Review

Pharmacological Treatments of Sleep-Wake Disorders: Update 2023

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Review

Pharmacological Treatments of Sleep-Wake Disorders: Update 2023

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Abstract: Biological, environmental, behavioral, and social factors can influence sleep and lead to sleep disorders or diseases. Sleep disorders are common, numerous and heterogeneous in terms of their etiology, pathogenesis, and symptomatology. Management of sleep-wake circadian disorders (SWCD) includes education to sleep hygiene, behavioral strategies, psychotherapy (cognitive behavioral therapy (CBT), particularly), instrument-based treatments (i.e. positive airway pressure therapy, hypoglossal nerve stimulation), and pharmacotherapy. Depending on the disease, therapy varies and is executed sequentially, or can be a combination of several forms of therapy. Drugs used for SWCD include traditional sleep or wake-promoting agents, chronotherapeutic agents. Recently, novel medications, which are more precisely acting on specific neurochemical systems (i.e. orexin system) important for sleep and wake, are also increasingly being used. In this review, the pharmacotherapy of common sleep disorders (insomnia, sleep-related breathing disorder, central disorders of hypersomnolence, circadian rhythm sleep wake disorders, parasomnias, and sleep-related movement disorders) embedded in the overall therapeutic concept of each disorder is presented. There is also an outlook on possible future pharmacotherapies.

Keywords: pharmacotherapy; sleep-wake disorders; hypersomnolence; restless legs; syndrome; parasomnias; sleep-related breathing disorders; insomnia; circadian disorders

1. Introduction

There is a growing understanding of the neurobiology and functions of sleep and its effects on human health, including brain and mental health [1]. More than 1/3 of the global population reports on sleep loss [2,3]. Insufficient, or irregular sleep, and sleep- wake disorders adversely affect human health in several dimensions, with both immediate effects such as sleepiness, impairment at work or reduced psychosocial wellbeing, and -being a chronic sleep disorders- as well as by an increased risk for (i.e.) dementia, stroke, cardiovascular disorders or depression [4–6].

There is also a high economic burden of sleep disorders. In a European study from 2010, the costs of disorders of the brain were calculated. The burden of sleep disorders were high and comparable with mental and neurological disorders [7], i.e. for narcolepsy the direct and indirect costs reached €10,000 per patient, annually. Recently, several professional societies aim at increasing awareness, education and research on sleep, and moving healthcare policy towards healthy sleep [1,6,8].

The neurobiology of sleep and wakefulness is complex and includes not only wake- or sleep-promoting systems, but also homeostatic, circadian, and motivational processes [9,10]. The neurobiology of sleep is beyond the scope of this review, and reference is made to the relevant literature.

Biological factors, environmental, behavioral, and social factors all can influence sleep. The individual may influence some of these factors, such as sleep times, sleep duration or body weight.

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Shift work, a noisy sleep environment, hunger, or psychomental stress due to occupational overload are examples for factors that often cannot be influenced, however.

Sleep disorders are heterogeneous in their pathogenesis and manifestation. The International Classification of Sleep Disorders [11] into the sections classifies them: insomnia, sleep-related breathing disorders, central disorders of hypersomnolence, circadian rhythm sleep-wake disorders, parasomnias, sleep-related movement disorders and other sleep disorders.

Management of sleep-wake circadian disorders (SWCD) includes behavioral strategies, psychotherapy, instrument-based treatments (i.e. positive airway pressure therapy), and pharmacotherapy, depending on the individual disorder. Often there is a combined or sequential treatment of the diseases, which includes the different forms of therapy.

Pharmacological treatment may sometimes be avoided if there were greater awareness of the need for longer and good sleep leading to lifestyle and behavioral changes (e.g., stress reduction, weight control).

Many SWCD need permanent pharmacological treatment. Drugs used act on the different neurochemical systems that generate wakefulness, or sleep respectively. Frequently used drugs and their pharmacological, neurobiological and clinical effect are shown in Table 1.

Table 1. Commonly used medications for SWCD: pharmacological, neurobiological and clinical effects. Adapted from [12].

Drug type	Examples	Pharmacological effect	Neurobiological effect	Clinical effect
Selective serotonin reuptake inhibitors (SSRIs)	Fluoxetine Citalopram	Increase extracellular levels of 5-HT	5-HT inhibits REM sleep-producing cells	Decreased REM sleep
Tricyclic antidepressants	Amitriptyline Nortriptyline Clomipramine	Increase extracellular levels of 5-HT and NE	5-HT and NE inhibit REM sleep-producing cells	Decreased REM sleep
Traditional, amphetamine-like stimulants	Amphetamine Methylphenidate	Increase extracellular levels of DA and NE	Increased DA and NE signaling	Increased wakefulness
Wake-promoting, non-traditional stimulants	Modafinil Armodafinil	Increase extracellular levels of DA	Increased DA signaling	Increased wakefulness
Wake-promoting agent	Pitolisant	Block H3 Receptors	Reduced H3 neurons activity leads to increased ACh, NA,DA release	Increased attention and wakefulness
Benzodiazepines	Diazepam Clonazepam Lorazepam	Enhance GABA signaling via $GABA_A$ receptors	GABA inhibits the arousal systems	Increased sleep
Non-benzodiazepine sedative hypnotics (“Z”)	Zolpidem Zaleplon Zopiclone	Enhance GABA signaling via $GABA_A$ receptors	GABA inhibits the arousal systems	Increased sleep

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Classic antihistamines	Diphenhydramine Triprolidine	Block HA H_1 receptors	Reduced HA signaling	Increased sleep
Typical antipsychotics	Haloperidol Chlorpromazine	Block DA receptors	Reduced DA signaling	Increased sleep
Sleep promoting agent	Sodium oxybate	Stimulation of $GABA_B$ receptors	Reduced DA neuronal activity and inhibition of arousal systems	Increases sleep
Orexin Rezeptor Agonisten	Daridorexant Lemborexant Suvorexant	Block OX1R and OX2R	Reduced orexin neuronal activity	Decreases wakefulness

2. Pharmacotherapy of sleep-wake circadian disorders

For most SWCD pharmacological treatment is recommended. In this review, pharmacological treatment refers to approved and not approved drugs used for the corresponding disorder. Natural or herbal medicines or any other complementary or alternative medicines are not included. We here also refer to the drug treatment in adults. Treatment of common SWCD disorders is presented. For pharmacotherapy of rare SWCD disorders, the specific literature is recommended.

2.1. Insomnia

Introduction: Chronic Insomnia refers to frequent and persistent complaint of initiating or maintaining sleep, resulting in dissatisfaction and daytime impairment. This definition may vary depending on the nosological system (ICD-10; ICD-11; ICSD-3 [11], or Diagnostic and Statistical Manual of Mental Disorders, DSM-V), used. Insomnia is the most frequent SWCD. Epidemiological data indicate for a frequency of 9 to 48%, depending on the criteria, frequency of complaints, and daytime consequences used [13,14].

