Milestones in Drug Therapy
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Antonio Guglietta *Editor*

Drug Treatment of Sleep Disorders

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Preface

Sleep disorders are very common in the modern society. In the United States it is calculated that between 50 and 70 million of people suffer from some kind of sleep disorder while it is estimated that in the developing countries across the world these conditions affect approx. 150 million people. Disorders of the sleep are on the rise worldwide and affect people of all ages, gender, and ethnicity. An inadequate sleep poor in quantity and quality and an excessive daytime sleepiness negatively affect daily activities causing, for example, poor concentration, memory difficulties, and impaired driving ability.

Given the magnitude and impact on the society, it is not surprising that there is an increasing interest by governments, universities, and media on sleep and sleep-related disorders. Several scientific societies such as The American Academy of Sleep Medicine, The National Sleep Foundation, and the Sleep Research Society have been established and disorders of sleep are now recognized as a separate medical subspecialty with specific training courses being offered in medical schools worldwide to prepare doctors to properly diagnose and treat these disorders.

The past decade has witnessed major advances in the understanding of sleep physiology and pharmacology which have provided a better understanding of the mechanisms that underlie sleep and have prompted promising research in this field which in turn have led to the development of new and better drugs to treat these conditions. The FDA has recently approved new drugs to treat disorders of sleep and other molecules are in advanced phase of clinical development or have just completed the development process. Furthermore, new regulatory and clinical guidelines for the development of drugs and treatment of these conditions have been issued or are in preparation.

The idea behind this book is to review some of the recent major breakthroughs in the drug treatment of sleep disorders. The drugs reviewed in the book, whether recently approved drugs (i.e., Doxepin), variations of previously approved molecules (i.e., Zolpidem sublingual preparation), or new chemical entities in late stage of clinical development (i.e., Lorediplon), have significantly changed or are expected to change the drug treatment of these disorders. Each chapter of the book was written by an expert in the field and is structured in such way that can

be read as stand-alone chapter or as part of the whole book. The final result is a comprehensive yet practical book that will bring all the scientists, clinicians, and drug developers up to date in this area[1].

Barcelona, Spain Antonio Guglietta
August 2014

[1] After this book went to press, on Aug 13th, 2014, the US Food and Drug Administration approved Suvorexant tablets (Belsomra) to treat difficulty in falling and staying asleep (insomnia). Suvorexant is the first approved drug of the orexin antagonists class.

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An Overview of Sleep Physiology and Sleep Regulation

Chiara Berteotti, Matteo Cerri, Marco Luppi, Alessandro Silvani, and Roberto Amici

Abstract Sleep is a complex behavior that cyclically alternates with wakefulness and is fundamental for both mental and physical wellness. During normal sleep the body acquires a specific posture; any active behavior is absent and mental activity typically oscillates between a state of "loss of consciousness" and the experience of dreaming.

Sleep is, by itself, a cyclical process characterized by the alternation of two phases, non-REM (NREM) sleep and "rapid eye movement" (REM) sleep, during which the typical synchronized electroencephalographic (EEG) pattern of NREM sleep is substituted by a "paradoxical" EEG desynchronization.

NREM sleep is a state of minimal energy expenditure and motor activity, during which cardiorespiratory and thermoregulatory variables are driven by the autonomic nervous system at a lower and more stable level compared to wakefulness. During REM sleep, beyond the occurrence of REMs, posture control is lost and dreams become more vivid. Furthermore, autonomic activity is highly unstable leading to centrally driven surges in heart rate and blood pressure, breathing becomes irregular, and thermoregulation is suspended or depressed, suggesting a derangement of the integrative regulation of physiological functions.

Overall sleep quality is one of the most important parameters considered for the subjective assessment of quality of life and general health status. However, although sleep function(s) is intuitively associated with some kind of rest that seems to be mostly required by the central nervous system, and many theories on sleep function have been proposed, a full comprehension of sleep function has not yet been achieved and is probably not imminent.

