

# Contents

**Preface: Sleep Medicine: The Uncertain Future** **xiii**

Ana C. Krieger and Teofilo Lee-Chiong Jr

**Prescription Drugs Used in Insomnia** **315**

Sylvie Dujardin, Angelique Pijpers, and Dirk Pevernagie

In insomnia, the subjective aspects of the sleep complaint are paramount in the diagnostic criteria. Epidemiologic studies increasingly point to a link between insomnia and somatic morbidity and mortality, but until now, only in the subgroup of objectively poor sleepers. Although pharmacologic treatment might offer some benefits to this subgroup of insomnia patients, to date, there is no evidence that hypnotics can ameliorate their health risks. Further unraveling of the neurobiology and genetics of sleep regulation and the pathophysiology of insomnia will help the development of drugs that not only improve subjective sleep complaints but also objective health outcomes.

**A Meta-Analysis of Mindfulness-Based Therapies for Insomnia and Sleep Disturbance Moving Toward Processes of Change** **329**

Joshua A. Rash, Victoria A.J. Kavanagh, and Sheila N. Garland

MBTs are increasingly being investigated as a viable treatment of insomnia or sleep disturbance. To date, 13 trials published since 2010 suggest that MBTs are efficacious for improving symptoms of insomnia and sleep quality relative to psychological placebos and inactive control conditions with medium to large effects. Limited evidence suggests that these effects are sustained at 3-month follow-up. Despite this, limited data were collected evaluating the empirically supported mechanisms or processes of change. The authors propose a testable model in the psychological process model of sleep that they hope will advance the next generation of research into MBTs for insomnia.

**Cognitive Behavioral Therapy for Insomnia in School-Aged Children and Adolescents** **355**

Julia Dewald-Kaufmann, Ed de Bruin, and Gradisar Michael

One of the most prevalent sleep disorders in children and adolescents is “insomnia,” which can be briefly described as problems with initiating and/or maintaining sleep with associated daytime consequences. These are typical insomnia symptoms, and when experienced for long enough and when they interfere with an important area of the young person’s life (eg, schooling), then a diagnosis of an insomnia disorder may be warranted. The authors strongly urge the scientific community to conduct further controlled trials, including dismantling trials that evaluate the relative effectiveness of individual cognitive behavioral therapy for insomnia components.

**Drugs Used in Parasomnia** **367**

Paola Proserpio, Michele Terzaghi, Raffaele Manni, and Lino Nobili

Parasomnias, especially disorders of arousal during childhood, are often relatively benign and transitory and do not usually require a pharmacologic therapy. A relevant aspect in both nonrapid eye movement and rapid eye movement parasomnia

treatment is to prevent sleep-related injuries by maintaining a safe environment. Physicians should always evaluate the possible presence of favoring and precipitating factors (sleep disorders and drugs). A pharmacologic treatment may be indicated in case of frequent, troublesome, or particularly dangerous events. The aim of this article is to review current available evidence on pharmacologic treatment of different forms of parasomnia.

### **Precision Medicine for Idiopathic Hypersomnia**

379

Isabelle Arnulf, Smaranda Leu-Semenescu, and Pauline Dodet

Idiopathic hypersomnia (IH) includes a clinical phenotype resembling narcolepsy (with repeated, short restorative naps), and a phenotype with an excess of sleep, sleep drunkenness, drowsiness, and infrequent long, nonrestorative naps. Sleep tests reflect this heterogeneity. MSLTs are greater than 8 min in 2/3 of the cases and poorly repeatable. Sleep excess is better captured by extended monitoring identifying 11 to 16h of sleep/24 h. Patients with IH are young and more often female. Possible mechanisms of IH include deficiencies in arousal systems, inappropriate stimulation of sleep-inducing systems, and long biological night. Treatments now include robust studies of modafinil, clarithromycin, and sodium oxybate.

### **Drugs Used in Narcolepsy and Other Hypersomnias**

399

Gert Jan Lammers

Lifestyle adjustment, in combination with symptomatic pharmacologic treatment, allows most patients, particularly those with an inability to stay awake during the day, to live a relatively normal life. New pharmacologic substances show encouraging results in phase 2 and 3 studies to improve the current situation. More dedicated studies in IH, particularly in those who suffer from an increased need for sleep, are needed.

### **Pharmacologic and Nonpharmacologic Treatment of Restless Legs Syndrome**

407

Galia V. Anguelova, Monique H.M. Vlask, Arthur G.Y. Kurvers, and Roselyne M. Rijsman

Restless legs syndrome (RLS) is a sleep-related disorder defined by an urgency to move the legs, usually combined with uncomfortable or unpleasant sensations, which occurs or worsens during rest, usually in the evening or at night, and disappears with the movement of the legs. RLS can be classified as idiopathic or primary, and secondary to comorbid conditions (eg, renal disease, polyneuropathy). The pathophysiology of RLS is still unclear. This article provides an updated practical guide for the treatment of primary RLS in adults.

