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A review of sleep disorders and melatonin

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ABSTRACT

Sleep disorders are a group of conditions that affect the ability to sleep well on a regular basis and cause significant impairments in social and occupational functions. Although currently approved medications are efficacious, they are far from satisfactory. Benzodiazepines, antidepressants, antihistamines and anxiolytics have the potential for dependence and addiction. Moreover, some of these medications can gradually impair cognition. Melatonin (N-acetyl-5-methoxytryptamine) is an endogenous hormone produced by the pineal gland and released exclusively at night. Exogenous melatonin supplementation is well tolerated and has no obvious short- or long-term adverse effects. Melatonin has been shown to synchronize the circadian rhythms, and improve the onset, duration and quality of sleep. It is centrally involved in anti-oxidation, circadian rhythmicity maintenance, sleep regulation and neuronal survival. This narrative review aims to provide a comprehensive overview of various therapeutic functions of melatonin in insomnia, sleep-related breathing disorders, hypersomnolence, circadian rhythm sleep–wake disorders and parasomnias. Melatonin offers an alternative treatment to the currently available pharmaceutical therapies for sleep disorders with significantly less side effects.

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Introduction

Sleep is fundamental to a person's emotional and physical health. Inadequate sleep is a known risk factor for obesity, diabetes, heart disease and depression. Sleep disorders create a significant burden on the health care system. The average annual medical expense of an individual with a chronic sleep disorder is \$2000 more than someone without a sleep disorder. Sleep disorders are a broad category of disorders that encompass all types of dysfunctions involving sleep, including difficulty falling asleep at night, poor sleep quality, early waking, circadian rhythm disorders, parasomnias, sleep-related movement disorders and sleep-related breathing disorders (SBDs). The consequence of sleep disorders is often daytime fatigue. People who have sleep disturbances report an impaired ability to fulfil daily tasks involving memory, learning, logical reasoning and mathematical operations [1].

A plethora of pharmacological treatments has been introduced to the market for various types of sleep disorders in recent decades. Current medications include chloral hydrate, barbiturates, benzodiazepine, benzodiazepine agonists, modafinil, antidepressants and anxiolytics. However, these medications have substantial side effects, including excessive daytime sleepiness,

poor tolerance to the medication, cognitive impairment, dependency and withdrawal. Because of these side effects, there has been an increased interest to find a new pharmaceutical approach with less side effects.

Melatonin is primarily produced by the pineal gland and released into the bloodstream exclusively at night following the circadian rhythm. It is tolerated well and has a low potential for dependence in contrast to other sleep medications [2]. Large oral doses of melatonin (20–100 mg/day) in healthy volunteers were well tolerated with no safety concerns and no clinically significant changes to any physiological or biochemical measures [3]. Melatonin supplementation has been shown to be a safe and effective method to improve sleep onset latency, duration, and quality in children [4], adolescents [5], older adults [6] and postmenopausal women [7]. Furthermore, consistent melatonin use produces a very low rebound rate [8].

Effect of melatonin on insomnia

Insomnia is defined as persistent difficulty with sleep initiation, sleep consolidation and staying asleep, resulting in poor sleep quality [9]. Individuals suffering from chronic insomnia show an increased predisposition for

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psychiatric conditions, including depression, anxiety and substance abuse. People who show a susceptibility to sleep disturbances have an overactive sympathetic nervous system, hyperarousal and have more intense responses to stressful events [1]. Melatonin levels decrease with age, thus older adults are more prone to suffer from inadequate melatonin levels [10]. As one ages, the ability to sleep decreases, and consequently the incidences of sleep disorders gradually increase. The sleep architecture begins to change during middle age, resulting in a dramatic decrease in non-rapid eye movement (NREM)-slow wave sleep; in contrast the amount of rapid eye movement (REM) sleep diminishes only slightly. Thus, reduced melatonin secretion may be involved in the mechanism of insomnia [11].

Melatonin has been approved in Europe for the management of primary insomnia in adults over the age of 55. Clinical trials have demonstrated that melatonin is effective for treating insomnia in other cohorts, including children with autism spectrum disorders [12], adolescents with depression [5], women with premenstrual dysphoric disorder [13], hypertensive patients taking beta-blockers [14] and children with attention-deficit/hyperactivity disorder [15].