Management: For chronic insomnia, cognitive behavioural therapy for insomnia (CBT-I) is recommended as first-line treatment. Pharmacological treatment should be offered if CBT-I is not sufficiently effective or not available [15]. In daily practice, many physicians prescribe drugs for insomnia as first option and exclusively, or in parallel to CBT-I.

Pharmacological treatment: See Table 2. Drug treatment of insomnia is purely symptomatic. In addition to drugs, education strategies, and CBT-I are often necessary for a successful long-term treatment of insomnia. Some guidelines and recommendations also differentiate between treatment of ”sleep onset” and “sleep maintenance” insomnia. A particular attention has to be made on the potential psychological dependence of Benzodiazepines.

Dual orexin receptor antagonists (DORAs) are novel treatments for insomnia. Several clinical trials and meta-analysis showed for all DORAs an improvement of total sleep time in a dose-dependent manner [20], and for an improvement of sleep maintenance (suvorexant [17,19–23], and for daridorexant [18–20]). Two meta-analyses on daridorexant however found no beneficial effect on insomnia [16,17]. The place of DORAs in the treatment of insomnia, in particular for long-term treatment still needs to be confirmed. The positive effects of the Z-drugs on insomnia was described in different meta-analyses, with Eszopiclone performing particularly well in one analysis [22].

Special conditions: Particular recommendations for elderly are indicated also Table 2. Efficacy and safety of DORA treatment for older individuals are not entirely clear [19,24–27].

Future directions: Dual Orexin Receptor Antagonists (DORA) are a new class of pharmacologic drugs for the treatment of insomnia, and further data on long-term efficacy and safety will appear. Additional studies are needed to evaluate the efficacy of combining newly available pharmacologic treatments, such as DORAs, with other drugs, or with non-pharmacologic treatments. Slow wave sleep (SWS) often is decreased in insomnia, in particular in the elderly. New drugs with a particular effect on SWS are needed.

Table 2. Pharmacological treatment of insomnia: Drug types, examples and recommendations.

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Drug group	Drug type	Example	Recommen-dation	O*	M+	Elderly	Remarks
Melatoninergic drugs	Melatonin		0	(+)		(+)	
	Melatonin extended release		(+)		(+)	+	
	Melatonin receptor agonists		+	(+)	(+)		Consider approval status
GABA-A receptor agonists	Benzodiazepines		(+)	+	+		Consider abuse or addiction liability
	Non-benzodia-zepines "Z"-drugs		++	++	+		
Antidepressants		Trazodone	++	+	+(+)	+	Use in dementia
		Mirtazapine	+	(+)	+		Caveat: Long half-life
	Tricyclic antidepressants	Amitriptyline	+	(+)	(+)		Low dose recommended
		Doxepin	++	+	+		
Dual orexin receptor agonists	Dual orexin receptor agonists	Daridorexant	++	+	+(+)	(+)	Further studies needed
Antipsychotic drugs		Quetiapine	0				Backup option
Antihistamines			0				

For the use in * Onset insomnia + Maintenance insomnia; 0: No recommendation; + weak for; and ++ strong for recommendation .

2.2. Sleep-related breathing disorder (SRBD)

Introduction: SRBD includes obstructive sleep apnea (OSA), central sleep apnea (CSA), sleep-related hypoventilation disorders, sleep-related hypoxemia disorder, and isolated symptom/normal variant. OSA is the most frequent SRB disorder and affects 2-24% (female), and 4-48% (male) of the general, middle-aged population in Western countries, depending on apnea- hypopnea index (AHI): >5 or >15/h, and on including additional symptoms for diagnosis [38,39]. The diagnosis of OSA includes obstructive respiratory events (AHI >5/h), but also complains of sleepiness, non-restorative sleep, fatigue, or insomnia symptoms [11].

Management: Therapeutic management of SRBD comprises general advice as to lifestyle, positional therapy, treatment of comorbid diseases, and treatment with oral devices, positive airway pressure (PAP) devices, surgical interventions, and hypoglossal nerve stimulation. For OSA and other forms of SRBD, different PAP treatments are often used as first- line therapy.

Pharmacological treatment: There yet is no primary pharmacological treatment for SRBD. Some data indicate that oxygen application and/or the use of acetazolamide may be helpful in some particular SRBD conditions, and as an adjunctive treatment.

Special conditions:

- Insomnia: Some patients experience improvement of their non-restorative or disturbed sleep quickly after initiation of therapy (i.e. with PAP). In others, insomnia symptoms are unchanged, and some describe novel difficulties in sleep initiation in particular. The treatment of insomnia in SRBD

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follows the general recommendations of the management of insomnia (see 2.1.). CBT-I also leads to an improvement of insomnia in treated and untreated comorbid sleep apnea patients [40]. It needs to be considered, that antidepressant and antipsychotic medicines for insomnia may exacerbate sleep apnea [41]. Several studies suggest a neutral response on respiration for GABA-A receptor agonists, (benzodiazepines, Z-drugs), and also for trazodone. In a recent study, using the DORA lemborexant, respiratory safety was demonstrated in subjects with moderate-to-severe OSA [42].

- Excessive daytime sleepiness (EDS)/ fatigue: 5-10% of OSA patients, who are under effective PAP treatment, still describe EDS [43]. This condition often is called "residual EDS (R-EDS) in OSA". The daytime symptomatology however still needs further differentiation (EDS vs. fatigue vs. cognitive disturbances). Further, it remains unclear whether EDS is the consequence of OSA at all [43]. In the last decades, Modafinil and Armodafinil have been used off-label for the treatment of persistent EDS in OSA. Recently, solriamfetol and pitolisant (see also 2.3.) have been studied and approved for the treatment of R-EDS in OSA. Both have shown to be efficacious in the reduction of EDS in these populations [44–47].

Future directions: Several new pathways for pharmacological treatment of OSA are currently being explored. They include i.e. the selective norepinephrine reuptake inhibitor atomoxetine in combination with the antimuscarinic oxybutynin. A trial of this combination lead to a reduction of the AHI by 62% [48]. Recently, a trial with the carbonic anhydrase inhibitor sulthiame in 68 patients with moderate-to-severe OSA resulted in the reduction of the AHI by 41% [49]. Although these are promising results, the state of medical evidence is at present too scarce for making any sound recommendations on a primary pharmacotherapy of OSA.

2.3. Central disorders of hypersomnolence (CDH)

Introduction: CDH include primary sleep-wake disorders (narcolepsies, hypersomnias), and hypersomnolence due to, or associated with other medical disorders, medication or substances. Also, insufficient sleep syndrome is part of this section. For the symptoms of excessive daytime sleepiness, and for excessive need for sleep (mean sleep duration >9h), the prevalence in the general population is 5% and 8%, respectively [50,51]. For narcolepsy, the prevalence is approx. 0.025 [52].

