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Review Article

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Melatonin and melatonergic drugs in sleep disorders

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ABSTRACT

Melatonin is an endogenous chronobiological regulator secreted mainly from the pineal gland, which has been used as a dietary supplement in the treatment of sleep problems, including insomnia, parasomnia, and circadian rhythm sleep disorders. However, the short half-life and rapid metabolism of melatonin limit its suitability as a drug. There are many melatonergic drugs used in the treatment of sleep disorders and several drugs are under investigation for approval. Ramelteon was the first melatonergic agonist approved as hypnotic agent by U.S. Food and Drug Administration for the treatment of insomnia. It exhibits higher selective affinity for melatonin 1a (MT_1) receptor than melatonin 1b (MT_2) receptor. This selectivity suggests that it targets sleep onset with no significant adverse effect or dependency. Agomelatin, naphtahalenic compound, act as a potent MT_1/MT_2 melatonergic receptor agonist and serotonergic receptor antagonist was approved for treatment of depression in 2009. This dual action drug is the first melatonergic agent used in depression. Another melatonergic agonist, tasimelteon has high affinity for the MT_1/MT_2 receptors in humans. It was approved for the treatment of non-24 hours sleep-wake rhythm disorder. The newly developed melatonin and melatonergic drugs have the potential to be used extensively in various clinical situations and substitute the old benzodiazepine and its derivatives in the treatment of insomnia. However, the efficacy and safety of newly developed melatonergic drugs should be elucidated through long-term clinical trials.

Keywords: Melatonin; Clinical Pharmacology; Sleep Disorders

INTRODUCTION

Sleep disorders constitute a wide spectrum of categorical disorders that include insomnia, sleep-related breathing disorders, central disorders of hypersomnolence, circadian rhythm sleep-wake disorders, parasomnias, and sleep-related movement disorders [1]. The most common type of sleep disorder is insomnia. The prevalence rate of insomnia in the Korean adult population has been estimated to range from 10% to 30% and is similar to the rate reported in adults in Western countries [2]. The consequences of sleep disorders are irritability, daytime sleepiness, low energy and motivation, physical discomfort, and impaired cognitive functioning [3,4]. Sleep disorders lead to a significant burden on the

healthcare system in Korea. Over the last few decades, the number of prescriptions for sleep medications has increased by 293% in outpatient visits in the United States [5]. This indicates an extremely high usage of second-generation benzodiazepines or Z-drugs (zopiclone, zolpidem, or zaleplon), benzodiazepine receptor agonists, and many other sleep medications [5]. A plethora of studies on these medications have shown significant adverse effects, including hangover on the next day, excessive daytime sleepiness, cognitive or memory impairment, car accidents or falls, abuse, and dependence [6,7]. Besides these adverse effects, these drugs can also causes another sleep related abnormal behavior, such as compulsive eating in the evening [8]. The problematic effects of benzodiazepine and Z-drugs have led clinicians to prescribe off-label medication, which is considered less liable to addiction or tolerance. Bertisch et al. [9] showed that off-label drugs such as trazodone, quetiapine, and doxepin are commonly used for the treatment of insomnia. In terms of sleep quality, both benzodiazepines and Z-drugs decrease sleep-onset latency; however, they are not very effective in increasing total sleep time or sleep efficiency [10,11]. An ideal drug for sleep disorders should not only decrease sleep latency but also increase total sleep time and sleep efficiency without producing undesirable adverse effects, such as cognition or memory impairment, daytime hangover, or psychomotor retardation and dependence.

