Melatonin agonists in the management of sleep disorders: A focus on ramelteon and tasimelteon

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ABSTRACT

Melatonin agonists have become an area of interest in the treatment of sleep disorders. This article reviews the available data on this class of medications, with a focus on ramelteon and tasimelteon.

KEYWORDS

melatonin agonist, insomnia, ramelteon, tasimelteon

BACKGROUND

Insomnia continues to be one of the most prevalent sleep disorders, with almost one-third to one-half of the United States (US) population experiencing a symptom of insomnia over the past year.[1,2] Currently in the US, most sedative hypnotics are targeted at improving insomnia symptoms and work via modulation of gamma-amino butyric acid (GABA) or as histamine H_1 receptor antagonists.[2] Melatonin supplementation is utilized in the treatment of insomnia, along with sleep disorders associated with jet lag and shift-work disorders. Over the last 10 years, medications targeting agonism of melatonin receptors are being developed to expand treatment options in sleep disorders beyond drugs targeting GABA (i.e., barbiturates, benzodiazepines and non-benzodiazepine receptor agonists) or histamine (e.g., diphenhydramine, doxepin).

Sleep disorders extend beyond insomnia, and research is being done for pharmaceutical targets of other disorders. Circadian rhythm disorders are related to sleep disturbances secondary to a change in the circadian system or discordance between the circadian rhythm and a person's sleep-wake schedule.[1] These disorders are further classified as delayed sleep phase type, advanced sleep phase type, irregular sleep-wake type, shift-work type, and non-24-hour sleep-wake disorder (non-24 SWD).[1] Non-24 SWD is a circadian rhythm sleep-wake disorder characterized by sleeping and being awake during times that are not synchronized with the typical 24-hour environment.[1] Persons with this disorder experience a consistent daily shift in the time of sleep onset and time awake, with sleep onset occurring at a later and later time.[1] Recently, Vanda Pharmaceuticals submitted a New Drug Application for tasimelteon (Hetlioz®), for the treatment of non-24 SWD in the totally blind. In November 2013, the Federal Drug Administration (FDA) advisory panel voted in favor of tasimelteon.[3] It is slated to be reviewed by the FDA in the first quarter of 2014.

MELATONIN AGONISTS

Melatonin and melatonin agonists have become an area of interest in studying medications to treat insomnia and circadian rhythm disorders. However, their role may not be exclusively in the treatment of sleep disorders; melatonin agonist's use may extend into major depression or irritable bowel syndrome based on recent research. Furthermore, the potential role of melatonin and melatonin agonists in improving blood pressure and other cardiovascular effects is being examined.[4]

Melatonin, which is released from the pineal gland, is increased during sleep and is suppressed by light.[2] Melatonin is available over-the-counter as an herbal supplement. ***Refer to the article discussing melatonin in this issue of The Mental Health Clinician for a detailed discussion of the herbal supplement's role in the Circadian Rhythm.***

Ramelteon was approved in July 2005 as the first non-controlled sleep agent that targeted melatonin receptors. Its role in the management of sleep disorders has primarily targeted sleep latency in insomnia.[5] Additional melatonin agonists including tasimelteon, agomelatine and piromelatine have been, or are being studied (Table 1). Tasimelteon is under review by the FDA for the

treatment of non-24 SWD in the totally blind. Agomelatine was approved for use in the European Union for Major Depressive Disorder, however its development in the US ceased after reports of liver failure.[6,7] Piromelatine (NEU-P11) and TIK-301 are still in early stages of development, therefore this article will focus mainly on the differences between ramelteon and tasimelteon and their role in the treatment of primary insomnia and circadian rhythm sleep-wake disorders.[8]

MECHANISM OF ACTION

Melatonin receptor agonists are believed to have sleep-promoting properties like endogenous melatonin by working as agonists at MT_1 and MT_2 receptors.[5] In the suprachiasmatic nucleus, MT_1 receptors appear to be related to the sleep-promoting effects of melatonin and MT_2 plays a major role in melatonin's resynchronizing activity.[9,10] It has also been postulated that MT_1 may mediate vasoconstriction, whereas MT_2 affects vasodilation.[9,10]