Management: For narcolepsy and idiopathic hypersomnia, management usually includes both behavioral strategies and pharmacotherapy [53]. Psychotherapeutic treatment is also necessary for some patients.

Pharmacological treatment: See Tables 3A and 3B [54–61]. Drug treatment is symptomatic and is oriented primarily to the main symptoms of the diseases (excessive daytime sleepiness, cataplexy, disturbed nocturnal sleep for narcolepsy and excessive daytime sleepiness and hypersomnia for idiopathic hypersomnia) [54].

Table 3. *A*: Pharmacotherapy of narcolepsy (drugs, and key symptoms) .

Drug	EDS	Cataplexy	DNS
Modafinil /Armodafinil	++		
Solriamfetol	++		
Pitolisant	++	+	
Sodium Oxybate	++	++	++
Antidepressants: Venlafaxine, Clomipramine		++	
Methylphenidate	+		
Amphetamines	+		
Baclofen			(+)
Non-benzodiazepines ("Z"-drugs)			+ *

EDS : Excessive daytime sleepiness; DNS: Disturbed nocturnal sleep; * short-term treatment ; 0: No recommendation; + weak for; and ++ strong for recommendation .

Table 3. *B*: Pharmacotherapy of idiopathic hypersomnia (drugs, and key symptoms).

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Drug	EDS	Hypersomnia
Modafinil	++	
Oxybates		+
Pitolisant	(+)	
Methlyphenidate	(+)	

EDS : Excessive daytime sleepiness; 0: No recommendation; + weak for; and ++ strong for recommendation .

Special conditions: Stimulant medications can be associated with an increase in heart rate or blood pressure. Pre-existing or comorbid disorders in particular cardiovascular diseases and psychiatric disorders have to be taken into consideration when starting or changing a drug treatment. This is particularly true for the group of elderly patients [54].

Future directions: Selective orexin receptor agonists are a promising new class of drugs. Recent pilot trials on orexin receptor agonists (TAK-994, TAK-861) indicated for a significant improvement of EDS and cataplexy [62]. Other histaminergic drugs and drugs acting also in the orexin system (i.e. mazindol) are under development [63]. Recently, a novel concept on the pathophysiology of narcolepsy has been presented [64]. If confirmed, different treatment pathways may become available.

2.4. Circadian rhythm sleep-wake disorders (CRSWD)

Introduction: CRSWD include disorders with alterations of the circadian timing system including delayed sleep-wake phase disorder, advanced sleep-wake phase disorder, irregular sleep-wake rhythm disorder, and non-24-hr sleep-wake rhythm disorder. The prevalence in these disorders amongst adults ranges from 0.1% to 7% depending on the definitions used [65,66]. In jet lag disorder and shift work disorder external factors are causing the individual's circadian rhythm to be out of phase with the environmental demands. In industrialized countries, approx. 20% of work force is employed in jobs with shift work. The prevalence of shift work disorder is estimated to be between 10%-40% [67,68].

Management: General approaches to treatment include sleep hygiene education, CBT, regular exercise, and planned light exposure. Usually also drug treatment (melatonin) is part of the management [69–71].

Pharmacological treatment: In the chronotherapy of CRSWD, melatonin plays the central pharmacotherapeutic role [31,72–74]. Different melatoninergic drugs are available: immediate, fast-acting melatonin, extended-release (ER) melatonin forms, and selective melatonin receptor agonists (Ramelteon, Agomelatin, and Tasimelteon). To induce sleep and a phase shift (chronobiotic effect) the use of an immediate form is appropriate. Often dosages between 0.5 and 5mg are recommended. Sometimes combinations of immediate-release and extended-release melatonin are necessary. For difficulties in maintaining sleep, ER melatonin or melatonin receptor agonists (MRA) are preferable. Stimulants and/or sleep-promoting treatments other than melatonin are not recommended for the long-term treatment of CRSWD [75].

Special conditions: Melatonin (2mg) can be used to promote daytime sleep after a night shift in shift workers [75]. There is no recommendation for the use of melatonin in dementia [72].

Future directions: In the context of personalized and precision drug therapy, circadian aspects and chronotherapeutic treatments could take on greater importance.

2.5. Parasomnias

Introduction: Parasomnias are grouped into non-rapid eye movement (NREM) parasomnias (i.e. confusional arousals, sleepwalking), rapid eye movement (REM) parasomnias (i.e. REM sleep behaviour disorder, RBD) and other parasomnias. Parasomnias are defined as an unpleasant physical events (movements or behaviours) or experiences that occur during sleep. NREM parasomnias are common in childood (10%-20%), in adults RBD, sleep-related eating disorder and sleep-related hallucinations are more frequent (1%-5%) [76,77] however.

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Management: First-line treatment usually refers to non-pharmacological approaches. This includes avoidance of triggering factor (i.e., sleep deficiency, other sleep disorders, or drugs), reassurance and environmental (bed, room) safety, and in some conditions scheduled awakenings, and psychological support. As some NREM- parasomnias are often benign and transitory, it may be possible to inform the patient, to wait and observe first. Drug treatment includes benzodiazepines, antidepressants, melatonin and others, and is symptomatic only [78–80].

Pharmacological treatment: See Table 4. Several aspects should be considered when it comes to starting permanent drug therapy: frequency of episodes, risk of injuries, and functional impairment. Potential side effects of drugs, in particular of GABAA receptor agonist treatments should be noted. Some other medications that are not described in Table 4 can be used in particular conditions (i.e. rivastigmine in dementia disorders, or i.e. sodium oxybate in narcolepsy) for parasomnias. No objective improvement of parasomnias by melatonin receptor agonists could be shown [81,82].

Table 4. Pharmacological treatment pf parasomnias (drugs, and parasomnias, divided into NREM and REM- parasomnias).

Drug	NREM parasomnia	REM parasomnia
Melatonin (3-10mg) *	+	++
Clonazepam (0.25-3mg)	++	++
Antidepressants: SSRI (i.e. Sertraline) or tricyclic (i.e. Clomipramine), or Trazodone	+	
Dopamine agonist (i.e. Pramipexole)		(+)

* For immediate, fast-acting formulation; effect of ER-formulation unclear. 0: No recommendation; + weak for; and ++ strong for recommendation .

Special conditions: Several drug classes or individual drugs may induce all types of parasomnias. The drugs may either cause "de novo" parasomnias, or exacerbate existing ones [83].

Future directions: Novel sleep-promoting drugs, e.g. DORA (see also 2.1.) may add to the current pharmacological treatments [84].