Saper and his colleagues [12] first proposed a sleep-switch model to describe the regulation of sleep-wakefulness. This model comprises "flip-flop" reciprocal inhibition among sleep-associated activities in the ventrolateral preoptic nucleus and wakefulness-associated activities in the locus coeruleus, dorsal raphe, and tuberomammillary nuclei. The promotion of wakefulness and sleep are controlled by the suprachiasmatic nuclei (SCN) of the hypothalamus and depend on a complex neuronal network and many neurotransmitters such as gamma-aminobutyric acid, glutamate, somatostatin, or arginine vasopressin [13]. Circulating melatonin (*N*-acetyl-5-methoxytryptamine), secreted in the pineal gland, which is controlled by the SCN, is a major chronobiological regulator involved in controlling the sleep/wake cycle. It induces sleep-promoting and circadian rhythm regulating action through the activation of 2 major G protein-coupled melatonin receptors, melatonin 1a (MT_1) and melatonin 1b (MT_2), which are abundant in the SCN.

Melatonin is an U.S. Food and Drug Administration (US FDA)-approved dietary supplement used to improve sleep quality in patients with insomnia and in people suffering from jet lag. There are no dosage restrictions for melatonin as it does not generate a hangover effect or lead to dependence. However, the suitability of melatonin to be used as a drug is limited, mainly because of its poor oral bioavailability and short half-life [14,15]. Owing to these pharmacokinetic properties, a need arose to develop controlled-release formulations and several synthetic melatonergic agonists, such as ramelteon, agomelatine and tasimelteon. Chemical structure of melatonin receptor agonists currently have reached the market are shown in **Fig. 1.** and pharmacokinetic parameters of drugs reviewed were summarized in **Table 1.**

Table 1. Summary of pharmacokinetic parameters of melatonin and melatonergic agents

Agents	t_{max} (hr)	$t_{1/2}$ (hr)	Bioavailability (%)
Immediate-release melatonin	0.8	0.75	15
Prolonged-release melatonin	3.0 (fed state)	3.5–4	15
Ramelteon	Less than 1	0.83–1.90	1.8
Agomelatin	1–2	1–2	Less than 5
Tasimelteon	1.9–3	1.3	38.3

t_{max}, time to maximum plasma concentration; $t_{1/2}$ (hr), elimination half-life.

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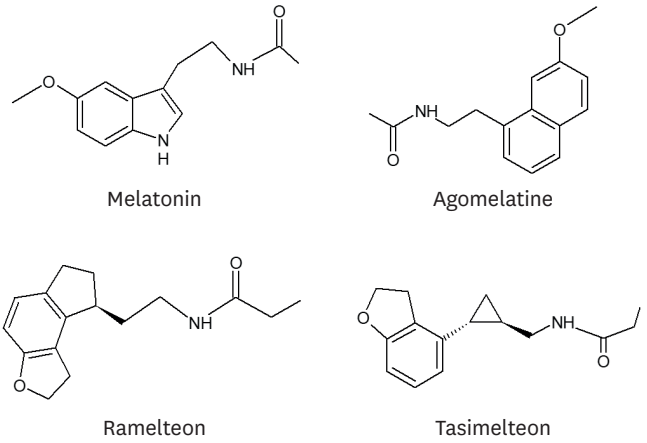

Figure 1. Melatonin and melatonin receptor agonists reviewed in the article.

PROLONGED-RELEASE MELATONIN

A controlled release formulation of melatonin (Circadin® 2 mg) was first approved by European Medicines Agency (EMA) as a monotherapy for the short-term treatment of primary insomnia in elderly patients aged over 55 years. The Ministry of Food and Drug Safety approved it as the same indication in 2014. As endogenous melatonin production declines with age, prolonged-release melatonin was designed to mimic the pharmacokinetic properties of endogenous melatonin in elderly patients [16]. A randomized, double-blind, placebo-controlled trial with 791 subjects showed that sleep latency and other sleep variables were significantly improved in the 55–80-year age group rather than in the 18–80-year age group [17]. Same investigators conducted a randomized clinical trial and showed that prolonged-release melatonin was not effective in the treatment of primary insomnia in younger adults [18]. This finding supported the idea that prolonged-release melatonin has targeted efficacy in the elderly. Another randomized clinical trial in patients with Alzheimer's disease, with and without comorbidity of insomnia, showed that add-on prolonged-release melatonin had a positive effect on cognitive functioning and sleep maintenance in patients with Alzheimer's disease compared with placebo, particularly in those with comorbidity of insomnia [19].