Ramelteon has high affinity, acting as a full agonist at the MT_1 and MT_2 receptors.[5] Tasimelteon, like ramelteon, has a high affinity for MT_1 (pKi = 9.45 ± 0.04 (0.35 nM) and MT_2 (pKi = 9.8 ± 0.07 (0.17 nM) which is similar to the affinity of melatonin for both receptors.[2]

Table 1. Melatonin and melatonin agonists[3,4,7-9]

Medication or Substance	Mechanism of action	FDA approved	Targeted Indication (s)	Comments
Agomelatine	MT_1 and MT_2 agonist $5HT_{2B}$ antagonist $5HT_{2C}$ antagonist	No; withdrawn secondary to hepatic impairment	MDD	Available in EU as 25 mg tablets
Melatonin	Melatonin	No	Primary insomnia	Available in the EU as 2 mg prolonged-release tablets as Circadin® Available as an OTC herbal supplement in the US
Piromelatine (Neu-P11)	Melatonin agonist $5HT_{1A}$ agonist $5HT_{1D}$ agonist $5HT_{2B}$ antagonist	Under development	Insomnia Diarrhea-predominant IBS Also being studied for its antidepressant, anxiolytic and pro-cognitive effects	Still in development Most studies in rodents Phase II study completed in primary insomnia targeting LPS (20 mg, 50 mg) Observation study on symptoms of diarrhea-predominant IBS Phase I studies included 5, 20, 50, and 200 mg
Ramelteon	MT_1 and MT_2 agonist	Yes	Insomnia characterized by difficulty with sleep onset	Available as 8 mg tablets
Tasimelteon (VEC-162) (BMS-214778)	MT_1 and MT_2 agonist	Submitted to FDA	Non-24 SWD	Phase III studies completed Studied 10, 20, 50 or 100 mg Targeting 20 mg 1 hour before bedtime for non-24 SWD
TIK-301	MT_1 and MT_2 agonist $5HT_{2B}$ antagonist $5HT_{2C}$ antagonist	Under development	Sleep disorders, chronic insomnia, circadian rhythm disorders	Doses used in studies included 20, 35, 40, 50 and 100 mg

EU = European Union; IBS = irritable bowel syndrome; LPS = latency to persistent sleep; MDD = Major Depressive Disorder; non-24 SWD = non-24 hour sleep-wake disorder; OTC = over-the-counter

PHARMACOKINETICS, METABOLISM AND DRUG INTERACTIONS

Both melatonin and ramelteon's peak concentrations (Cmax) occur about 45 minutes (range 30 to 90 minutes for ramelteon) after administration.[5,11] In Phase II trials, tasimelteon's time to reach maximum plasma concentration (Tmax) ranged from 1.9 hours with low dose to 3 hours with higher doses. When melatonin, as the delayed release form, is taken with food, its peak is delayed to 3 hours and its Cmax is approximately 15% lower.[11] When ramelteon is taken with a high-fat meal, its AUC is 31% higher, Cmax 22% lower, and its peak is delayed by 45 minutes. Therefore, it is recommended that melatonin and ramelteon not be taken with a high-fat meal.[5] The effect of food on tasimelteon absorption is not known.

