people who are awake or asleep at unusual times. In the sleep diary, the word "day" is the time when you choose or are required to be awake. The term "bed" means the place where you usually sleep.

Will answering these questions about my sleep keep me awake? This is not usually a problem. You should not worry about giving exact times, and you should not watch the clock. Just give your best estimate.

Morning Sleep Diary Item Instructions

Use the guide below to clarify what is being asked for each item of the Sleep Diary. Date: Write the date of the morning you are filling out the diary.

1. What time did you get into bed? Write the time that you got into bed. This may not be the time you began "trying" to fall asleep.

2. What time did you try to go to sleep? Record the time that you began "trying" to fall asleep.

3. How long did it take you to fall asleep? Beginning at the time you wrote in question 2, how long did it take you to fall asleep?

4. How many times did you wake up, not counting your final awakening? How many times did you wake up between the time you first fell asleep and your final awakening?

5. In total, how long did these awakenings last? What was the total time you were awake between the time you first fell asleep and your final awakening? For example, if you woke 3 times for 20 minutes, 35 minutes, and 15 minutes, add them all up (20 + 35 + 15 = 70 min or 1 hr. and 10 min).

6a. What time was your final awakening? Record the last time you woke up in the morning.

6b. After your final awakening, how long did you spend in bed trying to sleep? After the last time, you woke up

(Item #6a), how many minutes did you spend in bed trying to sleep? For example, if you woke up at 8 am but continued to try and sleep until 9 am, record 1 hour.

6c. Did you wake up earlier than you planned? If you woke up or were awakened earlier than you planned, check yes. If you woke up at your planned time, check no.

6d. If yes, how much earlier? If you answered "yes" to question 6c, write the number of minutes you woke up earlier than you had planned on waking up. For

example, if you woke up 15 minutes before the alarm went off, record 15 minutes here.

7. **What time did you get out of bed for the day?** What time did you get out of bed with no further attempt at sleeping? This may be different from your final awakening time (e.g., you may have woken up at 6:35 a.m. but did not get out of bed to start your day until 7:20 a.m.)
8. **In total, how long did you sleep?** This should just be your best estimate, based on when you went to bed and woke up, how long it took you to fall asleep, and how long you were awake. You do not need to calculate this by adding and subtracting; just give your best estimate.
9. **How would you rate the quality of your sleep?** "Sleep Quality" is your sense of whether your sleep was good or poor.
10. **How restful or refreshed did you feel when you woke up for the day?** This refers to how you felt after you were done sleeping for the night, during the first few minutes that you were awake.

Nighttime Sleep Diary Item Instructions

Please complete the following items before you go to bed.

Date: Write the date of the evening you are filling out the diary.

11a. **How many times did you nap or doze?** A nap is a time you decided to sleep during the day, whether in bed or not in bed. "Dozing" is a time you may have nodded off for a few minutes, without meaning to, such as while watching TV. Count all the times you napped or dozed at any time from when you first got out of bed in the morning until you got into bed again at night.

11b. **In total, how long did you nap or doze?** Estimate the total amount of time you spent napping or dozing, in hours and minutes. For instance, if you napped twice, once for 30 minutes and once for 60 minutes, and dozed for 10 minutes, you would answer "1 hour 40 minutes." If you did not nap or doze, write "N/A" (not applicable).

12a. **How many drinks containing alcohol did you have?** Enter the number of alcoholic drinks you had where 1 drink is defined as one 12 oz. beer (can), 5 oz. wine, or 1.5 oz. liquor (one shot).

12b. **What time was your last drink?** If you had an alcoholic drink yesterday, enter the time of day in hours and minutes of your last drink. If you did not have a drink, write "N/A" (not applicable).

13a. **How many caffeinated drinks (coffee, tea, soda, energy drinks) did you have?** Enter the number of caffeinated drinks (coffee, tea, soda, energy drinks) you had where for coffee and tea, one drink = 6–8 oz.; while for caffeinated soda one drink = 12 oz.

13b. **What time was your last drink?** If you had a caffeinated drink, enter the time of day in hours and minutes of your last drink. If you did not have a caffeinated drink, write "N/A" (not applicable).

14. **Did you take any over-the-counter or prescription medication(s) to help you sleep?** If so, list medication(s), dose, and time taken: List the medication name,

how much and when you took EACH different medication you took tonight to help you sleep. Include medication available over the counter, prescription medications, and herbals (e.g., "Sleepwell 50 mg 11 pm"). If every night is the same, write "same" after the first day.

15. Comments: If you have anything that you would like to say that is relevant to your sleep, feel free to write it here.

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Objective Assessment of Sleep

Maria Júlia Figueiró Reis, Eliana Lottenberg Vago, Cristina Frange, and Fernando Morgadinho Santos Coelho

In this chapter, we present some of the objective examinations of sleep. Like in any area of clinical practice, the history, anamnesis, and physical assessment generally offer most of the essential clues needed to establish which additional instruments would be most useful in the diagnostic assessment process. When necessary, objective examinations of sleep can help physicians with the sleep disorders diagnosis. The investigation of sleep per se is preferable to be done during the nighttime period, or the usual sleep period. Although the prescription of objective examinations of sleep is not within the scope of practice of physiotherapists, the understanding of the exams will help in clinical practice and in interdisciplinary work.

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1 Polysomnography

Diagnostic overnight polysomnography (PSG) examination, also known as a sleep study, is the main exam for assessment and diagnosis of sleep disorders and must be prescribed by a physician. PSG monitors the sleep stages and cycles to identify if or when our sleep patterns are disrupted and why. Sleep staging and marking of the associated events can be performed by a single trained PSG technician based on the criteria recommended by the Standard Manual for Staging Sleep and Associated Events at the American Academy of Sleep Medicine [1]. Physical therapists (PTs) can act as PSG technicians (as any other health professional) and learn how to "read" and interpret the exam, after attending some courses and being approved in the examination of the Board of Registered Polysomnographic Technologists.

The PSG records multiple physiological variables that are monitored simultaneously: electroencephalogram (EEG), electrooculogram (EOG), electrocardiogram (ECG), airflow, surface electromyogram (EMG, submental, temporal, masseter, and tibialis anterior muscles), respiratory effort of the thorax and abdomen (using inductance plethysmography belts), snoring, body position, saturation of peripheral oxygen (SpO_2), and heart rate (Fig. 1). Sleep staging is based on EEG, EOG, and submental (chin) EMG criteria. To detect stage R in particular, EOG and EMG submental recordings are mandatory for detecting saccadic eye movements and muscle atonia [2]. The nomenclature of EEG electrodes follows the International 10–20 system [3].

In a sleep recording study, that is PSG, it is possible to visualize brain waveforms derived from EEG by multiple time windows, known as epochs. An *epoch* can have a duration of 10, 15, 30, 60, 90, 120, or 240 seconds. A 30-second window is used to stage sleep, whereas a 10-second window is used for clinical EEG monitoring. Nowadays sleep is staged in sequential 30-second *epochs*, but digital PSG allows for use of different time windows based on the examiner's purpose, as for scoring of respiratory events, when 60 to 120-second epochs are frequently used. Many variables appear in a PSG examination, including sleep architecture (sleep structure, sleep pattern), and they depend on the duration of sleep and exam (Table 1). In addition, heart rate, saturation index, mean, minimum and maximum saturation (oximetry evolution), snoring, movement of limbs (legs and arms) during sleep and respiratory data, such as obstructive, central and mixed apneas and hypopneas, respiratory effort related arousal, the duration of each of these events in specific sleep stages, and the decubitus in which these events happened can also be described (Fig. 2).