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1 Neurophysiology and Neurobiology of Sleep

1.1 What Is Sleep?

Sleep is a specific behavior, common to humans and other animals, that cyclically alternates with wakefulness and is undoubtedly fundamental for both mental and physical wellness. Everyone is aware of the importance of having a good sleep and a proper daily sleep time. Sleep quality is among the most important parameters considered for the subjective assessment of quality of life and general health status.

During sleep the body needs to acquire a typical posture; any active behavior is absent and, following a normal sleep time, there is a clear perception of bodily restoration as well as that of the mind. In fact, the strong "pressure" to fall asleep after either a long period of waking or a very tiring activity is a very common subjective experience. The mental activity during sleep is also quite peculiar and after the subjective experience of the "loss of consciousness" when falling asleep, the experience of dreaming is characteristic: a mental phenomenon that, historically, represents one of the main topics in cultures and arts.

Falling asleep is a kind of progressive reduction of the awareness of self and environment; hence, in the past, sleep was considered to be a mere passive process, in which brain activity was reduced, and even absent, compared to wakefulness (Dement 2011). Some clinical observations by the neurologist Constantin von Economo in 1916, as well as experimental data obtained in the 1930s by Frédéric Bremer with his milestone experimental preparations on cats named "cerveau isolé" and "encéphale isolé", apparently supported this view. Von Economo observed that patients affected by "encephalitis lethargica" typically presented lesions localized at the boundary between the mesencephalon and the diencephalon, while Bremer, on the basis of his experimental results, postulated that sleep was the result of the reduction of afferent sensory stimuli to the forebrain.

In 1929, Hans Berger introduced electroencephalography (EEG) as a tool to record the cortical electrical activity from the scalp. The EEG was an amazing technical advancement in neuroscience and soon it was considered of primary importance for the investigation of the sleeping brain. In support of Bremer's theory, Giuseppe Moruzzi and Horace Magoun found, in the late 1940s, that the stimulation of the pontine reticular formation induced a waking EEG in the anesthetized cat. Therefore, they suggested that the "deafferentation" of the sensory signals to the telencephalon was reasonably due to a transient change in the functional activity of the reticular formation (Kumar 2010).

Although the "passive" theory of sleep was the most widely accepted, some experimental results suggested that sleep was actively induced by some neural structure. Some of the patients studied by Von Economo presented an insomnia that was associated with a lesion of the anterior hypothalamus. Moreover, in the 1940s, Rudolph Hess showed that a low frequency stimulation of the thalamus could induce sleep in the cat, while Walle Nauta proposed, on the basis of

brain-lesion studies in the rat, that the rostral part of the hypothalamus was the site for the "capacity of sleep" (Kumar 2010).

However, the definitive turning point leading to the concept that sleep is a state that is actively promoted by the brain was the discovery of an "active" sleep phase; it was in 1953 that Eugene Aserinsky and Nathaniel Kleitman described the existence of a sleep phase which cyclically interrupted the typical synchronized EEG pattern of sleep. During this phase it was possible to observe frequent eye movements under the closed eyelids and the EEG signal was desynchronized and very similar to that observed in wakefulness.

It took several years before this functional state was recognized as a distinct sleep phase. It was Michel Jouvet who, in 1959, defined this particular state as "paradoxical sleep" (Kumar 2010). Soon, sleep would be divided into two main phases: the "rapid eye movement" (REM) phase and the nonREM (NREM) phase (Dement 2011). Also, William Dement, while working with Kleitman, associated REM sleep with dream occurrence (Dement 2011). REM sleep was soon considered a very peculiar sleep phase, due to the paradoxical EEG signal and the occurrence of REMs, as well as several other physiological features, such as the paralysis of anti-gravitational muscles, the occurrence of ponto-geniculo-occipital (PGO) waves, and, as firstly assessed by Pier Luigi Parmeggiani, a dramatic functional change in physiological regulation, with a large autonomic instability.