2.6. Sleep-related movement disorders

Introduction: Sleep-related movement disorders (SRMDs) have a clinically heterogeneous presentation. Mostly, movements are simple, stereotyped and involuntary. SRMD are distinguished according to the part(s) of the body affected, and the type of motor activity presenting. Restless legs syndrome (RLS), and periodic limb movement (PLM) disorder are most common SRMDs with a (global) prevalence of 1-10% for RLS. Higher rates are found for women and in the elderly [85]. The prevalence for PLM in sleep is approx. 30% in the general population [86]. Other SRMDs include sleep-related leg cramps, bruxism, and sleep-related rhythmic movement disorders.

Management: For RLS, first treatment steps includes education to sleep hygiene, behavioral strategies, and abstinence from caffeine and alcohol in particular. Drugs that may increase RLS should be avoided [87]. Further, in patients with low iron status (for details please see references) iron replacement therapy is recommended and presents the only disease-modifying strategy available for RLS [88–90]. In intermittent RLS, pharmacotherapy can be on demand and different to the daily pharmacological treatment which is given in chronic RLS. See Table 5.

PLMS as symptom of RLS, or as single symptom may reflect a risk factor for cardiovascular and cerebrovascular disease. PLMD refers to PLMS accompanied by fragmented sleep, insomnia, or daytime sleepiness [91].

Pharmacological treatment: Iron substitution is the first component of treatment [88,92,93]. Symptomatic drug treatment includes dopaminergic medication (levodopa, dopamine agonists), $\alpha 2\delta$ ligands (Gabapentin, Pregabalin), and opioids and GABAA receptor agonists. See Table 5 [94–100].

In RLS, augmentation may occur. It refers to an overall increase in RLS severity, and represents the main complication of dopaminergic treatment [89]. Therefore, dopaminergic agents should be

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avoided, or, if necessary to treat RLS, be given low-dose and long acting. Other more complex secondary options include combination of drugs, add-on of opioids, and split dosing [101,102].

For PLMD, DA treatment, or alternatively α2δ ligands, low-potency opioids, or clonazepam may be used [90,91].

Table 5. Pharmacological treatment of RLS (divided into RLS types, and first- and second- line drugs).

RLS type	Drugs		Remarks
	First-line	Second- line	
Intermittent	L-Dopa or DA (i.e. Pramipexole)	Low-potency opioids; or clonazepam or Z-drugs	Drug only on demand
Chronic	α2δ ligands (Gabapentin, Pregabalin), or * DA (Pramipexole, Ropinirole, Rotigotine**)	Combination of first-line drugs; change to, or add low-potency opioids	* Whenever possible start with α2δ ligands ** Rotigotine when also RLS symptoms at daytime

DA: dopamine agonist.

Special conditions: In pregnant RLS patients, iron supplementation is recommended. After the first trimester, and only in severe cases of RLS, clonazepam or low-dose oxycodone may be considered [103,104].

Future directions: Current studies on novel pharmacotherapies for RLS include pitolisant and apomorphine.

3. Conclusion

Several factors contribute to sleep, and leading to SWCDs. The treatment of the individual sleep disorder is also multifaceted and includes different forms of therapy. However, for the vast majority of diseases, drug treatment is part of the treatment concept, often even a central component. Fortunately, effective drugs are available for most SWCDs. For some of these diseases (i.e. narcolepsy), new and more specific drugs have been developed in recent years, and a comprehensive range of therapies is now available for sufferers. Unfortunately, there are still many other diseases where there are fewer (new) drug treatment options (i.e. RLS), especially also for the rare SWCDs. Further and greater efforts should be made to obtain more therapy options here as well.

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References

1. Ramar, K.; Malhotra, R.K.; Carden, K.A.; et al. Sleep is essential to health: an American Academy of Sleep Medicine position statement. J Clin Sleep Med. 2021, 17, 2115–2119.