Mechanistically, human endogenous melatonin levels start to increase approximately 2 hours before natural sleep onset and peak approximately 5 hours later [5]. Psychophysiological insomnia (PPI) – insomnia perpetuated by both psychological and physiological factors – usually presents with a history of taking hours to fall asleep and having extreme difficulty waking up in the morning for school or work [5]. Melatonin alters specific aspects of the sleep architecture, thereby improving sleep quality [13]. Beta-blockers suppress endogenous night-time melatonin secretion, which may explain the reported side effect of insomnia. In these patients, melatonin supplementation significantly increased total sleep time, improved sleep efficiency and decreased sleep onset latency to Stage 2 [14]. Exogenous melatonin can effectively treat insomnia by mimicking the natural endogenous melatonin, binding to the same receptors and activating the same downstream pathways.

Melatonin and melatonin agonists play important roles in the treatment of insomnia by activating MT1 and MT2 melatonin receptors. By studying MT1 and MT2 receptor knockout mice, Comai et al. showed that MT1 and MT2 receptors play different roles in sleep [16]. Merica et al. demonstrated a connection between slow wave sleep and insomnia. They reported lower slow wave activity levels during NREM sleep in patients with insomnia compared to healthy cohorts, as well as increased Stage 1 sleep and less Stage 4 sleep. Selective MT2 receptor agonists increase NREMS duration compared to melatonin and non-selective MT1/MT2 agonists [17]. MT1 receptor knockout mice exhibited a significant increase in NREMS during the active/dark phase [18], whereas MT2 receptor knockout

mice showed decreased NREMS duration [18]. Taken together, these knockout studies seem to suggest that MT1 and MT2 receptors modulate NREMS in an opposite manner [16]. By activating MT1 and MT2 receptors, melatonin and non-selective MT1/MT2 receptor agonists have shown to improve sleep quality, increase total sleep time, improve sleep efficiency and decrease sleep onset latency in insomnia patients.

Effect of melatonin on reducing the complications caused by SBDs

SBDs are characterized by abnormalities in respiration during sleep. These disorders are subcategorized into obstructive sleep apnoea (OSA) disorders, central sleep apnea disorders, sleep-related hypoventilation disorders and sleep-related hypoxemia disorders [9]. It is well documented that SBDs are a risk factor for cognitive impairment [19], type 2 diabetes [20], early renal damage [21], heart failure [22], atrial fibrillation [23], coronary disease [24], as well as ischemic stroke [25]. The most common treatments for SBDs are continuous positive airway pressure (CPAP), surgery, oral appliances, postural therapy and weight loss. However, there are significant disadvantages related to the above treatments, including postoperative recurrence, dental injury in the case of oral appliance, poor tolerance to CPAP, poor sleep quality secondary to postural therapy, and difficulty with weight loss. Considering these complications and disadvantages, new therapies for SBDs are urgently needed.

Melatonin has been shown to ameliorate the complications caused by SBDs in both animal models, as well as human clinical trials. Melatonin prevents the well-recognized increase in glucose levels that usually follows exposure to intermittent hypoxia in animal models of sleep apnea [26]. By modulating autophagy through the 5' adenosine monophosphate-activated protein kinase pathway, melatonin protects against chronic intermittent hypoxia-induced cardiac hypertrophy in rats [27]. Additionally, melatonin inhibits the expression of inflammatory cytokines (Tumor necrosis factor alpha, Interleukin-6, and Cyclooxygenase-2) and fibrotic markers (PC1 and TGF-beta). Moreover, melatonin treatment mitigates Ca(2+) overloading, decreased Ca(2+) content and lower expression and activity of Ca(2+), leading to decreased cardiac contractility. These aforementioned mechanisms contribute to cardiac inflammation, vascular endothelium dysfunction and ultimately secondary hypertension, which are interceded by melatonin.