Many monitoring PSG types can be prescribed by the physician, specifically when there is suspicion of associated diseases, such as (i) PSG with neurological assembly, which includes an increased number of "channels" or electrodes added to the EEG compared to the basal PSG. It is requested by the physician in cases of suspected epilepsy or other neurological conditions; (ii) PSG for bruxism, focusing on the evaluation of chewing movements or jaw contraction, which may include video recordings; (iii) PSG for positive air pressure (PAP) titration in patients with sleep-related breathing disorders, to define the adequate treatment pressure for each patient and mask type. It is possible for technicians, during titration, to make adjustments in the level of air pressure necessary to completely eliminate respiratory events. Adjusting

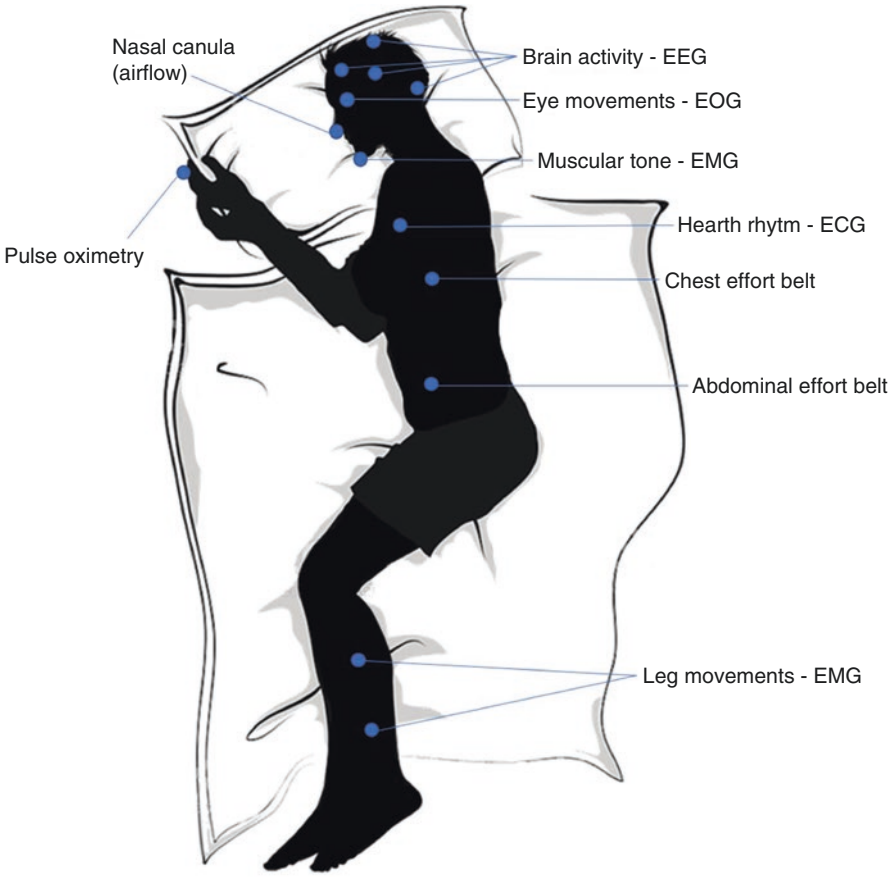

Fig. 1 Schematic representation of basic electrodes for sleep monitoring – polysomnography examination
Brain activity is measured bilaterally, at frontal, central, occipital, mastoid, central midline (vertex), and frontopolar midline (above and between the eyes). Eye movements are recorded using electrodes poisoned near the eyes, below and above, and at both sides. Chin activity is monitored via one electrode poisoned above the inferior edge of the mandible and two electrodes positioned below the inferior edge of the mandible, right and left. EEG electroencephalography, EOG electrooculography, EMG electromyography, ECG electrocardiography. (Image courtesy Dr. Cristina Frange. Original figure.)

the pressure of the PAP device is a simple procedure, but requires great knowledge from the technician and patient's collaboration, as the degree of airway "closure" can vary throughout the night, depending on the stages of sleep or the sleeping position; (iv) PSG for ventilation therapy adjustment, including types of PAP devices such as Bilevel or Servo Ventilator, which treat more complex respiratory or neuromuscular diseases, and are also adjusted during a PSG night examination; (v) PSG for confirmation of the efficacy of Mandibular Advancement Device (MAD) after subjective titration or, more recently, for its objective titration [4]. MAD promotes changes in the position of the mandible by bringing it forward and increasing the space for air to

Table 1 American Academy of Sleep Medicine recommended reporting parameters of polysomnographic examination

Parameter		Definition	Values for normal adults
Lights out time (h:min)		Time of the start of the recording	–
Lights on time (h:min)		Time of the ending of the recording	–
Time in bed or total recording time (TRT, min)		Total time spent in bed, from lights out to lights on, which includes sleep and wakefulness	Varies accordingly to age, chronotype, and circadian preferences
Total sleep time (TST, min)		Total time of sleep recorded over the PSG, time spent in stages N1, N2, N3, or R (Most PSGs are performed in the hope that at least 6–7 hours of TST will be recorded, but useful data can be acquired in many patients even with 2–3 hours of TST)	
Sleep efficiency (SE, %)		Total sleep time divided by The total time in bed multiplied by 100% (SE in sleep laboratories are highly variable, and this value is usually not given all that much weight in clinical practice unless the SE is very low or very high)	>85%
Sleep latency or sleep onset latency (SL, min)		The amount of time it takes to go from being fully awake to sleeping	<30 min
Stage R latency (REMSL, min)		The elapsed time between sleep onset and the onset of the first REM sleep period	70–120 min
Wake after sleep onset (WASO, min)		Total time of scored wakefulness that occurred after the initial epoch of sleep, linked to the fragmentation of sleep	<30 min
Arousal index (#/hr)		Total number of arousals divided by TST	<10–25 (large variation by age)
Stage wake (W, min)		All minutes of stage wake during TRT	
Sleep stages	N1 (%)	Total time in each sleep stage divided by TST and multiplied by 100% Also shown in minutes	2–5% of TST
	N2 (%)		45–55% of TST
	N3 (%)		20% of TST
	R (%)		20–25% of TST
Periodic limb movement index (PLMi)		PLMi is calculated by dividing the total number of PLMs by sleep time in hours	Normal: PLMi ≤5 Mild: >5 PLMi <25 Moderate: >25 PLMi <50 Severe: PMLi ≥50
Apnea hypopnea index (AHI)		Represents the number of apnea and hypopnea events per hour of sleep	Normal: AHI < 5 Mild: 5 ≤ AHI < 15 Moderate: ≥15 AHI <30 Severe: AHI ≥30
Respiratory disturbance index (RDI)		Apnea hypopnea index + hypopnea + RERA: Respiratory effort related arousal	