The dietary supplement melatonin displays high first-pass metabolism, and has an extremely short half-life of 20-30 minutes.[9] Similar to melatonin, ramelteon also undergoes substantial first-pass metabolism. Its half-life ranges from 1 to 2.6 hours, and the half-life of its active metabolite (M-II) ranges from 2 to 5 hours.[5] In the elderly, the half-life of ramelteon is 2.6 hours.[5] Tasimelteon's half-life is 1.32 ± 0.43 hours.[3] Tasimelteon has six main metabolites (M3, M9, M11, M12, M13 and M14) and they were retained from 73 to 87 days in clinical trials.[2-3]

Melatonin metabolism is primarily via cytochrome P450 (CYP) 1A1 and CYP1A2; with potentially some CYP2C19 enzyme involvement.[11] Melatonin's primary metabolite is 6-sulphatoxy-melatonin (6-S-MT) which is inactive. Ramelteon is primarily hepatically metabolized by oxidation, and secondarily via glucuronidation. The primary enzyme involved in its metabolism is CYP1A2. CYP2D6 and CYP3A4 may play minor roles.[5] The primary active metabolite of ramelteon is M-II; exposure to M-II is 20 to 100 times higher than that of the parent drug.[5] Tasimelteon is primarily metabolized by CYP1A2 and CYP3A4 .[3]

Fluvoxamine, a strong CYP1A2 inhibitor, significantly increases levels of CYP1A2 substrates and its use is cautioned with melatonin, contraindicated with ramelteon, and most likely will be contraindicated with tasimelteon. Fluvoxamine increases melatonin's AUC by 17-fold, and its Cmax by 12-fold.[11] It is reported that a single-dose of 16 mg of ramelteon added to fluvoxamine increased ramelteon's AUC by 190-fold, and Cmax by 70-fold.[5] Concurrent administration of fluvoxamine yielded an 85% reduction in clearance and a 6.5-fold increase in tasimelteon exposure.[3]

Rifampin is a strong CYP3A4 inducer, and moderate CYP2C9 and CYP2C19 inducer, and reduced ramelteon exposure and its metabolite by 80%.[5] Rifampin reduced tasimelteon exposure by almost 90%. Additionally, co-administration of donepezil with ramelteon resulted in an approximate 100% increase in AUC and 87% increase in Cmax of ramelteon.[5].

Induction of CYP1A2 occurs in cigarette smokers.[3,11] Smoking may reduce levels of melatonin.[11] Although not specifically studied, one could postulate smoking will also reduce ramelteon levels. Change in tasimelteon exposure was studied in cigarette smokers, which resulted in a 40% reduction in exposure.[3]

Although melatonin agonists do not mediate GABA, it is recommended that melatonin and ramelteon not be combined with alcohol. Alcohol may reduce melatonin's efficacy on sleep, and may have additive CNS effects and increase risk of sleep-related complex behaviors when combined with ramelteon.[5,11] One can postulate that tasimelteon should not be combined with alcohol either.

Use of ramelteon with concurrent fluvoxamine is contraindicated.[5] At this time, it has been recommended by the FDA advisory committee that tasimelteon use be contraindicated in persons taking moderate to strong CYP1A2 inhibitors and moderate to strong CYP3A4 inducers.[3]

PLACE IN THERAPY

Initial efficacy data supporting the use of ramelteon in adults for insomnia was based on one short-term and one longer-term clinical trial which both utilized polysomnography (PSG) to assess latency to persistent sleep (LPS).[12] The first was a 5-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial. Participants were 18-64 years of age with a diagnosis of primary insomnia, reporting subjective sleep latency of at least 30 minutes, subjective total sleep time (TST) less than 6.5 hours per night and symptoms during the day related to their disrupted sleep. Notable exclusions included patients who participate in shift work, had recently taken a flight across greater than 3 time zones, or had any mental illness or other significant disease states. During the treatment period, participants received 8 or 16 mg of ramelteon or placebo 30 minutes prior to bedtime and start of PSG. Three hundred sixty seven participants completed the study, the majority of which were Caucasian females. During assessments at week 1, 3, and 5, participants who received 8 or 16 mg of ramelteon had significant improvements in LPS compared to those who received placebo (at week 1: 32.2,

28.9 and 47.9 minutes respectively; p<0.001). The authors reported a 15-17 minute greater reduction in LPS in participants who received ramelteon than those who received placebo. Additional secondary outcomes such as TST and sleep efficiency were also statistically significantly improved with ramelteon compared to placebo at the week 1 assessment (both p<0.001).