Melatonin prevents the development of cardiovascular diseases secondary to SBDs through several mechanisms. Prophylactic melatonin in OSA patients has been shown to protect against chronic intermittent hypoxia-induced myocardial inflammation and fibrosis [28] by activating MT1 and MT2 receptors downstreams [29]. Melatonin and melatonin-mimicking agents inhibit B2

bradykinin receptors (B2Rs), as well as the dimerization of angiotensin converting enzyme I (ACE) to inhibit ACE activity, thereby lowering blood pressure [30]. Melatonin and its agonist stabilize ACE-B2R dimers [31] and angiotensin type II receptors (AT2R). B2R complex (AT2R-B2R) [32] activation increases nitric oxide production by endothelial cells to dilate arterials to increase blood flow in poorly perfused tissues. Interestingly, the MT1 receptor mediates vasoconstriction, while the MT2 receptor mediates vasodilation [32]. By ameliorating the endogenous circadian system, melatonin may provide a novel therapeutic target for modulating sleep apnea-induced cardiovascular disease and hypertension [33]. Furthermore, melatonin shows good compliance and moderate efficiency for the treatment of SBDs. However, large-scale clinical trials are warranted.

Effect of melatonin on hypersomnolence

Central Disorders of Hypersomnolence are characterized by episodes of excessive need for daytime sleep despite normal quality and quantity of nocturnal sleep. Recent classification distinguishes three subtypes: narcolepsy type 1, narcolepsy type 2 and idiopathic hypersomnia. Sleepiness may vary in severity and is more likely to occur in sedentary, uninteresting and monotonous situations that require little active participation [9].

Current treatments focus on managing the consequences of the disorder, which is daytime sleepiness. Two major classes of medications approved by the Food and Drug Administration for the treatment of hypersomnia include methylphenidate and Modafinil [34]. Methylphenidate, which is mechanistically analogous to amphetamines, blocks dopamine transporters and norepinephrine transporters, resulting in increased concentrations of dopamine and norepinephrine within the synaptic cleft. Stimulants, such as methylphenidate, are contraindicated in patients with hypertension, chest pain, cardiac arrhythmias, mitral valve prolapse, ventricular hypertrophy, angina and acute myocardial infarction. Patients with glaucoma, anxiety, epilepsy or Tourette's syndrome are prescribed methylphenidate with strong caution [35]. Modafinil, on the other hand, is well tolerated for the treatment of excessive sleepiness and has no cardiovascular or sleep-related side effects [36]. However, minor tolerance issues, including headache, nausea, dry mouth, anorexia, nervousness, insomnia, anxiety, hypertension and pharyngitis, have been reported. Furthermore, Modafinil has the potential for abuse and has been shown to exhibit psychological dependence [36].

Based on the latest research, melatonin may provide a novel option for improving central disorder of hypersomnolence. As mentioned before, melatonin alters sleep architecture in narcolepsy, a disorder of circadian rhythm and REM sleep deficit. Changes in REM pattern in narcolepsy patients are similar to those seen in patients and animal models with the pineal gland

removed. Furthermore, exogenous doses of melatonin significantly increase REM sleep time in both normal cohorts, as well as patients with central disorder of hypersomnolence.

By ameliorating the circadian rhythm, melatonin has been shown to relieve sleepiness in shift workers [37]. Craniopharyngioma patients who present with altered circadian pattern have been shown to benefit from exogenous melatonin [38]. A high prevalence of sleep-wake disturbances and daytime sleepiness occurs in Parkinson's disease (PD) patients. Excessive sleepiness in PD patients has been hypothesized to be caused by a melatonin dysfunction [39]. Melatonin, thus, offers hope as a well-tolerated, low-side effect treatment for central hypersomnolence.

Compared to PD patients without excessive daytime sleepiness, patients with hypersomnolence have a significantly lower melatonin amplitude and 24-hour melatonin area under the curve values [39]. Several studies demonstrated melatonin treatment prevents dopamine-producing neuronal loss and dopamine transporter down-regulation in a rotenone model of PD [40]. Hendaus et al. demonstrated that melatonin plays a role in neuroprotection in a phenylhydrazine hydrochloride (PHZ)-induced perinatal hypoxic-ischemic encephalopathy model in rats. Melatonin can cross the blood-brain barrier, upregulate brain-derived neurotrophic factor (BDNF) and cyclooxygenase-10, while down regulate plasma TNF-alpha and IL-1beta levels. The increase in apoptotic cells in the hippocampus of the PHZ group was ameliorated by melatonin treatment. These studies validate melatonin's role in neuroprotection and anti-apoptosis in oxidative-related neuronal injury [41].