Therefore, sleep is now considered to be a complex and active behavioral state, during which the brain works differently from normal waking. Sleep cyclically alternates with wakefulness every single day and is, by itself, a cyclical process characterized by the alternation of two phases, NREM sleep and REM sleep.

1.2 Sleep Architecture

In every species studied, sleep propensity is closely related to the time of day and consequently to the circadian rest-activity cycle, and in humans, the majority of sleep time is concomitant with the nocturnal hours (Achermann and Borbély 2011).

During NREM sleep, the EEG becomes typically synchronized, i.e., rich in slow-frequency and high-voltage waves, in contrast to the fast-frequency and low-voltage waves of the typical waking EEG (Brown et al. 2012). In humans the structure of NREM sleep is further subdivided into four stages (S1–S4, Rechtschaffen and Kales classification, R&K) or three stages (N1–N3, American Academy of Sleep Medicine classification, AASM) (Carskadon and Dement 2011) based on the degree (intensity) of the EEG synchronization. During sleep occurrence, the NREM sleep stages and REM sleep appear in a precise order:

1. NREM sleep S1 (N1) represents the transition from wakefulness to sleep and is considered to be the first step of EEG synchronization; theta (4.0–7.0 Hz) activity is predominant.

2. The beginning of S2 (N2) is characterized by the appearance in the EEG of two typical signs, the "K-complex" (a single high voltage negative wave, followed by a single slow positive wave) and the "spindle" (a 12–14 Hz oscillation with an increasing and then a decreasing amplitude, lasting around 1–2 s).
3. The deeper stages of NREM sleep are S3 and S4 of the R&K classification, which essentially constitute together the N3 stage of the AASM classification. In these stages, the EEG is rich in (S3) or fully dominated by (S4) high-amplitude activity in the slow delta range (0.5–2.0 Hz). This slow-wave activity (SWA) is considered to be the macroscopic result of a cellular phenomenon, called "slow-oscillation," during which cortical neurons oscillate between two functional states, the hyperpolarized and silent "down-state" and the high-frequency (around 40 Hz) discharging "up-state" (Steriade et al. 2001). Actually, the "slow-oscillation" is a travelling wave, involving almost all the cortical areas, apparently starting from the frontal cortex and then propagating towards the posterior regions (Massimini et al. 2004).
4. During a normal NREM-REM sleep cycle, S4 is followed by a reverse progression, through S3, to light NREM sleep stages (S2–S1), until REM sleep occurs. REM sleep is followed by either an awakening or by S1–S2. In the latter case, the whole sequence to S3–S4 and back to S2–S1 and REM sleep usually starts again.

Typically, in humans, this cyclic process lasts about 90–100 min (Carskadon and Dement 2011) and during a standard night-time sleep period 4–5 cycles are completed. The deepest NREM sleep stage (S4) is usually reached only during the first part of the night. Also, late cycles are generally characterized by the occurrence of longer REM sleep phases, lasting up to 20–25 min in the very last cycle before waking (Carskadon and Dement 2011). Normally, morning awakening directly follows a completed REM sleep phase.

In the young adult the overall night sleep duration is between 7 and 8 h, and REM sleep represents 20–25 % of the total sleep amount. The daily amount of sleep and the quantity of SWA progressively decrease from childhood to old age, while the proportion of REM sleep, which is apparently almost double in the newborn compared to the young child, is then maintained at a stable level throughout the life span.

1.3 Sleep Mechanisms

In recent years, great steps forward have been made in the understanding of the brain mechanisms underlying sleep and wakefulness control and regulation (cf. Brown et al. 2012). Schematically, the cyclical alternation of wakefulness and sleep is considered to be mainly due to the cyclical activation and inhibition, respectively, of a key neural structure defined as the ascending reticular activating system. This system consists of a network of fibers projecting from the brainstem to