2. Kryger M.H.; Roth, T.; Dement, W.C. Principles and Practice of Sleep Medicine. 7th ed.; Elsevier: Amsterdam, The Netherlands, 2021
3. Watson, N.F.; Badr, M.S.; Belenky, G.; et al. Joint consensus statement of the American Academy of Sleep Medicine and Sleep Research Society on the recommended amount of sleep for a healthy adult: methodology and discussion. J Clin Sleep Med. 2015, 11, 931–952.
4. Robbins, R.; Quan, S.F.; Weaver, M.D.; Bormes, G.; Barger, L.K.; Czeisler, C.A. Examining sleep deficiency and disturbance and their risk for incident dementia and all-cause mortality in older adults across 5 years in the United States. Aging. 2021, 13, 3254-3268
5. Bassetti, C.L.A.; Randerath, W.; Vignatelli, L.; et al. EAN/ERS/ESO/ESRS statement on the impact of sleep disorders on risk and outcome of stroke. Eur J Neurol. 2020, 27, 1117-1136.
6. Lim, D.C.; Najafi, A.; Afifi, L.; et al. The need to promote sleep health in public health agendas across the globe. Lancet Public Health. 2023, 8, e820-e826.
7. Gustavsson, A.; et al. Cost of disorders of the brain in Europe 2010. Eur. Neuropsychopharmacol. 2011, 21, 718-779.
8. Bassetti, C.L.A.; Endres, M.; Sander, A.; et al. The European Academy of Neurology Brain Health Strategy: one brain, one life, one approach. Eur J Neurol. 2022, 29, 2559-2566.
9. Scammell, T.E.; Arrigoni, E.; Lipton, J. Neural Circuitry of Wakefulness and Sleep. Neuron. 2017, 93, 747–765.
10. Eban-Rothschild, A.; Appelbaum, L.; De Lecea, L. Neuronal Mechanisms for Sleep/Wake Regulation and Modulatory Drive. Neuropsychopharmacology. 2018, 43, 937–952.
11. American Academy of Sleep Medicine. The International Classification of Sleep Disorders, 3rd ed.; (ICSD-3); Wolters Kluwer: Alphen aan den Rijn, The Netherlands, 2023.
12. España, R.A.; Scammell, T.E. Sleep Neurobiology from a Clinical Perspective. Sleep. 2011, 34, 845–858.
13. Ohayon, M.M.; Reynolds, C. F. III. Epidemiological and clinical relevance of insomnia diagnosis algorithms according to the DSM-IV and the International Classification of Sleep Disorders (ICSD). Sleep Med. 2009, 10, 952-960.
14. Ohayon, M.M. Epidemiology of insomnia: What we know and what we still need to learn. Sleep Med Rev. 2002, 6, 97-111.
15. Riemann, D.; Baglioni, C.; Bassetti, C.; Bjorvatn, B.; Dolenc Groselj, L.; Ellis, J. G.; et al. European guideline for the diagnosis and treatment of insomnia. J Sleep Res. 2017, 26, 675-700.
16. De Crescenzo, F.; D'Alò, G.L.; Ostinelli, E.G.; Ciabattini, M.; Di Franco, V.; Watanabe, N.; Kurtulmus, A.; Tomlinson, A.; Mitrova, Z.; Foti, F.; Del Giovane, C.; Quested, D.J.; Cowen, P.J.; Barbui, C.; Amato, L.; Efthimiou, O.; Cipriani, A. Comparative effects of pharmacological interventions for the acute and long-term management of insomnia disorder in adults: a systematic review and network meta-analysis. Lancet. 2022, 400, 170-184.
17. Pan, B.; Ge, L.; Lai, H.; Hou, L.; Tian, C.; Wang, Q.; Yang, K.; Lu, Y.; Zhu, H.; Li, M.; Wang, D.; Li, X.; Zhang, Y.; Gao, Y.; Liu, M.; Ding, G.; Tian, J.; Yang, K. The Comparative Effectiveness and Safety of Insomnia Drugs: A Systematic Review and Network Meta-Analysis of 153 Randomized Trials. Drugs. 2023, 83, 587-619.
18. Hasan, F.; Lee, H.C.; Chen, P.Y.; et al. Comparative efficacy of hypnotics in young and middle-aged adults with insomnia: a systematic review and network meta-analysis. Sleep Breath. 2023, 27, 2021-2030.
19. Jiang, F.; Li, H.; Chen, Y.; Lu, H.; Ni, J.; Chen, G. Daridorexant for the treatment of insomnia disorder: A systematic review and meta-analysis of randomized controlled trials. Medicine (Baltimore). 2023, 102, e32754.
20. Rocha, R.B.; Bomtempo, F.F.; Nager, G.B.; Cenci, G.I.; Telles, J.P.M. Dual orexin receptor antagonists for the treatment of insomnia: systematic review and network meta-analysis. Arq Neuropsiquiatr. 2023, 81, 475-483.
21. McElroy, H.; O'Leary, B.; Adena, M.; Campbell, R.; Monfared, A.A.T.; Meier, G. Comparative efficacy of lemborexant and other insomnia treatments: a network meta-analysis. J Manag Care Spec Pharm. 2021, 27, 1296-1308.
22. Zheng, X.; He, Y.; Yin, F.; Liu, H.; Li, Y.; Zheng, Q.; Li, L. Pharmacological interventions for the treatment of insomnia: quantitative comparison of drug efficacy. Sleep Med. 2020, 72, 41-49.
23. Kishi, T.; Nomura, I.; Matsuda, Y.; Sakuma, K.; Okuya, M.; Ikuta, T.; Iwata, N. Lemborexant vs suvorexant for insomnia: A systematic review and network meta-analysis. J Psychiatr Res. 2020, 128, 68-74.
24. Wang, L.; Pan, Y.; Ye, C.; Guo, L.; Luo, S.; Dai, S.; Chen, N.; Wang, E. A network meta-analysis of the long- and short-term efficacy of sleep medicines in adults and older adults. Neurosci Biobehav Rev. 2021, 131, 489-496.
25. Chiu, H.Y.; Lee, H.C.; Liu, J.W.; Hua, S.J.; Chen, P.Y.; Tsai, P.S.; Tu, Y.K.; Comparative efficacy and safety of hypnotics for insomnia in older adults: a systematic review and network meta-analysis. Sleep. 2021, 44, zsaa260.

26. Samara, M.T.; Huhn, M.; Chiocchia, V.; Schneider-Thoma, J.; Wiegand, M.; Salanti, G.; Leucht, S.; Efficacy, acceptability, and tolerability of all available treatments for insomnia in the elderly: a systematic review and network meta-analysis. Acta Psychiatr Scand. 2020, 142, 6-17.
27. Xu, S.; Cui, Y.; Shen, J.; Wang, P. Suvorexant for the prevention of delirium: A meta-analysis. Medicine (Baltimore). 2020, 99, e21043.
28. Tabelle pharma Insomnie: 28-37
29. Sateia, M.J.; Buysse, D.J.; Krystal, A.D.; Neubauer, D.N.; Heald, J.L. Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med. 2017, 13, 307-349.
30. Choi, H.; Youn, S.; Um, Y.H.; Kim, T.W.; Ju, G.; Lee, H.J.; Lee, C.; Lee, S.D.; Bae, K.; Kim, S.J.; Lee, J.H.; Kim, T.; Chung, S. Korean Clinical Practice Guideline for the Diagnosis and Treatment of Insomnia in Adults. Psychiatry Investig. 2020, 17, 1048-1059.
31. Qaseem, A.; Kansagara, D.; Forciea, M.A.; Cooke, M.; Denberg, T.D. Clinical Guidelines Committee of the American College of Physicians. Management of Chronic Insomnia Disorder in Adults: A Clinical Practice Guideline From the American College of Physicians. Ann Intern Med. 2016, 165, 125-33.
32. Wilson, S.; Anderson, K.; Baldwin, D.; Dijk, D.J.; Espie, A.; Espie, C.; Gringras, P.; Krystal, A.; Nutt, D.; Selsick, H.; Sharpley, A. British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders: An update. J Psychopharmacol. 2019, 33, 923-947.
33. Mysliwiec, V.; Martin, J.L.; Ulmer, C.S.; Chowdhuri, S.; Brock, M.S.; Spevak, C.; Sall, J. The Management of Chronic Insomnia Disorder and Obstructive Sleep Apnea: Synopsis of the 2019 U.S. Department of Veterans Affairs and U.S. Department of Defense Clinical Practice Guidelines. Ann Intern Med. 2020, 172, 325-336.
34. Pottie, K.; Thompson, W.; Davies, S.; Grenier, J.; Sadowski, C.A.; Welch, V.; Holbrook, A.; Boyd, C.; Swenson, R.; Ma, A.; Farrell, B. Deprescribing benzodiazepine receptor agonists: Evidence-based clinical practice guideline. Can Fam Physician. 2018, 64, 339-351.
35. Wichniak, A.; Bieńkowski, P.; Dąbrowski, R.; Mastalerz-Migas, A.; Rymaszewska, J. Treatment of insomnia in older adults. Recommendations of the Polish Sleep Research Society, Polish Society of Family Medicine and the Polish Psychiatric Association. Psychiatr Pol. 2023, 57, 495–516.
36. Takaesu, Y.; Sakurai, H.; Aoki, Y.; Takeshima, M.; Ie, K.; Matsui, K.; Utsumi, T.; Shimura, A.; Okajima, I.; Kotorii, N.; Yamashita, H.; Suzuki, M.; Kuriyama, K.; Shimizu, E.; Mishima, K.; Watanabe, K.; Inada, K. Treatment strategy for insomnia disorder: Japanese expert consensus. Front Psychiatry. 2023, 14, 1168100.
37. Vecchierini, M.F.; Kilic-Huck, U.; Quera-Salva, M.A. Members of the MEL consensus group of the SFRMS. Melatonin (MEL) and its use in neurological diseases and insomnia: Recommendations of the French Medical and Research Sleep Society (SFRMS). Rev Neurol (Paris). 2021, 177, 245-259.
38. Palagini, L.; Manni, R.; Aguglia, E.; Amore, M.; Brugnoli, R.; Girardi, P.; Grassi, L.; Mencacci, C.; Plazzi, G.; Minervino, A.; Nobili, L.; Biggio, G. Expert Opinions and Consensus Recommendations for the Evaluation and Management of Insomnia in Clinical Practice: Joint Statements of Five Italian Scientific Societies. Front Psychiatry. 2020, 11, 558.
39. Heinzer, R.; Vat, S.; Marques-Vidal, P.; Marti-Soler, H.; Andries, D.; Tobback, N.; et al. Prevalence of sleep-disordered breathing in the general population: The HypnoLaus study. Lancet Respir Med. 2015, 3, 310-318.
40. Young, T.; Palta, M.; Dempsey, J.; Skatrud, J.; Weber, S.; Badr, S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med. 1993, 328, 1230-1235.
41. Sweetman, A.; Farrell, S.; Wallace, D.M.; Crawford, M. The effect of cognitive behavioural therapy for insomnia in people with comorbid insomnia and sleep apnoea: A systematic review and meta-analysis. J Sleep Res 2023, e13847.
42. Khazaie, H.; Sharafkhaneh, A.; Khazaie, S.; Ghadami, M.R. A weight-independent association between atypical antipsychotic medications and obstructive sleep apnea. Sleep Breath. 2018, 22, 109–114.
43. 42: Cheng, J.Y.; Lorch, D.; Lowe, A.D.; Uchimura, N.; Hall, N.; Shah, D.; Moline, M. A randomized, double-blind, placebo-controlled, crossover study of respiratory safety of lemborexant in moderate-to-severe obstructive sleep apnea. J Clin Sleep Med. 2023, Online ahead of print. PMID: 37677076
44. Kallweit, U.; Pevernagie, D.; Lammers, G.J. "Sleepiness" in obstructive sleep apnea: getting into deep water. Sleep Med. 2022, 92, 64-66.
45. Schweitzer, P.K.; Rosenberg, R.; Zammit, G.K.; et al. Solriamfetol for excessive sleepiness in obstructive sleep apnea (TONES 3). A randomized controlled trial. Am J Respir Crit Care Med. 2019, 199, 1421-1431.
46. Dauvilliers, Y.; Verbraecken, J.; Partinen, M.; et al. Pitolisant for daytime sleepiness in patients with obstructive sleep apnea who refuse continuous positive airway pressure treatment. A randomized trial. Am J Respir Crit Care Med. 2020, 201, 1135-1145.