The second trial was a 6-month, multicenter, randomized, double-blind, placebo-controlled study that evaluated ramelteon 8 mg in a similar patient population and with similar medication administration.[13] Included participants were adults with chronic insomnia with similar symptoms as the previous trial but with a subjective sleep latency of at least 45 minutes and a regular bedtime between 10 pm and 1 am. Exclusion criteria were also similar, except patients with sleep disorders other than insomnia were also excluded. Three hundred thirty five participants completed the treatment period. Again, the majority of participants were Caucasian women with an average age of 46.2 years. Participants who received ramelteon had statistically significant improvements in LPS compared with placebo throughout the 6 month treatment period (week 1, months 1, 3, 5 and 6; all p<0.05). However, a significant increase in TST was only observed during evaluations at week 1 in participants who received ramelteon compared to placebo (281.1 minutes vs. 365.7 minutes; p<0.001). The results from these two trials led to the FDA approval of ramelteon in adults for the treatment of insomnia characterized by difficulty with sleep onset, but not sleep maintenance as its use did not lead to sustained increases in TST during the duration of these studies.[5]

While the majority of research with ramelteon has surrounded use in primary insomnia, studies have also attempted to evaluate its use in circadian rhythm sleep disorders. One such study enrolled 75 patients age 18-45 years with subjective sleep latency less than 30 minutes and subjective TST between 6.5 and 9 hours in a randomized, double-blind, placebo controlled trial.[14] Of note, the participants were healthy adults with no history of sleep disorder or any recent change in sleep schedule. Participants were in a sleep laboratory for five nights and received fixed doses of ramelteon (1, 2, 4 or 8 mg) once daily for 4 days. On the first night of treatment, the sleep cycle was advanced by setting bedtime at 5 hours prior to the participant's usual bedtime and this schedule was maintained during the entire treatment period. The authors sought to determine whether ramelteon would improve the re-entrainment of circadian rhythms compared to placebo utilizing a measure of dim-light melatonin offset time (DLMoff). The authors did find statistically significant changes in DLMoff in the 1 mg, 2 mg and 4 mg ramelteon groups compared to placebo (all p<0.05). However, the clinical relevance of this objective and therefore the author's conclusion that these results support the potential use of ramelteon in circadian rhythm sleep disorders is questionable. Additionally, no PSG measurement (including LPS, TST, sleep efficiency, etc.) was statistically significantly improved in patients who received any dose of ramelteon compared to placebo. It is unclear whether Takeda Pharmaceuticals will pursue FDA indications for ramelteon for circadian rhythm disorders given these results.

In contrast to ramelteon, the majority of research with tasimelteon has evaluated its role in the treatment of circadian rhythm sleep disorders. Phase II and III randomized, double-blind, placebo-controlled, parallel-group trials assessing the use of tasimelteon in simulated circadian rhythm sleep disorders were published in 2009.[15] Eligible participants were healthy adults less than 50 years of age with no sleep disorders. In the phase II study, 39 participants had their sleep cycle advanced by 5 hours and then were randomized to receive tasimelteon 10, 20, 50 or 100 mg 30 minutes before their scheduled bedtime for 3 nights. The phase III study followed a similar procedure; however, 412 participants were randomized to receive tasimelteon 20, 50 or 100 mg for 1 night. In both the phase II and III trial, participants who received any dose of tasimelteon experienced statistically significant improvement in sleep efficiency compared with placebo and those who received 20, 50 or 100 mg experienced significant increases in TST (all p<0.05). However, given the patient population and short duration of these trials, the role of tasimelteon and effectiveness for these indications remains to be seen.