Adapted with permission from Carskadon and Dement [12]
H hour, *Min* minutes

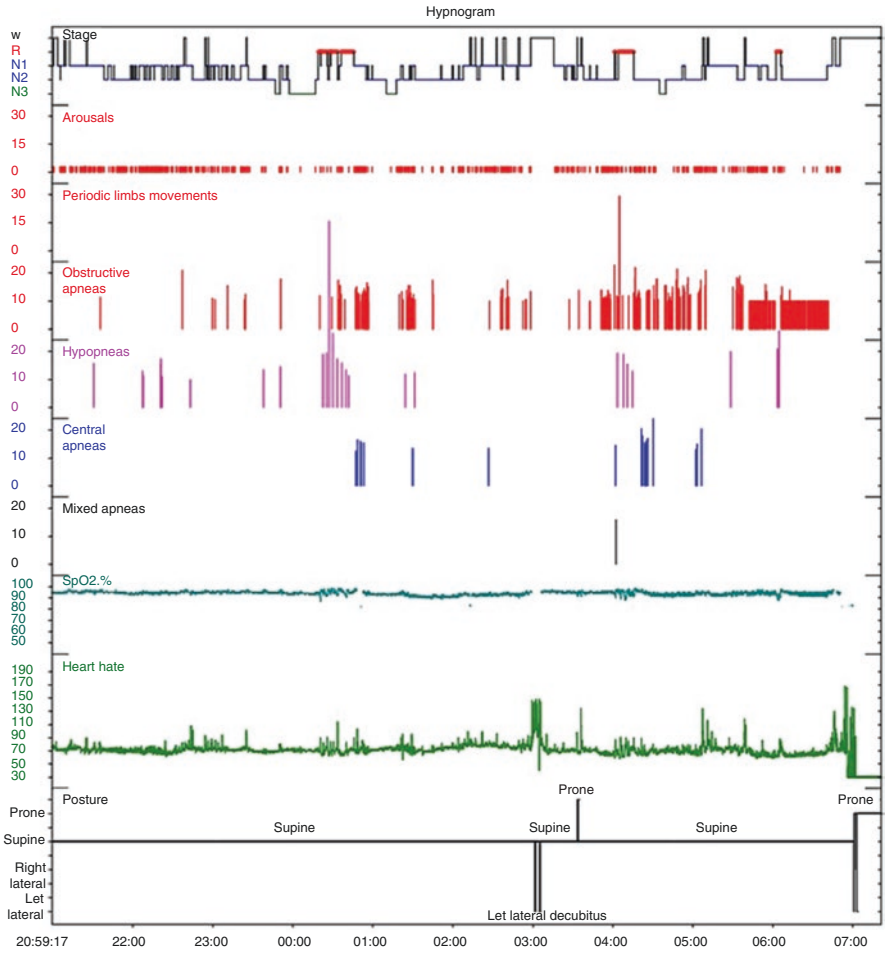

Fig. 2 Result sheet from an overnight polysomnography examination in the laboratory, from 20:59 until 7 hours in the morning (time at the bottom). Hypnogram showing each sleep stage according to time of the night, R stage (red line), N1 (black line), N2 (blue line) and N3, green line; arousal (in red); periodic limb movements (this patient had none); obstructive sleep apnea (in red lines, seconds); hypopneas (in pink lines, seconds); central apneas (blue lines, seconds); mixed apnea (black line, seconds); oxygen saturation (in, %); heart rate (in green, bpm); and time spent in each posture (supine, prone, left or right lateral decubitus). Note that this patient slept in the supine position for the most part of the night, and during the R sleep stage, when obstructive sleep apneas and hypopneas occurred, he had a desaturation of oxygen at both moments, and increased heart rate. W wake, R REM sleep stage, N1 NREM N1 sleep stage, N2 NREM N2 sleep stage, N3 NREM N3 sleep stage. (Image courtesy Dr. Cristina Frange)

pass through the airway. As PAP devices, it is also recommended to treat obstructive sleep apnea, but in less severe cases or when the patient is unable to adapt to the use of PAP or ventilatory therapy; (vi) split-night PSG, where the night of PSG exam is divided into two parts: in the first half of the night, a basal PSG is performed, which is then followed by a treatment intervention in the second half, more traditionally PAP titration. Split night, although not usually recommended because of bias, may be prescribed by physicians in some very specific cases.

PSG can be performed in any age group, even in newborns. PSG is commonly performed in sleep laboratories, but, in some cases, it can be performed at home or in a hospital setting. It can include different procedures and setups, which must be defined and requested by a physician and may vary according to the environment in which PSG will be performed. At home, PSG is usually simpler and more suitable for the assessment of sleep events or respiratory disorders. The night and day before the PSG exam are especially important, and the preparation should be discussed in detail with the patient. PSG are categorized into four types:

- Type 1 – standard attended in-lab PSG
- Type 2 – comprehensive portable PSG
- Type 3 – modified portable sleep apnea testing (also referred to as cardiorespiratory sleep studies)
- Type 4 – continuous single or dual bio parameter recording, ambulatory overnight pulse oximetry

In Type 2 PSG, either a technologist will come to the patient's house to set the device up, or the patient can pick it up at the sleep center. It is often prescribed for a patient who is under a sleep specialist's care when there is a high suspicion of sleep apnea after other sleep disorders have been ruled out. To perform this exam, it is usually recommended that the patient doesn't present with lung disease, heart disease, or any other serious health problem. In a recent investigation, it has been demonstrated that home sleep monitoring has a good correlation with Laboratory "gold standard" PSG, representing a growing trend for diagnosing sleep disturbances in selected patients [5].

2 Overnight Oximetry (Type 4 PSG)

New research is being performed to improve the accuracy of methods based on pulse oximetry. A good example of this new frontier of knowledge has been recently validated [6]. A wireless pulse oximeter coupled with an internal accelerometer reports data on oxygen desaturation index (ODI) and sleep movement during the night (Fig. 3). The analyzed algorithm shares information of ODI positively related to moderate to severe OSA diagnosis. Using the 3% desaturation recommended criteria for hypopnea detection, cutoff of 12 events/hour for ODI has a sensitivity of 95.1%, a specificity of 80.2%, and an accuracy of 90.1%, with a good performance considering positive and negative predictive values, and positive and negative

Fig. 3 Wireless pulse oximeter coupled with an internal accelerometer, destined to remotely monitor the risk patients. (Reprinted with permission from Biologix)

likelihood ratio. Performance for the 4% desaturation accepted criteria for hypopnea, using an ODI cutoff of 14 events/hour, is also reliable for clinical practice. This pulse oximeter can be used by physiotherapists to help within the treatment of OSA for patients with nocturnal desaturation.

3 Multiple Sleep Latency Test

Diagnostic daytime multiple sleep latency test (MSLT) is performed to assess the degree of daytime sleepiness as the patient stays in a dark and silent environment. In other words, it measures how quickly the patient falls asleep in a quiet environment during the day. MSLT is essential for the diagnosis of narcolepsy and hypersomnias. MSLT is a full-day test that consists of 5 scheduled naps separated by 2-hour breaks (Fig. 4). During each nap trial, the patient will lie quietly in bed and try to go to sleep, and the sleeping posture is *ad libitum*. Once the lights go off, the test will measure how long it takes for the patient to fall asleep. The patient will be awakened after sleeping 15 minutes. If the patient does not fall asleep within 20 minutes, the nap trial will end. A series of sensors will measure whether the patient is asleep and determine the sleep stage [7]. MSLT is performed by a trained sleep technologist. A baseline PSG on the night before the MSLT is required.