Effect of melatonin on circadian rhythm sleep-wake disorders

Circadian rhythm sleep-wake disorder (CRSWD) is caused by alterations of the circadian time-keeping system leading to the misalignment of the endogenous circadian rhythm and the external environment [9]. Common CRSWDs include delayed sleep-wake phase disorder, advanced sleep-wake phase disorder, irregular sleep-wake rhythm disorder and non-24-hour sleep-wake rhythm disorder. CRSWD, secondary to abnormal melatonin profiles, has been associated with psychiatric and neurological disorders (e.g. major depression, obsessive compulsive disorder, PD) [42].

The circadian rhythm is regulated by melatonin secretion, and external factors regulate melatonin secretion. Kyba et al. showed that electronic device use reduces melatonin secretion in adolescents [43]. Electric lighting delays sleep onset, reduces sleep duration and appears to interfere with the alignment of the circadian timing system to the natural light/dark cycle [44]. The increased sensitivity to light in younger adolescents suggests that exposure to evening light could be particularly disruptive

to sleep regulation in this group [45]. Melatonin secretion between dim-light melatonin onset (DLMO) and acrophase was less prominent in delayed sleep phase disorder (DSPD) patients than in good sleepers, who showed a more acute initial surge of melatonin following DLMO. These results, therefore, suggest that in addition to a delayed endogenous circadian rhythm, a diminished initial surge of melatonin secretion following DLMO may contribute to the aetiology of DSPD [42].

Exercise induces a phase advancement of the melatonin rhythm, restoring its acrophase, according to the chronotype of the athlete. The rising phase of the plasma melatonin rhythm was delayed by 1.1 hours without exercise. However, the falling phase was shifted after evening exercise only by 1 hour. REM sleep was decreased by 10.5% after evening exercise [46]. Daily physical exercise accelerated the re-entrainment of the sleep-wake cycle, but not that of the circadian melatonin rhythm under dim light conditions [47]. Interestingly, re-entrainment of both the sleep-wake cycle and circadian melatonin rhythm was accelerated by physical exercise under bright light conditions. Physical exercise resets the circadian melatonin rhythm indirectly through stimulation of the sympathetic activity, which enhanced the light influx to the circadian pacemaker [48]. These changes included a 1-hour phase advancement in the WT rhythm before bedtime, with a longer nocturnal steady state and a smaller reduction when waking in the morning. In summary, melatonin can effectively modulate the circadian components of the sleep-wake cycle and improve sleep efficiency [49].

Melatonin receptors are present in the suprachiasmatic nuclei (SCN); therefore, circulating melatonin can provide feedback to the SCN clock. The SCN is affected by exogenous melatonin *in vivo* and *in vitro*, as shown by the phase-shifting effects on the firing rate of SCN neurons [50]. The effect of melatonin on sleep is believed to be a consequence of mechanisms that involves an increase in sleep propensity by enhancing the amplitude of circadian clock oscillations via MT1 receptors

and the synchronization of the circadian clock via MT2 receptors [51].

Effect of melatonin on parasomnias

Parasomnias are undesirable physical events or experiences that may occur during NREM, REM sleep or transitions to and from sleep. Parasomnias are characterized based on the stage of sleep in which they occur (i.e. REM or NREM sleep). Parasomnias encompass abnormal sleep-related complex movements, behaviours, emotions, perceptions, dreams and autonomic nervous system activity that result in physical injuries, sleep disruption, adverse health effects and untoward psychosocial effects. The clinical consequences of parasomnias can affect the patient, the bed partner or both [9]. Without an appropriate diagnosis, patients may undergo an extensive medical workup and exposure to unnecessary pharmacotherapy [52]. REM sleep behaviour disorder (RBD) is a parasomnia associated with dream enactment often involving violent or potentially injurious behaviours during REM sleep, and is strongly associated with synucleinopathy and neurodegeneration. NREM parasomnias include night terrors, somnambulism, and confusion during arousals, which are most prevalent in the paediatric population. In contrast to NREM parasomnias, the age of onset for REM parasomnia is between 40 and 70 [53]. RBD is believed to be the result of brainstem dysfunction, most likely involving the dorsal pontine sublaterodorsal nucleus and/or magnocellular reticular formation (or their afferent and efferent connections), leading to a loss of function in the brain's ability to regulate physiological REM sleep atonia [54].