47. El-Solh, A.A.; Rudraraju, A.; Pasrija, D.; Bui, H. Pharmacotherapy of residual excessive sleepiness among continuous positive airway pressure (CPAP) treated patients with sleep apnea. Expert Opin Pharmacother. 2022, 23, 507-516.
48. 47: Craig, S.; Pépin, J.L.; Randerath, W.; Caussé, C.; Verbraecken, J.; Asin, J.; Barbé, F.; Bonsignore M.R. Investigation and management of residual sleepiness in CPAP-treated patients with obstructive sleep apnoea: the European view. Eur Respir Rev. 2022, 31, 210230.
49. 48. Taranto-Montemurro, L.; Messineo, L.; Sands, S.A.; et al. The combination of atomoxetine and oxybutynin greatly reduces obstructive sleep apnea severity. A randomized, placebo-controlled, double-blind crossover trial. Am J Respir Crit Care Med. 2019, 199, 1267–1276.
50. 49. Hedner, J.; Stenlöf, K.; Zou, D.; et al. A randomized controlled clinical trial exploring safety and tolerability of sulthiame in sleep apnea. Am J Respir Crit Care Med. 2022, 205, 1461–1469.
51. 50. Ohayon, M.M. From wakefulness to excessive sleepiness: What we know and still need to know. Sleep Med Rev. 2008, 12, 129-141.
52. 51. Ohayon, M.M.; Reynolds, C. F.; Dauvilliers, Y. Excessive sleep duration and quality of life. Ann Neurol. 2013, 73, 785-794.
53. 52. Heier, M.S.; Evsiukova, T.; Wilson, J.; Abdelnoor, M.; Hublin, C.; Ervik, S. Prevalence of narcolepsy with cataplexy in Norway. Acta Neurol Scand. 2009, 120, 276-280.
54. 53. Latorre, D.; Sallusto, F.; Bassetti, C.L.A.; Kallweit, U. Narcolepsy: a model interaction between immune system, nervous system, and sleep-wake regulation. Semin Immunopathol. 2022, 44, 611-623.
55. 54. Bassetti, C.L.A.; Kallweit, U.; Vignatelli, L.; et al. European guideline and expert statements on the management of narcolepsy in adults and children. Eur J Neurol. 2021, 28, 2815-2830.
56. 55. Maski, K.; Trotti, L.M.; Kotagal, S.; Auger, R.R.; Rowley, J.A.; Hashmi, S.D.; Watson, N.F. Treatment of central disorders of hypersomnolence: an American Academy of Sleep Medicine clinical practice guideline. J Clin Sleep Med. 2021 ,17, 1881-1893.
57. 56. Maski, K.; Trotti, L.M.; Kotagal, S.; Auger,R.R.; Swick, T.J.; Rowley, J.A.; Hashmi, S.D.; Watson, N.F. Treatment of central disorders of hypersomnolence: an American Academy of Sleep Medicine systematic review, meta-analysis, and GRADE assessment. J Clin Sleep Med. 2021 ,17, 1895-1945.
58. 57. Morse, A.M.; Naik, S. Idiopathic Hypersomnia: Neurobiology, Diagnosis, and Management. CNS Drugs. 2023, 37, 305-322.
59. 58. Lammers, G.J. Drugs Used in Narcolepsy and Other Hypersomnias. Sleep Med Clin. 2022, 17, 399-405.
60. 59. Wang, J.; Li, X.; Yang, S.; Wang, T.; Xu, Z.; Xu, J.; Gao, H.; Chen, G. Pitolisant versus placebo for excessive daytime sleepiness in narcolepsy and obstructive sleep apnea: A meta-analysis from randomized controlled trials. Pharmacol Res. 2021, 167, 105522.
61. 60. Subedi, R.; Singh, R.; Thakur, R.K.; K.C., B.; Jha, D.; Ray, B.K. Efficacy and safety of solriamfetol for excessive daytime sleepiness in narcolepsy and obstructive sleep apnea: a systematic review and meta-analysis of clinical trials. Sleep Med. 2020, 75, 510-521.
62. 61. Xu, X.M.; Wei, Y.D.; Liu, Y.; Li, Z.X. Gamma-hydroxybutyrate (GHB) for narcolepsy in adults: an updated systematic review and meta-analysis. Sleep Med. 2019, 64, 62-70.
63. 62: Dauvilliers, Y.; Mignot, E.; Del Río Villegas, R.; et al. Oral Orexin Receptor 2 Agonist in Narcolepsy Type 1. N Engl J Med. 2023, 389, 309-321.
64. 63. https://clinicaltrials.gov/study/NCT04923594. Four-week Study of the Safety and Efficacy of NLS-2 (Mazindol Extended Release) in the Treatment of Narcolepsy. ClinicalTrials.gov ID NCT04923594
65. 64. Seifinejad, A.; Ramosaj, M.; Shan, L.; et al. Epigenetic silencing of selected hypothalamic neuropeptides in narcolepsy with cataplexy. Proc Natl Acad Sci USA. 2023 May, 120, :e2220911120.
66. 65. Schrader, H.; Bovim, G.; Sand, T. The prevalence of delayed and advanced sleep phase syndromes. J Sleep Res. 1993, 2, 51-55.
67. 66. Paine, S.J.; Fink, J.; Gander, P.H.; Warman, G.R. Identifying advanced and delayed sleep phase disorders in the general population: A national survey of New Zealand adults. Chronobiol Int. 2014, 31, 627-636.
68. 67. Flo, E.; Pallesen, S.; Magerøy, N.; Moen, B E.; Grønli, J.; Nordhus, I.H.; Bjorvatn, B. Shift Work Disorder in nurses - Assessment, prevalence and related health outcome. PLoS One 2012, 7, e33981.
69. 68. Rajaratnam, S.; Barger, L.K., Lockley, S.W.; Shea, S.A., Wang, W.; Landrigan, C.P., et al. Sleep disorders, health and safety in police officers, JAMA. 2011, 306, 2567-2578.
70. 69. Emens, J.S.; Burgess, H.J. Effect of light and melatonin and other melatonin receptor agonists on human circadian physiology. Sleep Med Clin. 2015, 10, 435-453.
71. 70. Arendt, J.; Skene, D.J. Melatonin as a chronobiotic. Sleep Med Rev. 2005, 9, 25-39.
72. 71. Wichniak, A.; Jankowski, K.S.; Skalski, M.; Skwarło-Sońta, K.; Zawilska, J.B.; Żarowski, M.; Poradowska, E.; Jernajczyk, W. Treatment guidelines for Circadian Rhythm Sleep - Wake Disorders of the Polish Sleep Research Society and the Section of Biological Psychiatry of the Polish Psychiatric Association. Part II. Diagnosis and treatment. Psychiatr Pol. 2017, 51, 815-832.
73. 72. Auger, R.R.; Burgess, H J.; Emens, J.S.; Deriy, L V.; Thomas, S.M.; & Sharkey, K.M. Clinical practice guideline for the treatment of intrinsic circadian rhythm sleep-wake disorders: Advanced sleep-wake