Hypnogram shows, in summary, the five periods in which the patient was allowed to sleep, evidencing three Sleep Onset Rapid Eye Movement Periods (SOREMPs), characterized by the presence of R stage (bold line) before its usual latency. The presence of two or more SOREMPs indicates the diagnosis of Narcolepsy in the context of hypersomnolence. In the summary table below, it is possible to see that

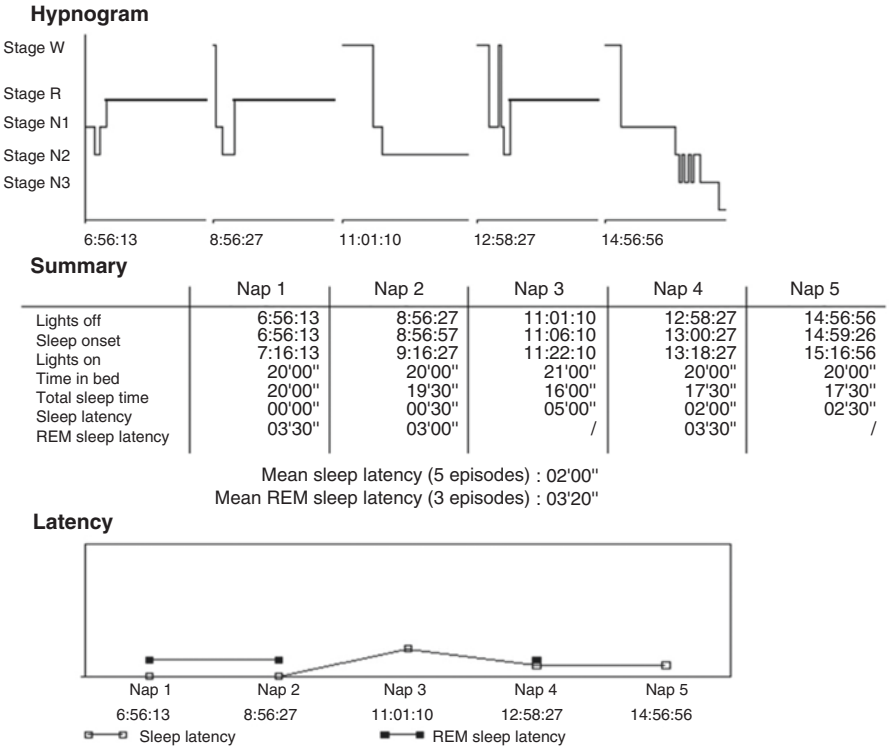

Fig. 4 Example of abnormal findings on the Multiple Sleep Latency Test. (Image courtesy from Dr. Fernando Morgadinho Santos Coelho. Original figure)

the mean sleep latency is ≤8 minutes (more precisely, 2 minutes), also suggesting hypersomnolence and reinforcing Narcolepsy diagnosis.

4 Maintenance of Wakefulness Test

The Maintenance of Wakefulness Test (MWT) assesses the individual's ability to stay awake for a period of time in a calm environment and without stimulation, also during the day. It measures wakefulness, showing whether an individual is able to stay awake for a defined period of time, usually beginning 90–180 minutes after the patient's usual wake-up time. Polysomnography and sleep logs may be useful before the test protocol, in selected cases [8]. Sleep latency is assessed by how long individuals take to fall asleep during the test. Four records are made with a duration of 40 minutes each, in which the patient is advised to try not to sleep, followed by intervals of 1h20min, in which one cannot sleep either (Fig. 5). The test is performed with the patient sited in bed with head supported and in dim light. MWT is

Example A – normal MW1

Nap	Initial sleep latency (minutes)	Unequivocal sleep latency (minutes)	SOREM?
1	40.0	40.0	No
2	40.0	40.0	No
3	34.0	34.0	No
4	40.0	40.0	No
Summary	Mean ISL: 38.5 min	Unequiv Mean ISL: 38.5 min	SOREMs: 0

Example B – abnormal MWT – indicative of hypersomnia

Nap	Initial sleep latency (minutes)	Unequivocal sleep latency (minutes)	SOREM?
1	20.0	20.0	No
2	24.0	24.0	No
3	12.0	15.0	No
4	30.0	30.0	No
Summary	Mean ISL: 21.5 min	Unequiv Mean ISL: 22.25 min	SOREMs: 0

Fig. 5 Example of normal and abnormal findings on the Maintenance of Wakefulness Test These are findings from a patient who is hypersomnolent on the MWT despite regular use of CPAP for OSA. A wake-promoting agent or psychostimulant may be indicated in this patient. MWT Maintenance of Wakefulness Test, ISL initial sleep latency, SOREM Sleep onset REM period. (Reprinted with permission from Boeve [13])

an indicator of how well individuals may be able to function and remain alert during quiet periods of inactivity [9].

The main difference between MWT and MSLT is that the former is intended to measure the ability to stay awake, while the latter quantifies the ability to fall asleep, although both express results based on the mean values of sleep latencies. MSLT is used as part of the diagnostic criteria of central disorders of hypersomnolence, especially narcolepsy and idiopathic hypersomnia [10]. On the other hand, MWT can be used to estimate safety in work environments in which somnolence would represent a risk and evaluate response to treatment in patients with excessive daytime sleepiness [8]. Nevertheless, because somnolence is a multifactorial clinical parameter, MWT results are difficult to interpret and predictive value for assessing accident risk is not clear [11].

5 Actigraphy

Due to its use in clinical practice for PTs, actigraphic devices will be explained in the next chapter.

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Actigraphy

Mario A. Leocadio-Miguel and John Fontenele-Araújo

It seems a new idea to predict a person's sleep health status based on the information of a simple wrist-worn device, like an ordinary wristwatch but equipped with multiple sensors, almost infinite memory, and state-of-the-art artificial intelligence (Fig. 1). However, this idea is far from being new. The desire to study someone's sleep in ordinary life, outside the domains and restrictions of a sleep laboratory, arose in the mid-1970s and that is the origin of actigraphy, the graphic representation of locomotor activity as a function of time. Actigraphy is being developed by the joint efforts of reasonably distinct science fields, including chronobiology, sports, and locomotor sciences, and, of course, sleep science. In the last decades, actigraphy has benefited from impressive technological advances in terms of sensors, battery, and memory constraints, allowing researchers and clinicians to explore this tool in sleep health research and sleep medicine. This chapter is dedicated to cover the basic science behind actigraphy, its main methods, its application in sleep medicine, as well as to present actigraphy as an already applied and promising tool to support physical therapy and rehabilitation practices.

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Fig. 1 Example of one actigraphy monitoring device. A wrist-worn device, like an ordinary wristwatch but equipped with multiple sensors, almost infinite memory, and state-of-the-art artificial intelligence. (Image courtesy from Dr. Fernando Morgadinho Santos Coelho)

1 From Chronobiology to the Emergence of Actigraphy

Briefly, it was from the adoption of the notion of time to the study of the living matter that the area of chronobiology emerged, a fundamental science for the description of the rhythmic phenomena that organisms express, from the oscillation throughout the 24 hours in the plasma concentration of a given hormone, to the marvelous sleep-wake cycle. Therefore, this reasoning guided researchers in the 1970s to the development of technology to capture locomotor activity over time, to infer the sleep-wake cycle. From this initiative emerged what we know today as actimetry (a measure of activity) or actigraphy (a graphic record of activity). In 1972, Foster and collaborators [1] described one of the first systems for continuous monitoring of locomotor activity, emphasizing that this mode of data collection would not interfere in the normal lives of the volunteers, in addition to allowing long time series, an important distinction from the restraints of the already established gold standard for the study of sleep, laboratory polysomnography. While this experiment represented a leap in our ability to measure sleep, although indirectly, it also resulted in an important methodological challenge – what to do now, or how to analyze these long time series?