RAMELTEON

Overview and mechanism of action

Ramelteon (Rozerem®), a tricyclic synthetic analog of melatonin developed by Takeda Pharmaceutical Company (Osaka, Japan), was the first melatonergic agonist to be approved as a hypnotic agent by the US FDA for the treatment of insomnia in 2005. It is a selective agonist for MT_1 and MT_2 receptors without significant affinity for other receptors such as benzodiazepine, dopamine, norepinephrine, acetylcholine, and opiate receptors [20,21]. *In vitro* binding studies showed that its affinity for MT_1 and MT_2 receptors is 3–16 times higher than that of melatonin. The affinity of ramelteon for the MT_1 receptor is eight times higher than that for the MT_2 receptor. This selectivity suggests that ramelteon targets sleep onset more specifically than melatonin [22]. Therefore, the hypnotic effect of ramelteon seems to be mediated mostly by its agonistic affinity for the melatonergic receptor.

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Pharmacokinetics

As ramelteon has a higher lipophilicity than melatonin, it is easily distributed and retained in tissues. Ramelteon is usually administered orally in the evening at a dose of 8 mg and is absorbed rapidly with a T_{max} of less than 1 hour [23]. Its half-life is 0.83–1.90 hours, which is longer than that of melatonin [20]. Ramelteon is extensively metabolized via oxidation to hydroxyl and carbonyl groups and then conjugated with glucuronide in the liver. Cytochrome P450 (CYP) 1A2 is the major hepatic enzyme involved in its metabolism. Four metabolites (M-I, M-II, M-III, and M-IV) were identified. Among these metabolites, M-II showed 20–100-fold higher systemic levels than ramelteon itself and exhibited an agonistic action on MT_1/MT_2 receptors. Although the potency of M-II is only 10% than that of ramelteon, its systemic levels are higher (30-fold), and its half-life (2–5 hours) is longer than that of ramelteon. These characteristics are thought to contribute to the significantly extended therapeutic effect of ramelteon [24].

Administration of ramelteon with a high-fat diet changes its pharmacokinetics. The area under the concentration-time curve for a single 16 mg dose was 31% higher, whereas the maximal concentration was 22% lower than when ramelteon was administered in a fasted state [25]. Therefore, the US FDA does not recommend administering ramelteon after a high-fat meal.

Efficacy and safety

Several meta-analyses have found ramelteon to be effective in reducing subjective sleep latency and thereby, improve sleep quality in patients with primary insomnia. Kuriyama et al. [26] analyzed 13 trials involving 5,812 patients with insomnia or insomnia symptoms with a mean study duration of 38 days. They reported that ramelteon was significantly associated with reduced subjective sleep latency and improved sleep quality, but was not associated with increased total subjective sleep time. Somnolence was the only significant adverse event related to ramelteon. However, given that insomnia is a chronic disorder, this study had a limitation that the duration of the trials included was relatively short.

Long-term safety and efficacy trials were also conducted in patients with chronic insomnia [27]. This study showed that ramelteon significantly decreases subjective sleep latency and total sleep time. Both reached a plateau by week 20 and were sustained thereafter. There were no signs of next-day residual effect, rebound insomnia, withdrawal symptoms, or dependence, which are frequently observed with benzodiazepine or Z-drug use. Long-term safety was evaluated using clinical laboratory tests and endocrine function tests based on levels of hormones for the pituitary, thyroid, reproductive, and adrenal axes. Although statistically significant changes in several hormone levels, including prolactin, thyroid stimulating hormone, thyroxine, and testosterone were observed, the overall changes were small and not considered clinically meaningful.

Caution should be exercised when ramelteon is co-administered with CYP3A4 inhibitors such as ketoconazole and fluconazole. Co-administration of these drugs has been shown to increase the area under the plasma or serum concentration-time curve, maximal concentration, and half-life of ramelteon [28]. Fluvoxamine co-administration causes increased exposure to ramelteon due to strong inhibition of CYP1A2 [29].