### **Drugs Used in Circadian Sleep-Wake Rhythm Disturbances**

421

Helen J. Burgess and Jonathan S. Emens

This article focuses on melatonin and other melatonin receptor agonists and summarizes their circadian phase shifting and sleep-enhancing properties, along with their associated possible safety concerns. The circadian system and circadian rhythm sleep-wake disorders are described, along with the latest American Academy of Sleep Medicine recommendations for the use of exogenous melatonin in treating them. In addition, the practical aspects of using exogenous melatonin obtainable over the counter in the United States, consideration of the effects of concomitant light exposure, and assessing treatment response are discussed.

**Chronic Opioid Use and Sleep Disorders** 433

Shahrokh Javaheri and Michelle Cao

Opioid medications are considered a significant component in the multidisciplinary management of chronic pain. In the past two decades, the use of opioid medications has dramatically risen in part because of an increased awareness by health care providers to treat chronic pain more effectively. In addition, patients are encouraged to seek treatment. The release of a sentinel joint statement in 1997 by the American Academy of Pain Medicine and the American Pain Society in a national effort to increase awareness and support the treatment of chronic pain has undoubtedly contributed to the opioid crisis.

**Pharmacologic Treatment of Sleep Disorders in Pregnancy** 445

Laura P. McLafferty, Meredith Spada, and Priya Gopalan

Pregnancy is a unique physiologic state whose characteristics often predispose women to new-onset sleep disturbances or exacerbations of preexisting sleep disorders. Pregnancy-related factors that can disrupt sleep include heartburn, nocturnal oxytocin secretion, nocturia, and fetal movement. Sleep disorders in pregnancy include insomnia (primary and secondary), restless legs syndrome, and narcolepsy.

**Turning Over a New Leaf—Pharmacologic Therapy in Obstructive Sleep Apnea** 453

Jan Hedner and Ding Zou

Despite extensive research, there is currently no approved drug for obstructive sleep apnea (OSA) treatment. OSA is a heterogeneous condition that involves multiple dominating pathophysiological traits. Drug development in this field needs to address both pathophysiological mechanisms and associated comorbid conditions in order to meet requirements for long-term therapy in OSA. Several drug candidates have been proposed and ongoing phase II trials that target various forms of sleep-disordered breathing have been initiated. The field is moving toward tailored therapeutic approaches in patients with OSA.

**Drug-Induced Insomnia and Excessive Sleepiness** 471

Ann Van Gastel

Undesirable side effects of insomnia and/or sleepiness may occur with many prescribed drugs, psychotropics as well as non-psychotropics. These central nervous system effects can be explained by the interactions of the drug with any of the numerous neurotransmitters and receptors that are involved in sleep and wakefulness. Also a close - sometimes bidirectional - relationship between disease and (disturbed) sleep/wakefulness is often present e.g. in chronic pain; drug effects may lead this vicious circle in both ways. Besides the importance for health and quality of life, effects on sleep or waking function can be a potential source of non-compliance.

**Pharmacologic Management of Excessive Daytime Sleepiness** 485

Taisuke Ono, Shinichi Takenoshita, and Seiji Nishino

Excessive daytime sleepiness (EDS) is defined as “irresistible sleepiness in a situation when an individual would be expected to be awake, and alert.” EDS has been a

big concern not only from a medical but also from a public health point of view. Patients with EDS have the possibility of falling asleep even when they should wake up and concentrate, for example, when they drive, play sports, or walk outside. In this article, clinical characteristics of common hypersomnia and pharmacologic treatments of each hypersomnia are described.

### **Brain Stimulation for Improving Sleep and Memory**

505

Roneil G. Malkani and Phyllis C. Zee

Sleep has been increasingly recognized for its importance in many functions, including cognition. Emerging techniques aim to stimulate the brain to enhance sleep, particularly slow wave sleep, and improve memory. Several methods have shown promise, such as transcranial electrical stimulation and transcranial magnetic stimulation. In particular, acoustic stimulation of slow wave sleep shows significant potential to enhance slow wave sleep, sleep spindles, their phase coupling and declarative memory. While these methods may enhance memory non-specifically, targeted memory reactivation uses associated cues to consolidate specific memories. Future research is necessary to determine long-term potential as tools in healthy and clinical populations.

### **Hypnotic Discontinuation in Chronic Insomnia**

523

Jonathan P. Hintze and Jack D. Edinger

Insomnia disorder is common in adults and children. The estimated prevalence ranges from 9% to 15% in the general population, with higher prevalence in certain subpopulations. Hypnotic medications are those that tend to produce sleep and are frequently used to treat insomnia. Commonly used hypnotics in adults include benzodiazepines (BZDs), BZD receptor agonists, antihistamines, antidepressants, melatonin receptor agonists, orexin receptor antagonists, and antipsychotics. However, hypnotic discontinuation is difficult and often unsuccessful. This article discusses strategies to discontinue hypnotics and evidence supporting their use.

### **Sleep-Related Drug Therapy in Special Conditions: Children**

531

Nicholas-Tiberio Economou, Luigi Ferini-Strambi, and Paschalis Steiropoulos

Pharmacologic treatment of the most common pediatric sleep disorders lacks evidence, and alternative methods, which have been proved to alleviate the symptoms, are preferred in most cases. The implementation of specific guidelines is of great importance because sleep disorders in children are not rare and they can negatively affect children's development and their cognitive and social skills. This article summarizes the current therapeutic management of sleep disorders in children, bearing in mind the absence of evidence-based guidelines on this topic.