Again, chronobiology was central to the methodological development of actigraphy. Assuming that the sleep-wake cycle could be inferred through the analysis of the 24-hour rhythm of locomotor activity, or circadian rhythm of rest-activity, several analytical tools have been developed in the past decades to better describe this rhythm. It can be assumed that one of the most important tools that were developed,

and used until today, was the method of adjusting cosine curves to the activity-rest rhythm data. Known as the Cosinor method [2], it allowed the observation and quantification of rhythmic phenomena, establishing standard metrics and the means to the comparison between records. Through this method (Fig. 2), we can assess the amplitude of a rhythm, the robustness of its rhythm, the average or mean level of activity, and the identification of the phases of minimum and maximum activity, among other important variables still in use [3].

Despite the successful use of the Cosinor and other methods of processing actigraphy data, a significant leap in quality in the analysis of time series of the rest-activity rhythm occurred in the mid-2000s, when the group of Professor Van Someren, from the Netherlands Institute for Neuroscience, proposed an alternative approach. Known as the non-parametric method of analyzing the rest-activity rhythm, this form of analysis considers the real format of the rhythm, which daily presents a sudden alternation between the high-level and low-level activity phases, related to wakefulness and sleep, respectively, therefore far from the shape of a standard cosine curve, which is the assumption of the Cosinor method. This has allowed an unparalleled advance in the actigraphy processing capacity, especially since the variables that are extracted through this method make it closer to the signal of the rest-activity rhythm and the sleep-wake cycle [4]. According to the recent

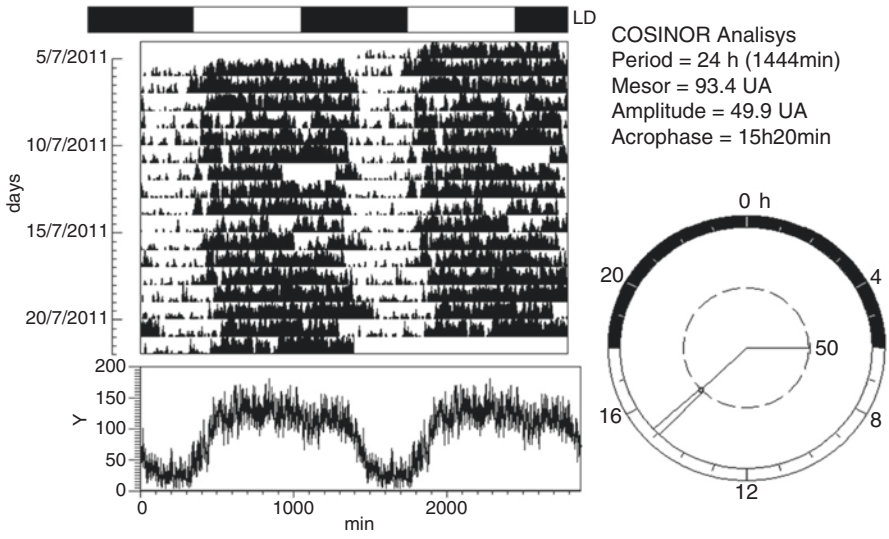

Fig. 2 Actigraphy and Cosinor method. Graphical representation of rest-activity rhythm. Double-plot actogram (upper left) and respective waveform (bottom left). Summary results of Cosinor analysis (upper right) and circular representation of Cosinor analysis, highlighting the acrophase around 15:00 hours. Created with El Temps software, using data from the authors (LNRB-UFRN). (Image courtesy from Dr. Mario A. Leocadio-Miguel and John Fontenele-Araújo. Original figure)

proposal by Gonçalves et al., we can even access, through non-parametric analysis of the rest-activity rhythm, indicators of the circadian and homeostatic components that control the sleep-wake cycle, measuring the stability of the rhythm over the days (interdaily stability) and the degree of fragmentation throughout the day (intradaily variation), respectively [5].

2 Actigraphy in the Assessment of Sleep

In parallel with the advances in the determination of the parameters of the rest-activity rhythm by actigraphy, the analysis of sleep through actimetry has undergone a succession of significant advances. Through the polysomnographic examination (PSG), it is possible to objectively determine sleep variables, such as sleep duration, markers of the sleep onset, sleep offset, sleep latency, number of nocturnal awakenings, time awake after sleep has started (WASO), sleep efficiency and total time in bed, besides, of course, the determination of the alternating phases during a sleep episode, culminating in the construction of the hypnogram [6]. To accomplish this goal, PSG requires the processing of multiple signals, both electrical (e.g., EEG) and mechanical (e.g., breathing), which provide enough information to help the analysis carried out by a trained and certified professional. However, the PSG is free of problems, especially since it is commonly performed outside the patient's home (in the sleep laboratory); it generates relative discomfort due to the number of elements connected to the patient during data collection, the high cost, and the need for trained and certified professionals. It is in this scenario that the original proposal of actigraphy is inserted, offering itself as a low-cost alternative, less cumbersome than PSG, with the ability to collect multiple days and nights in the individual's real sleep scenario, being essential for both long-term monitoring of patients and the screening of large groups of people [7].

However, can we measure and extract sleep variables using actigraphy? This is a question that has guided the efforts of different research groups. Partially based on the excellent performance of specialists in the visual analysis of the PSG traces, which demonstrates the capacity of our nervous system to recognize visual patterns, Kripke and collaborators described, still in 1978, that the actigraphy would be able to estimate, with agreement close to 90% with polysomnography, total sleep time, waking time after the sleep episode started, sleep onset, and, to a lesser degree, sleep latency [8]. However, despite enough performance, the analysis of the actigraphy data moved toward the automation of the processes, looking for cost reduction, velocity, and, fundamentally, an increase in the reproducibility capacity. In this sense, it was developed, in 1982, the first algorithm for automatic analysis of actigraphy, already with excellent results. This simple algorithm was based on the assessment, on a minute basis, of the degree of locomotor activity, and the determination of sleep or wakefulness for each minute was dependent on the measurement of the minutes around that given point, using a linear combination [9]. Multiple algorithms have been developed in the last decades, specially designed to validate actigraphy

against PSG for distinct populations, from young adults (91% agreement with PSG) to postmenopausal women (85% agreement with PSG) [10].

Even with all the described advantages of actigraphy over polysomnography, the need for multiple channels of PSG signals makes clear the complexity, or rather, the difficulty of estimating the characteristics of human sleep. Therefore, considering the relative simplicity of actigraphy, it is expected that there are limitations to its performance. It has been achieved a consensus that actigraphy has high accuracy and high sensitivity, that is, it is perfect for the correct identification of the presence of sleep. However, despite the efforts of different research groups and their algorithms, actigraphy has low specificity, that is, there is a difficulty in identifying epochs of wakefulness during sleep [11]. This represents the difficulty in differentiating rest with relative immobility and a real episode of sleep. Therefore, there is a tendency for an overestimation of total sleep time and an underestimation of wake time after the start of the sleep episode (WASO), in addition to a clear difficulty in identifying the sleep onset, especially in the presence of increased sleep latency, as commonly observed in insomnia patients. Outside the sleep laboratory, there is still a difficulty in specifying the exact interval in which the individual is in bed, something essential for calculating sleep latency and sleep efficiency (ratio between total sleep time and time total in bed). For this purpose, different algorithms use additional information, such as an input from the patient himself, through an event button, indicating going to and leaving the bed, as well as additional signal channels, such as the light exposure channel [12]. A final limitation, so far not overcome, is the inability to estimate sleep stages through actigraphy, despite the efforts of different research groups [13]. By far, from the technical point of view, we should highlight the effort of Ancoli-Israel and collaborators, acting as a board of specialists from the Society of Behavioral Sleep Medicine (SBSM) of the United States of America, that developed the most comprehensive guide to actigraphy monitoring, for both the clinical and the research applications [7].