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AGOMELATINE

Overview and mechanism of action

Disturbances in sleep and circadian rhythms are major features of depression. Hence, in the treatment of depressive disorders, alleviation of sleep disturbances is foremost, which will subsequently lead to better therapeutic results. Agomelatine (Valdoxan®; Servier, Neuilly-sur-Seine, France), a naphthalenic compound, acts as a potent agonist on both MT_1 and MT_2 melatonergic receptors (with pK_i values of 10.21 and 9.75, respectively) and acts as an antagonist to $5HT_{2c}$ receptors(pK_i = 6.68) [30]. It has no significant affinities for muscarinic, histaminergic, adrenergic, and dopaminergic receptor subtypes [31]. This is the first melatonergic antidepressant that has been licensed and approved in the European Union and Canada for the treatment of major depressive disorder, but not approved in the United States.

Pharmacokinetics

Agomelatine is rapidly and well-absorbed following oral administration but undergoes extensive first-pass metabolism and hence has a low bioavailability (less than 5%). Its elimination half-life is 2.3 hours and it is extensively protein bound (95%). It is metabolized to a major extent (90%) by CYP1A2 and CYP2C9 (10%) isoenzymes, with initial hydroxylation (CYP1A2) and demethylation (CYP2C9), followed by glucuronide conjugation and sulfonation [28]. Since it is mainly metabolized in the liver, caution should be exercised during the administration of agomelatine to patients with liver disease.

Efficacy and safety

In a multicenter clinical trial of agomelatine on depressive disorders in Europe, agomelatine was administered at a dose of 25 mg/day to patients with major depressive disorder for 8 weeks, and its effect was compared with that of paroxetine (20 mg/day), a selective serotonin reuptake inhibitor. Both agomelatine and paroxetine showed significantly higher remission rates than the placebo. In the subgroup analysis of patients with severe depression, agomelatine showed better outcomes that were statistically significant. The effectiveness of agomelatine in patients with severe depression is particularly important because the symptoms of these patient groups were not improved by selective serotonin reuptake inhibitors or selective norepinephrine reuptake inhibitors [32]. In addition, agomelatine increased the duration of non-rapid eye movement sleep without affecting rapid eye movement sleep. This property led to improvement of sleep quality in patients with depression and sleep disturbance [33]. Another study showed evidence of the superior chronobiological effects of agomelatine in patients with major depressive disorder [34]. Agomelatine treatment showed a favorable effect on the relative amplitude of the circadian rest-activity/sleep-wake cycle in depressed patients at week 1, which implied better improvement in sleep and daytime functioning. It was observed that agomelatine was more effective than sertraline in treating depression and anxiety symptoms over a 6-week period. It has been hypothesized that the better efficacy of agomelatine over other antidepressants is because of its unique chronobiological action. The effects of agomelatine are mediated through MT_1 and MT_2 melatonergic receptors and $5\text{-}HT_{2c}$ serotonergic receptors. They act differently during different circadian phases of the day-night cycle [35]. Agomelatine may promote and maintain sleep at night and help to maintain alertness during the day. At night, melatonergic sleep-promoting effects prevail over its potentially antihypnotic $5\text{-}HT_{2c}$ antagonism. In contrast, during the day, antagonism of agomelatine to the $5\text{-}HT_{2c}$ receptor would be more potent than the melatonergic action, thus exerting an alerting effect [28]. These properties met the criteria of an ideal antidepressant, which does not only decrease

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sleep onset difficulties and wakefulness after sleep onset, but also promotes freshness and alertness during daytime.

Excellent tolerability and safety were observed in several clinical trials of agomelatine. A double-blind placebo-controlled study conducted for 6 weeks in 212 patients showed that administration of agomelatine at 25–50 mg dose resulted in significant improvement in the clinical state of the patients when compared with placebo [36]. Another double-blind placebo-controlled study conducted for 12 weeks demonstrated excellent efficacy and tolerability of agomelatine in 412 patients with generalized anxiety disorder [37].