Violent behaviours secondary to RBD places both the patient and bed partner at risk of physical harm. Approximately 55% of the RBD patients have a history of injuring either themselves or their bed partner [55]. Clonazepam, a benzodiazepine, is the first-line treatment for RBD [56]. However, patients taking clonazepam report significant adverse effects compared to those using melatonin [56]. The benefit of melatonin

Table 1. Functions of melatonin.

Sleep disorders	Benefits	References
Insomnia	<ul style="list-style-type: none"> Improves sleep quality Increases total sleep time Improves sleep efficiency Decreases sleep onset latency 	Shechter et al. [13] Scheer et al. [14]
SBDs	<ul style="list-style-type: none"> Lowers blood pressure Increases blood flow in poorly perfused tissues Anti-hypertensive effects Cardiovascular disease management 	Abadir et al. [29] Sabatini et al. [30] Masana et al. [32]
Central disorders of hypersomnolence	<ul style="list-style-type: none"> Decreases plasma TNF-alpha and IL-1-beta levels Increases BDNF, S100B, and IL-10 Prevents dopamine neuronal loss or dopamine transporter down-regulation Anti-apoptotic effects 	Lin et al. [40] Pazar et al. [41]
CRSWDs	<ul style="list-style-type: none"> Reduces nocturnal activity Reduces activity and position changes during naps Modulates the circadian rhythm of the sleep-wake cycle Improves sleep efficiency 	Leonardo-Mendonca et al. [49]
Parasomnias	<ul style="list-style-type: none"> Decreases muscle tonicity during REM sleep Reduces injuries; Fewer adverse effects 	McCarter et al. [56] McGrane et al. [58]

over clonazepam for the treatment of RBD was first described in 1997 by Kunz et al. Subsequent research and clinical trials have suggested that melatonin provides clinical benefits for patients who require pharmacologic treatment for RBD [56]. Melatonin-treated patients reported significantly fewer injuries and adverse effects. Melatonin and clonazepam both have shown efficacy in reducing RBD behaviours and injuries. Based on our experience, melatonin is equally efficacious as clonazepam, and report far fewer adverse effects. The results of a small pilot prospective trial showed that melatonin administration of 3 mg nightly produced a significant decrease in REM sleep without atonia, as well as subjective improvements in clinical symptoms of RBD [57]. Melatonin appears to be beneficial for the management of RBD with reductions in clinical behavioural outcomes and a decrease in muscle tonicity during REM sleep. Melatonin also has a favourable safety and tolerability profile compared to clonazepam with limited potential for drug–drug interactions, which is an important consideration, especially in elderly individuals with RBD receiving polypharmacy, as adverse events were minimal [58].

Conclusions

Melatonin is a hormone secreted by the pineal gland and is involved in the regulation of the human sleep–wake cycle and circadian rhythm [59]. This review discusses the use of exogenous melatonin for sleep disorders in humans. Although there has been an increase in interest in all aspects of sleep function/disorders, and the importance of hypnagogue in the regulation of sleep is well documented, our knowledge of the role of melatonin in sleep architecture, sleep breathing, hypersomnolence and parasomnia is limited. Few clinical trials have investigated these areas, and most of the literature focuses on CRSWDs and insomnia. In this paper, the effects of melatonin on sleep disorders are comprehensively described (Table 1). For SBDs, current treatments such as CPAP, orthodontic appliances and surgery do not achieve satisfactory results. Melatonin is effective for ameliorating insomnia, SBDs, central disorders of hypersomnolence, CRSWDs and parasomnias without physical dependence, addiction and other significant adverse reactions. More studies – especially large-scale clinical trials – are warranted, and long-term adverse effects of melatonin must be addressed.

Contributors

ZX conceived and designed the study, and obtained funded and ethics approval. FC conceived and designed the study. WA.L wrote the article in whole/part. XG, CL, XM, YF and WL revised the article. FY revised the article and obtained funded and ethics approval.

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