3 Actigraphy in the Monitoring of Sleep Disorders

Considering the advantages and disadvantages of actigraphy, especially in the view of the gold standard of polysomnography, how useful is actigraphy to help us in screening, diagnosing, and monitoring the treatment of sleep disorders? Actigraphy can be considered a consolidated tool in the sleep field. Actigraphy can provide consistent objective sleep data, as recently stated by the American Academy of Sleep Medicine task force [14].

Sadeh and collaborators were the precursors in demonstrating, back in 1989, the validation and clinical potential of actigraphy for sleep disorders, though making clear the methodological challenge of its application. Despite the success in the minute-by-minute comparison with polysomnography in healthy populations, in which the degree of agreement for identifying sleep and wakefulness was 90.2% for normal adults, 89.9% for children, clinical populations represent a real challenge:

78.2% of the agreement for patients with insomnia and 85.7% for patients with sleep apnea [15].

However, is actigraphy useful or recommended to assist researchers and clinicians to correctly identify, design a treatment, or perform follow-up evaluations to treat every sort of sleep disturbance? Here we summarize the use of actigraphy based on the established recommendations found in the literature.

Considering the characteristics of the actigraphic examination, this tool is absolutely recommended in the scenario of a rather specific class of sleep disorders known as sleep disorders linked to circadian rhythmicity. They primarily result from the phenomena of desynchronization or friction between the endogenous expression of an individual's biological rhythmicity and external synchronizing agents, such as the environmental light-dark cycle, or even by the imposition of an incompatible sleep phase with high quality, restful sleep, as in night shift situations [16]. We can include here the challenges of working schedules that involve alternating shifts and night work, resulting in the imposition of an unnatural time allocation on workers' sleep, resulting in superficial, non-restorative, fragmented sleep, incompatible with health [17]. Moreover, usually, night workers exhibit short sleep duration, presence of naps, and great variability in sleep episodes [18]. Importantly, not all subjects submitted to shift work develop a sleep disorder. However, for those with shift work disorder, the treatment aims to improve sleep quality and adjust the circadian rhythms. Actigraphy is recommended to assess the allocation of the sleep phase and to quantify the irregularity of the sleep-wake cycle. One possibility is also the determination of the light phase, as actigraphy devices also register the light exposition. Therefore, it is possible to assess whether the worker is sleeping in a lighted environment or not and, thereby, impairing the quality of his sleep. With the actigraphic data, both activity and light, it is possible to instruct the patients on good practices of sleep hygiene.

In this group of diseases, we can also include the advanced and delayed syndromes of the sleep-wake cycle, in which patients have extreme times of sleep onset and offset, conditions often overlapping or confused with insomnia (Fig. 3). Finally, it is important to highlight the presence of a non-24-hour sleep-wake disorder (Fig. 4), or free-running sleep cycle, resulting from the inability to synchronize with external synchronizers. In this condition, common in individuals with total blindness or lesions of the central nervous system, sleeping and waking times are irregular, commonly happening with a cumulative delay day after day [19]. Actigraphy plays a central role in its diagnosis and monitoring here, mainly because the gold standard for diagnosis and monitoring of sleep disorders, polysomnography, is not useful in these cases (Fig. 5). Therefore, through actigraphy it is possible to monitor multiple days, multiple episodes of sleep, and, at the same time, assess their synchronization situation, allowing the determination of the most common therapeutic approaches of treating these disorders, such as melatonin therapy or light therapy for example [20].

Affecting a significant proportion of the world's population, reaching values above 30% in prevalence, as the case of Sao Paulo, Brazil [21], insomnia is an

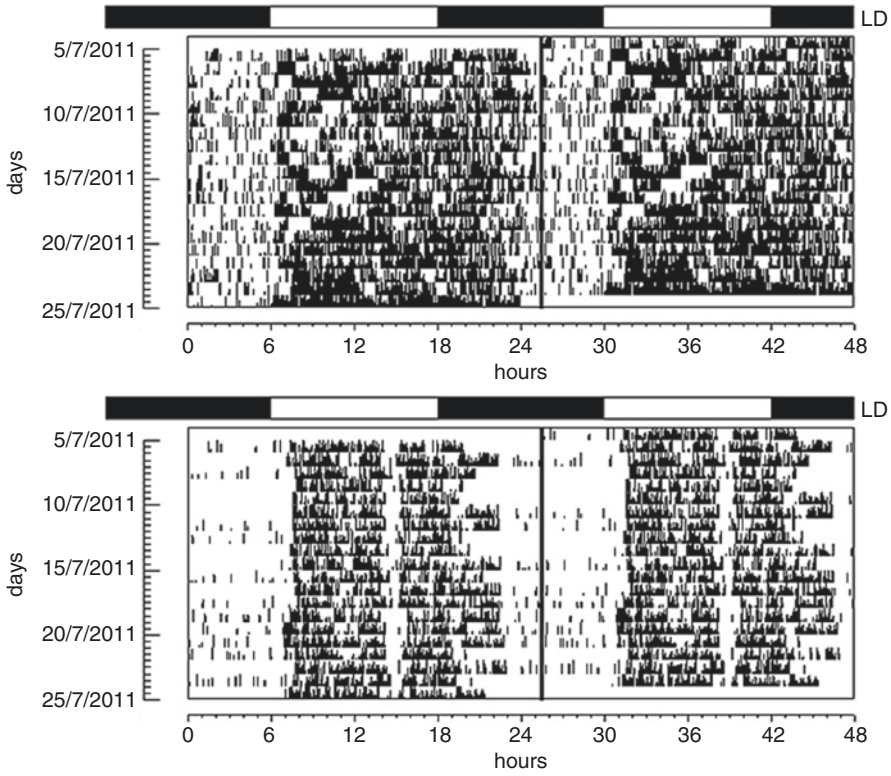

Fig. 3 Sleep-wake phase disorders. Upper actogram depicting a patient with delayed sleep phase disorder, highlighting late offset and onset of activity. Bottom actogram representative of a patient with advanced sleep phase disorder, highlighting daily long nap episodes. Created with El Temps software, using data from the authors (LNRB-UFRN). (Image courtesy from Dr. Mario A. Leocadio-Miguel and John Fontenele-Araújo. Original figure)

example of a condition that can benefit from actigraphy, especially since it provides continuous monitoring of the patient for multiple days in the natural, real scenario of occurrence of sleep, without the difficulties and artifacts arising from the laboratory polysomnographic examination [22]. Typically, patients with insomnia tend to overestimate their sleep latency, as well as to underestimate total sleep time, when compared to objective data from polysomnography, especially in sleep diary reports. Also, considering the high variability between nights, the collection of actigraphy data must be carried out as long as possible, with a duration of 1 week as a minimum recommendation [23].