TASIMELTEON

Tasimelteon is a melatonin receptor agonist that was originally developed by Bristol Myers Squibb Co. (New York, NY, USA) and licensed to Vanda Pharmaceuticals (Washington, D.C., USA) in 2004. It exhibits a high affinity for MT_1 and MT_2 melatonergic receptors in humans. These affinities for both melatonergic receptors are similar to those of melatonin [38]. After several clinical trials, the US FDA granted orphan drug status to tasimelteon, which was indicated for blind individuals without light perception in 2010. Approximately half of totally blind individuals have a condition called non-24-hours sleep-wake rhythm disorder, which results from the SCN not being entrained to 24 hours due to a lack of light perception. A randomized controlled study demonstrated that 90% of patients who continued tasimelteon treatment maintained circadian entrainment, and its long-term administration was safe and well tolerated [39]. Therefore, it is the only drug approved by the US FDA and the EMA for treating non-24-hours sleep-wake rhythm disorder.

DISCUSSION AND CONCLUSIONS

The criteria for insomnia are defined in three separate texts: the Diagnostic and Statistical Manual of Mental Disorders, the International Classification of Sleep Disorders, and the International Classification of Diseases, Tenth Revision, Classification of Mental and Behavioral Disorders. In general, the inconsistencies in definition and use of diagnostic criteria prevent researchers from estimating the exact prevalence rates of insomnia. However, in Korea, the estimated prevalence rate of insomnia varies from 10% to 30% of the population. In general terms, insomnia has been defined as a condition that leads to difficulty in initiating or maintaining sleep, waking up too early, or not being refreshed after sleep. Both benzodiazepines and non-benzodiazepines have been used for more than 40 years in the pharmacological treatment of insomnia. Benzodiazepine causes adverse side effects such as cognitive and memory impairment, psychomotor retardation, and can cause hangover on the next day. Non-benzodiazepine drugs can reduce sleep onset time but are not very effective in increasing total sleep time.

Melatonin is an endogenous compound that mainly regulates the sleep-wake cycle and indicates numerous endocrine protective actions. This means that it can be administered safely in children, adults, and elderly people who suffer from insomnia. Its short half-life and rapid metabolism after oral administration provided the basis for the development of a prolonged release formulation of melatonin, which was later introduced and showed good results in the treatment of insomnia. The British Association for Psychopharmacology

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on evidence-based treatment of insomnia reported that melatonin should be tried first in insomnia patients aged over 55 years [40]. Prolonged released melatonin preparation (Circadin®) and agomelatin are melatonin related drugs that are currently available in Korea. Ramelteon and tasimelteon are approved for insomnia in other countries, but are not yet available in Korea. Except for the drugs reviewed in this article, several other melatonergic drugs are under clinical trials or investigations. TIK-301 has been granted orphan drug designation in the USA. Several investigational drugs belong to nonselective MT_1/MT_2 melatonergic ligands, selective MT_2 melatonergic ligands, and selective MT_1 melatonergic ligands, respectively [41]. It is expected that new melatonergic drugs that can be used to treat sleep disorders may be introduced in the near future and can be used as substitutes for a significant portion of old benzodiazepine or non-benzodiazepine sleeping pills.

It is important to understand that melatonin and the melatonergic effects of drugs on sleep architecture are different from those of benzodiazepines and their derivatives. They exert a sleep promoting effect by modulating the circadian rhythm and displaying modest sleep-inducing properties, which are quite mild compared to the properties of benzodiazepines and their derivatives.

Melatonin and melatonergic drugs showed beneficial effects not only in the treatment of insomnia but also in various related conditions such as parasomnia, circadian rhythm disorders, night eating disorders, and depression. The newly developed melatonin and melatonergic drugs have the potential to be used extensively in various clinical situations. However, the efficacy and safety of these newly developed melatonergic drugs should be elucidated through long-term clinical trials.

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