phase disorder (ASWPD), delayed sleep-wake phase disorder (DSWPD), non-24-hour sleep-wake rhythm disorder (N24SWD), and irregular sleep-wake rhythm disorder (ISWRD). An update for 2015: An American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med. 2015, 11, 1199-1236.
74. 73. Arendt, J. Approaches to the pharmacological management of jet lag. Drugs 2018, 78, 1419-1431.
75. 74. van Geijlswijk. I.M.; Korzilius, H.P.; Smits, M.G. The use of exogenous melatonin in delayed sleep phase disorder: A meta-analysis. Sleep 2010, 33, 1605-1614.
76. 75. Liira, J.; Verbeek, J.; Ruotsalainen, J. Pharmacological interventions for sleepiness and sleep disturbances caused by shift work. JAMA. 2015, 313, 961-962.
77. 76. Manni, R.; Toscano, G.; Terzaghi, M. Therapeutic symptomatic strategies in the parasomnias. Current Treatment Options in Neurology 2018, 20, 26.
78. 77. Drakatos, P.; Marples, L.; Muza, R.; Higgins, S.; Gildeh, N.; Macavei, R.; et al. NREM parasomnias: A treatment approach based upon a retrospective case series of 512 patients. Sleep Med. 2019, 53, 181-188.
79. 78. Proserpio, P.; Terzaghi, M.; Manni, R.; Nobili, L. Drugs used in parasomnia. Sleep Med Clin. 2018, 13, 191-202.
80. 79. Aurora, R.N.; Zak, R.S.; Maganti, R.K.; Auerbach, S.H.; Casey, K.R.; Chowdhuri, S.; et al. Best practice guide for the treatment of REM sleep behavior disorder (RBD). Journal of Clinical Sleep Medicine 2010, 6, 85-95.
81. 80. Boeve, B.F.; Silber, M.H.; Ferman, T J. Melatonin for treatment of REM sleep behavior disorder in neurologic disorders: Results in 14 patients, Sleep Med. 2003, 4, 281-284.
82. 81. Bonakis, A.; Economou, N.-T.; Papageorgiou, S.G.; Vagiakis, E.; Nanas, S.; Paparrigopoulos, T. Agomelatine may improve REM sleep behavior disorder symptoms. J Clin Psychopharmacol. 2012, 32, 732-734.
83. 82. Esaki, Y.; Kitajima, T.; Koike, S.; Fujishiro, H.; Iwata, Y.; Tsuchiya, A.; ... Iwata, N. An Open-Labeled Trial of Ramelteon in Idiopathic Rapid Eye Movement Sleep Behavior Disorder. J Sleep Med. 2016, 12, 689-693.
84. 83. Hoque, R.; Chesson, A.L.J. Pharmacologically induced/exacerbated restless legs syndrome, periodic limb movements of sleep, and REM behavior disorder/REM sleep without atonia: Literature review, qualitative scoring, and comparative analysis. J Clin Sleep Med. 2010, 6, 79-83.
85. 84. Kam, K.; Vetter, K.; Tejiram, R.A.; Pettibone, W.D.; Shim, K.; Audrain, M.; Yu, L.; Daehn, I.S.; Ehrlich, M.E.; Varga, A.W. Effect of Aging and a Dual Orexin Receptor Antagonist on Sleep Architecture and Non-REM Oscillations Including an REM Behavior Disorder Phenotype in the PS19 Mouse Model of Tauopathy. J Neurosci. 2023, 43, 4738-4749.
86. 85. Koo, B.B. Restless leg syndrome across the globe: Epidemiology of the restless legs syndrome/Willis-Ekbom disease. Sleep Med Clin, 2015, 10, 189-205
87. 86. Haba-Rubio, J.; Marti-Soler, H.; Marques-Vidal, P.; Tobback, N.; Andries, D.; Preisig, M.; et al. Prevalence and determinants of periodic limb movements in the general population. Ann Neurol. 2016, 79, 464-474.
88. 87. Kolla, B.P.; Mansukhani, M.P.; Bostwick, J.M.; The influence of antidepressants on restless legs syndrome and periodic limb movements: A systematic review. Sleep Med Rev. 2018, 38, 131-140.
89. 88. Allen, R.P.; Picchietti, D.L.; Auerbach, M.; Cho, Y.W.; Connor, J.R.; Earley, C.J.; Garcia-Borreguero, D.; Kotagal, S.; Manconi, M.; Ondo, W.; Ulfberg, J.; Winkelman, J.W. International Restless Legs Syndrome Study Group (IRLSSG). Evidence-based and consensus clinical practice guidelines for the iron treatment of restless legs syndrome/Willis-Ekbom disease in adults and children: an IRLSSG task force report. Sleep Med. 2018, 41, 27-44.
90. 89. Winkelman, J.W.; Armstrong, M.J.; Allen, R.P.; Chaudhuri, K.R.; Ondo, W.; Trenkwalder, C.; Zee, P.C.; Gronseth, G.S.; Gloss, D.; Zesiewicz, T. Practice guideline summary: Treatment of restless legs syndrome in adults: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology. 2016, 87, 2585-2593.
91. 90. Aurora, R.N.; Kristo, D.A.; Bista, S.R.; Rowley, J.A.; Zak, R.S.; Casey, K.R.; Lamm, C.I.; Tracy, S.L.; Rosenberg, R.S. American Academy of Sleep Medicine. The treatment of restless legs syndrome and periodic limb movement disorder in adults--an update for 2012: practice parameters with an evidence-based systematic review and meta-analyses: an American Academy of Sleep Medicine Clinical Practice Guideline. Sleep. 2012, 35, 1039-62.
92. 91. Drakatos, P.; Olaithe, M.; Verma, D.; Ilic, K.; Cash, D.; Fatima, Y.; Higgins, S.; Young, A.H.; Chaudhuri, K.R.; Steier, J.; Skinner, T.; Bucks, R.; Rosenzweig, I. Periodic limb movements during sleep: a narrative review. J Thorac Dis. 202, 13, 6476-6494.
93. 92. Trotti, L.M.; Becker, L.A.; Iron for the treatment of restless legs syndrome. Cochrane Database Syst Rev. 2019, 1, CD007834.
94. 93. Yang, X.; Yang, B.; Ming,M.; Li, S.; Wang, F.; Zhu, Z.; Ji, C.; Long, J.; Hu, F.; Xu,Z.; Ren, H.; Liu, B. Efficacy and tolerability of intravenous iron for patients with restless legs syndrome: evidence from randomized trials and observational studies. Sleep Med. 2019, 61, 110-117.