Despite the controversy in the literature about the actual validation of actimetry for patients with insomnia, the adoption of this methodology is recommended for this type of sleep disorder. Williams and colleagues recently compared objective data of home polysomnography and actigraphy in insomnia patients, demonstrating that actigraphy can be considered a valid objective measure for measuring sleep

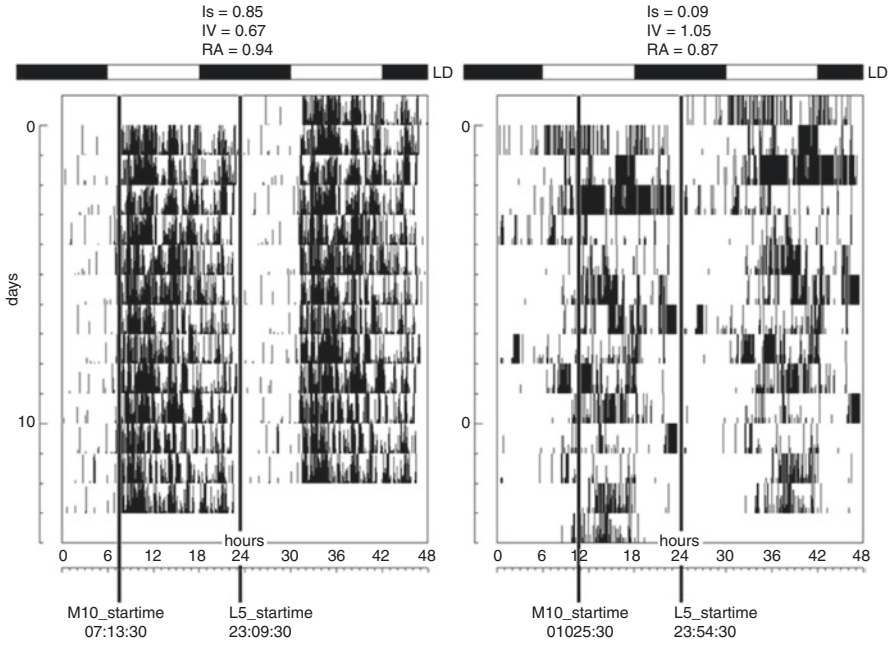

Fig. 4 Non-24-hour sleep-wake disorder. Left actogram representative of healthy 65+ years old volunteer. The right actogram represents an age-matched patient with moderate dementia, showing an irregular sleep-wake rhythm, decreased interdaily stability, and increased intradaily variability. Created with El Temps software, using data from the authors (LNRB-UFRN). (Image courtesy from Dr. Mario A. Leocadio-Miguel and John Fontenele-Araújo. Original figure)

latency, WASO, total sleep time, and sleep efficiency in patients with insomnia, corroborating the literature findings with patients in the sleep laboratory. However, an essential addition should be the adoption of an event button to specify the time in bed [24]. Actigraphy can also detect the coexistence of sleep disorders related to circadian rhythmicity in patients with insomnia, something impossible through polysomnographic examination. Importantly, actigraphy is a particularly important tool to discriminate insomnia from delayed sleep-wake phase disorder in adolescents and young adults [25]. Finally, actigraphy can be extremely useful for monitoring clinical interventions for insomnia, as it allows long-term data collection, therefore providing an interesting tool for the follow-up of sleep hygiene, self-awareness, metacognition, and sleep education.

A fraction of people suffering from insomnia presents a discrepancy between objectively measured (PSG or actigraphy) and subjectively experienced sleep. This condition, formerly known as sleep-state misperception, was renamed paradoxical insomnia and results in the overestimation of sleep latency and underestimation of total sleep time (TST) [26]. The role of actigraphy in this condition is to provide a long time series (several days), applied together with a sleep diary, to provide means for calculation of the misperception index (objective total sleep

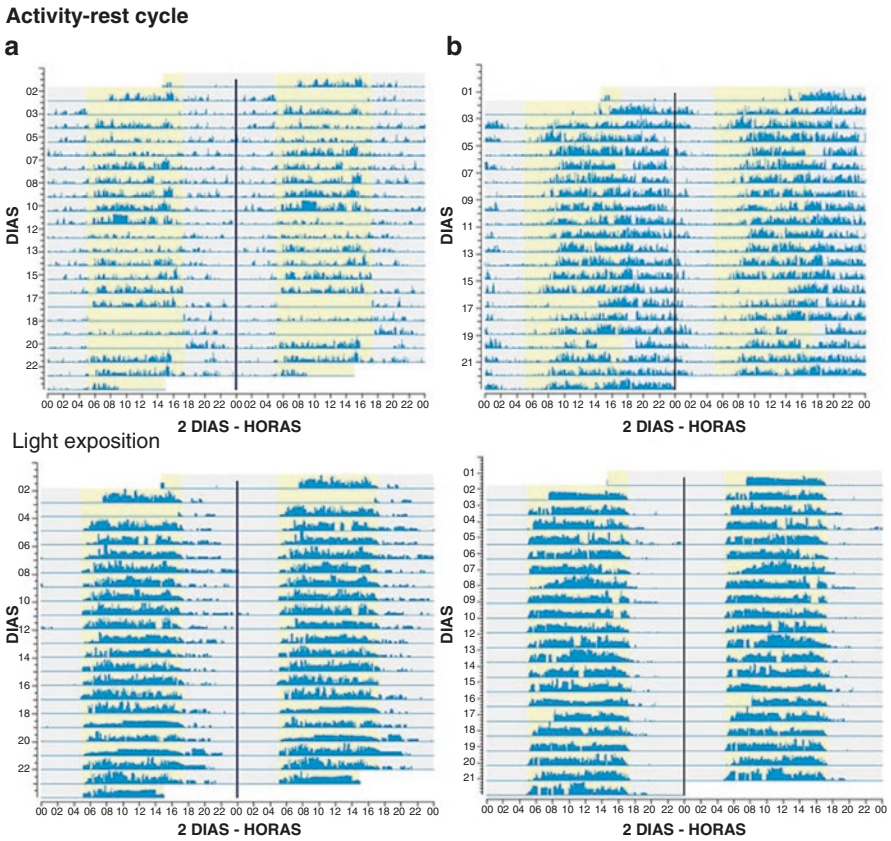

Fig. 5 Actigraphy assessment of blind volunteers exhibiting clear 24-hour sleep-wake rhythms, but with distinct phase relationship with natural light-dark (LD) cycle. Upper actogram demonstrating a delay in the rest-activity rhythm, considering the LD cycle. Bottom actogram demonstrating the onset of activity superposed with the beginning of the light phase of the day. Light exposition data from both volunteers were collected in the days and at the same location. Figure created with ActStudio Software using data from the authors (LNRB-UFRN). (Image courtesy from Dr. Mario A. Leocadio-Miguel and John Fontenele-Araújo. Original figure)

time (oTST) – subjective total sleep time (sTST)]/oTST). Interestingly, it was recently described that some individuals show increasing or decreasing trends in misperception across several nights of data collection. Therefore, it seems reasonable to collect actigraphy data for more than 1 week to capture this phenomenon [27].

Another sleep disorder, with prevalence in the population already equivalent to that of insomnia, is the group of respiratory sleep disorders, with emphasis on obstructive sleep apnea [28]. Although considering that actigraphy is unable to provide means for the diagnosis of sleep apnea, which primarily requires information about the interruption of breathing and desaturation [29], actigraphy is useful for

monitoring sleep fragmentation and the presence of outbreaks of locomotor activity during sleep, which follows the potential multiple awakenings throughout the night in these patients [30]. Not by chance, monitoring the effectiveness of therapeutic measures, as in the case of the adoption of ventilatory support during sleep, is a possible use for actigraphy in patients with obstructive sleep apnea. Moreover, it is known that the addition of the actigraphic measure to cardiopulmonary sensors or apnea detectors is beneficial because it allows the study of sleep measures associated with ventilatory interruptions. After all, it provides a better analysis of the total sleep time and sleep efficiency [31].