Recent research has focused on the use of tasimelteon in blind individuals with non-24 SWD. Vanda Pharmaceuticals is currently studying tasimelteon for the treatment of non-24 SWD in patients who are blind.[16,17] The company has already completed two phase III trials, SET (Safety and Efficacy of Tasimelteon) and RESET (Randomized-withdrawal study of the Efficacy and Safety of Tasimelteon to treat Non-24-Hour Disorder). Both studies were multicenter, randomized, double-masked, placebo-controlled parallel trials that sought to evaluate the efficacy of tasimelteon in entraining the circadian rhythm in patients with non-24 SWD. During SET, participants were randomized to receive tasimelteon 20 mg or placebo daily 1 hour before bedtime for 26 weeks. For RESET, eligible participants were enrolled from SET

and received tasimelteon 20 mg daily for 6 weeks during a run-in phase and then were randomized to receive either tasimelteon or placebo during the 8-week withdrawal phase. Results for SET and RESET have been presented in abstract form but have not yet been published. Vanda is currently recruiting for two other trials evaluating the use of tasimelteon in non-24 SWD patients with blindness and no light perception.[16,17]

ADVERSE EFFECTS

The most common adverse effects experienced during clinical trials of ramelteon include headache, somnolence and fatigue.[12] Additional adverse effects reported include upper respiratory tract infection, nasopharyngitis, urinary tract infection, dizziness, and nausea.[13,14]

An advantage over other frequently used hypnotics is that ramelteon neither causes dependence nor withdrawal effects.[10] No rebound insomnia nor withdrawal effects were observed following discontinuation of ramelteon in clinical trials.[12,13] Additionally, next-day effects of ramelteon on memory and psychomotor functioning have been assessed in clinical trials. A multicenter, randomized, double-blind, placebo-controlled, 3-way crossover study evaluated the effects of ramelteon on balance, mobility and memory in patients greater than 65 years of age with chronic insomnia. When tested two hours after dosing, participants who received ramelteon 8 mg had no difference in measures of balance or memory recall when compared to placebo.[18] Conversely, effects on next morning driving were significantly impaired in both genders after evening ramelteon administration when compared with placebo.[19]

In clinical trials, the most frequent adverse effects associated with tasimelteon included decreased hemoglobin and hematocrit, somnolence, nausea and headache.[2,15] Assessment of next-day symptoms associated with tasimelteon in clinical trials is limited. Available reports have not revealed significant differences between tasimelteon and placebo, except in elderly female patients who experienced more sedation in clinical trials.[2,3,15]

Overall, the adverse effects associated with ramelteon and tasimelteon are mild and these medications appear to be well-tolerated.

CONCLUSION

Targeting melatonin receptor agonism may widen the treatment options for insomnia beyond barbiturates, benzodiazepines and non-benzodiazepine receptor agonists. Melatonin is already widely used for the treatment of insomnia. Although ramelteon has been available for over seven years, other medications for insomnia like zolpidem, temazepam, and eszopiclone continue to be prescribed more frequently than ramelteon. Despite the preliminary demonstrated efficacy of agomelatine and its role in depression and insomnia, it is doubtful it will ever be available in the US due to its potential for hepatic impairment. Based on the results of Phase II and III trials, tasimelteon appears promising, especially in circadian rhythm disorders. The FDA peripheral and central nervous system drugs advisory committee is in support of approval of tasimelteon for non-24 SWD and it is targeted to be reviewed by the FDA in early 2014. If approved, tasimelteon will have a niche in its target indication to regulate the sleep-wake cycle of patients who are fully blind. At this time it is unknown if tasimelteon will seek approval for primary insomnia or what its role in the management of insomnia will be.

As melatonin receptor agonists are further developed and studied, it will be interesting to see what their role in other circadian rhythm disorders will be including shift-work disorders, jet-lag, and potentially even "sundowning" associated with Alzheimer's Disease. While the role of melatonin agonists is further examined, pharmacists and practitioners should anticipate additional melatonergic agents being studied, approved and prescribed.

ADDENDUM

Since the writing of this article,Tasimelteon (Hetlioz, Vanda Pharmaceuticals, Inc.) was FDA approved for the treatment of non-24 hour sleep-wake disorder (non-24) on Jan 31, 2014.

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