95. 94. Garcia-Borreguero, D.; Ferini-Strambi, L.; Kohnen, R.; O'Keeffe, S.; Trenkwalder, C.; Högl, B.; et al. European Federation of Neurological Societies; European Neurological Society; European Sleep Research Society. European guidelines on management of restless legs syndrome: report of a joint task force by the European Federation of Neurological Societies, the European Neurological Society and the European Sleep Research Society. Eur J Neurol. 2012, 19, 1385-1396.
96. 95. Garcia-Borreguero, D.; Kohnen, R.; Silber, M.H.; Winkelman, J.W.; Earley, C.J.; Högl, B.; et al. The long-term treatment of restless legs syndrome/Willis-Ekbom disease: evidence-based guidelines and clinical consensus best practice guidance: a report from the International Restless Legs Syndrome Study Group. Sleep Med. 2013, 14, 675-84.
97. 96. Silber, M.H.; Becker, P.M.; Earley, C.; Garcia-Borreguero, D.; Ondo, W.G.; et al. Willis-Ekbom Disease Foundation revised consensus statement on the management of restless legs syndrome. Mayo Clin Proc. 2013, 88, 977-86.
98. 97. Iftikhar, I.H.; Alghothani, L.; Trotti, L.M.; Gabapentin enacarbil, pregabalin and rotigotine are equally effective in restless legs syndrome: a comparative meta-analysis. Eur J Neurol. 2017, 24, 1446-1456.
99. 98. Liu, G.J.; Wu, L.; Lin Wang, S.; Xu, L.L.; Ying Chang, L.; Fu Wang, Y. Efficacy of Pramipexole for the Treatment of Primary Restless Leg Syndrome: A Systematic Review and Meta-analysis of Randomized Clinical Trials. Clin Ther. 2016, , 162-179.e6.
100. 99. Ding, J.; Fan, W.; Chen, H.H.; Yan, P.; Sun, S.G.; Zheng,J. Rotigotine in the treatment of primary restless legs syndrome: A meta-analysis of randomized placebo-controlled trials. J Huazhong Univ Sci Technolog Med Sci. 2015, 35, 169-175.
101. 100. Högl, B.; Comella, C. Therapeutic advances in restless legs syndrome (RLS). Mov Disord. 2015, 30, 1574-9.
102. 101. Allen, R.P.; Ondo, W.G.; Ball, E.; Calloway, M.O.; Manjunath, R.; Higbie, R.L.; et al. Restless legs syndrome (RLS) augmentation associated with dopamine agonist and levodopa usage in a community sample. Sleep Med. 2011, 12, 431-439.
103. 102. Garcia-Borreguero, D.; Silber, M.H.; Winkelman, J.W.; Högl, B.; Bainbridge, J.; Buchfuhrer, M.; et al. Guidelines for the first-line treatment of restless legs syndrome/Willis-Ekbom disease, prevention and treatment of dopaminergic augmentation: a combined task force of the IRLSSG, EURLSSG, and the RLS-foundation. Sleep Med. 2016, 21, 1-11.
104. 103. Picchietti, D.L.; Hensley, J.G.; Bainbridge, J.L.; Lee, K.A.; Manconi, M.; McGregor, J.A.; Silver, R.M.; Trenkwalder, C.; Walters, A.S. International Restless Legs Syndrome Study Group (IRLSSG). Consensus clinical practice guidelines for the diagnosis and treatment of restless legs syndrome/Willis-Ekbom disease during pregnancy and lactation. Sleep Med Rev. 2015, 22, 64-77.
105. 104. Jahani Kondori, M.; Kolla, B.P.; Moore, K.M.; Mansukhani, M.P. Management of Restless Legs Syndrome in Pregnancy and Lactation. J Prim Care Community Health. 2020, 11, 2150132720905950.