Actigraphy also presents itself as an interesting tool in the pictures of periodic limb movement disorder (PLMD). The typical assessment of this condition involves the analysis of the surface electroneuromyography (EMG) of the anterior tibial muscle performed during polysomnography. However, considering periodic movement as an essential phenomenon of this disorder, actigraphy could be applied successfully. Importantly, there is a positive correlation between the amplitude of EMG of the anterior tibial muscle and the actigraphy, precisely regarding the number of movements per hour of sleep. Still, considering the high variability between nights in patients with PLMS, actigraphy is even more important, which includes its potential for monitoring the treatment of this condition [32].

Actigraphy is also fundamental in the assessment of total sleep time as a first step before the multiple sleep latency test (MSLT) in patients suspected of disorders of hypersomnolence, such as narcolepsy [33]. Importantly, actigraphy is an underestimated tool in clinics able to discriminate narcolepsy type 1 from primary insomnia [34]. Finally, actigraphy is essential in the assessment of daytime sleep, naps, and could reflect daytime somnolence in those suffering from hypersomnolence.

4 Actigraphy in the Context of Rehabilitation

Considering the fundamental role of actigraphy as a tool for measuring the amount of locomotor activity as a function of time, are we allowed to use actigraphy in the diagnosis and the follow-up of patients with secondary sleep disorders? The most direct answer is yes, particularly in conditions that compromise, either acutely or chronically, the motor function, although the particularities of the distinct motor phenotypes of the different disorders affect the generalization and efficiency of sleep detection algorithms [35].

One of the most well-known associations is between pain and sleep. It is a bidirectional relationship where poor sleep and increased pain positively feedback one another [36]. A clear example of this relationship is the recent report of postmenopausal women suffering from insomnia and chronic pain. Actigraphy was essential to disclose that sleep duration is a predictor of pain intensity in the following morning and that pain intensity at bedtime predicts both time in bed and sleep duration [37].

The use of accelerometry to monitor motor patterns, the amount of physical activity, and even the metabolic equivalent associated with energy expenditure is already established in the literature, including for patients with motor limitations [38]. Most studies in this area, however, use the actigraph in the hip region, which limits the ability to estimate total sleep time, sleep efficiency, and WASO, but could be overcome when the actigraph device is worn on the wrist [39]. However, actigraphy can provide measures of locomotor activity, an essential feature because multiple clinical conditions have a clear association with impairments in biological rhythms, especially regarding the sleep-wake cycle, highlighting the potential of this methodology beyond sleep medicine. An especially useful example for the rehabilitation field is the use of the total activity score, derived from the sum of locomotor activity over the 24 hours, that has successfully been used to monitor the evolution of patients with motor disorders, as in the case of stroke [40]. In a recent effort, Fleming and colleagues studied the relationship between the evolution of functional independence in patients with injuries in the central nervous system and the degree of sleep fragmentation measured through actigraphy. The authors demonstrated that the degree and speed of recovery in these patients can be predicted by sleep fragmentation [41]. The non-parametric analysis of actigraphy is also a powerful tool in the context of rehabilitation, and it has been shown that in patients with spinal cord injury, both the measurement of intraday variability (a proxy of sleep fragmentation) and the relative amplitude between the phases of maximum and minimal locomotor activity (wakefulness and sleep, respectively) are associated with poor sleep quality. Besides, the variable called interdaily stability (a proxy of synchronization of the sleep-wake cycle) is a predictor of pain in these patients [42].

5 Final Words

Multidisciplinary since its beginning, the limits of the usefulness of actigraphy are yet to be determined. However, it must be crystal clear that actigraphy is not meant to be a mere substitute for polysomnography, despite the relatively high agreement in some sleep variables. Rather, it must be considered as a broad-spectrum tool that may also be used as a supplement in sleep health. Actigraphy is mandatory in the assessment of sleep disorders related to circadian rhythmicity. Moreover, it is also highly recommended for differential diagnosis, especially for young patients with insomnia complaints and delayed syndrome of the sleep-wake cycle. Another interesting role of actigraphy is in sleep misperception (Fig. 6), in which the actogram can be adopted to clarify, directly to the patient, the pattern of the sleep-wake cycle. This approach is also useful for sleep education and as a follow-up tool in interventions. Finally, as a graphical representation of the motor output, actigraphy is being progressively more applied in the scenario of rehabilitation, ideally in patients recovering from neurological diseases or other pathologies compromising the movement expression and locomotion, usually displaying concurrent alterations of the sleep-wake cycle.

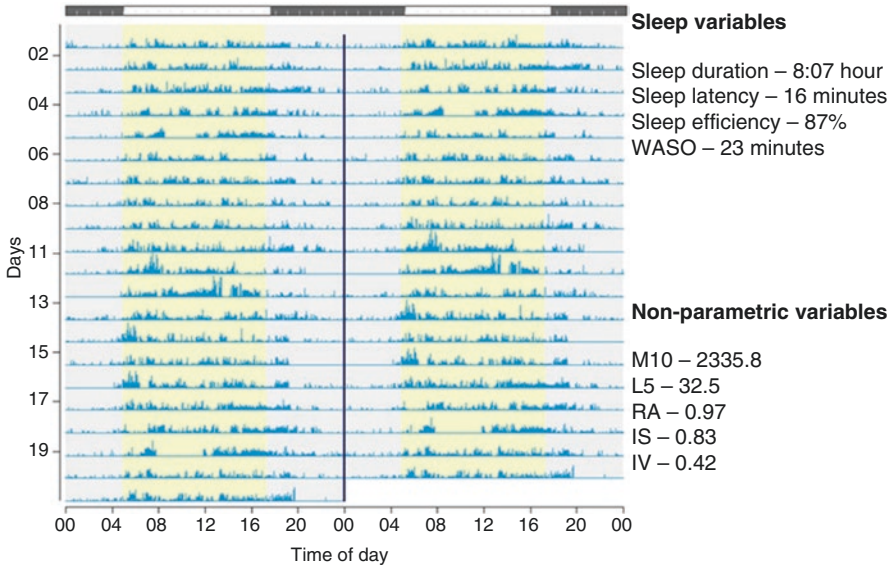

Fig. 6 Actogram of 21 days of actigraphy assessment of a patient with complaints of short sleep, but with an absence of diurnal sleepiness. Actigraphy revealed a regular 24-hour rest-activity rhythm, high levels of M10 (activity phase), and low level of activity during sleep (rest phase), with an estimated sleep duration of 7:30 hours, suggesting a sleep-wake cycle within a normal range. A patient diagnosed with sleep misperception. Actigraphy examination was essential as an explanation tool for the patient. Graphics created with ActStudio Software, using data from the authors (LNRB-UFRN). (Image courtesy from Dr. Mario A. Leocadio-Miguel and John Fontenele-Araújo. Original figure)

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Correction to: Normal Sleep: Interindividual Differences and Sleep Variability

Maria Júlia Figueiró Reis

Corrections to:

Chapter 2 in: C. Frange, F. M. S. Coelho (eds.), Sleep Medicine and Physical Therapy, https://doi.org/10.1007/978-3-030-85074-6_2

The order of references in Chapter 2 has been published incorrectly. This has been corrected now in the revised version.

The updated version of chapter can be found at https://doi.org/10.1007/978-3-030-85074-6_2

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