Comparative Review of Approved Melatonin Agonists for the Treatment of Circadian Rhythm Sleep-Wake Disorders

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Circadian rhythm sleep-wake disorders (CRSWDs) are characterized by persistent or recurrent patterns of sleep disturbance related primarily to alterations of the circadian rhythm system or the misalignment between the endogenous circadian rhythm and exogenous factors that affect the timing or duration of sleep. These disorders collectively represent a significant unmet medical need, with a total prevalence in the millions, a substantial negative impact on quality of life, and a lack of studied treatments for most of these disorders. Activation of the endogenous melatonin receptors appears to play an important role in setting the circadian clock in the suprachiasmatic nucleus of the hypothalamus. Therefore, melatonin agonists, which may be able to shift and/or stabilize the circadian phase, have been identified as potential therapeutic candidates for the treatment of CRSWDs. Currently, only one melatonin receptor agonist, tasimelteon, is approved for the treatment of a CRSWD: non–24-hour sleep-wake disorder (or non-24). However, three additional commercially available melatonin receptor agonists—agomelatine, prolonged-release melatonin, and ramelteon—have been investigated for potential use for treatment of CRSWDs. Data indicate that these melatonin receptor agonists have distinct pharmacologic profiles that may help clarify their clinical use in CRSWDs. We review the pharmacokinetic and pharmacodynamic properties of these melatonin agonists and summarize their efficacy profiles when used for the treatment of CRSWDs. Further studies are needed to determine the therapeutic potential of these melatonin agonists for most CRSWDs.

Key Words melatonin agonists, sleep drug effects, circadian rhythm, drug effects.
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Misalignment between the circadian system and the external environment can have a pronounced impact on physiologic functioning, overall health, and disease susceptibility, including increased risk for metabolic disturbances, coronary disease, cancer, psychiatric disorders,

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Social media summary: Circadian rhythm sleep-wake disorders (CRSWDs) substantially impact millions of lives. Although melatonin receptors represent compelling therapeutic targets, only one drug currently has a CRSWD indication. This article compares the pharmacology and clinical data of melatonin agonists for CRSWD treatment.

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and other chronic diseases.[1] Disruption of the sleep-wake cycle is a salient consequence of this misalignment and represents the primary clinical feature of circadian rhythm sleep-wake disorders (CRSWDs). These disorders collectively represent a significant unmet medical need, with a total prevalence in the millions, a substantial negative impact on quality of life, and a lack of studied treatments for most of these disorders.[2–4] The ability of melatonin receptor activation to phase-shift the circadian clock during discrete time windows[5] provides a compelling rationale for the therapeutic potential of this system in the treatment of CRSWDs. Currently, four melatonin receptor agonists are commercially available, but only one, tasimelteon, is specifically approved for the treatment of a CRSWD: non–24-hour sleep-wake disorder (non-24). Additional studies have assessed the use of other melatonin agonists for the treatment of various CRSWDs, although, to our knowledge, a systematic review has not been recently published. The objectives of this review are to compare the pharmacokinetic and pharmacodynamic properties of these compounds, review the existing data describing their use in CRSWDs, and examine the potential impact of their distinct pharmacologic properties on clinical efficacy in the treatment of CRSWDs.

The Circadian Timing System

The term "circadian" is derived from the Latin *circa dies,* which means "around a day." Circadian rhythms are endogenously generated oscillations in behavior or physiology that occur within a period of ~24 hours. In humans, the average circadian period is ~24.2 hours, with a wide interindividual range of 23.7–25.3 hours.[6] Many processes critical for overall health are strongly influenced by the circadian system including sleep-wake rhythms.[7, 8] Central to this regulation is a circadian timing system (CTS), consisting of input signals, a central "pacemaker," and output signals that relay timing information to the "subordinate" oscillators throughout the brain and body. Because the endogenous circadian system runs slightly longer than 24 hours, the CTS must be reset by external zeitgebers, or "time givers," on a daily basis to maintain alignment with the 24-hour day. The light-dark cycle is the primary environmental zeitgeber, with an ability to alter the timing of the circadian system and ensure that the multitude of downstream rhythms is aligned to the 24-hour day.[9] In mammals, specialized photoreceptors in the retina are responsible for capturing the environmental light information used by the CTS. These intrinsically photosensitive retinal ganglion cells (ipRGCs) are distinct from the rods and cones responsible for vision, and they are the principal photoreceptors of the circadian system.[10] The ipRGCs convey light information directly to the central pacemaker located in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus.[11] In turn, the SCN relays this information via output signals that maintain harmony among the numerous physiologic processes that are locally organized at the level of individual tissues.[12]

The timing of the sleep-wake cycle, which is appropriately synchronized to nighttime in most individuals,[13] is regulated by the CTS. The SCN promotes the timing of sleep by sending direct and indirect projections to brain regions involved with sleep and arousal.[14] As a result, circadian rhythms in alertness, drowsiness, mood, and other behaviors (process C) interact with the homeostatic sleep pressure (process S) that builds as a function of time spent awake.[15] Ideally, these two processes are coordinated so that the human body is primed for activity that coincides with light onset and is maintained throughout the day and evening, whereas sleep pressure and reduced circadian arousal are synchronized to facilitate nighttime sleep onset and maintenance that ultimately facilitates repair and restoration during the night phase.[16] As discussed in the next section, circadian disruption or environmental misalignment can compromise the timing of the sleep-wake cycle, which forms the clinical basis of all CRSWDs.

CRSWD Classification

The *International Classification of Sleep Disorders, Third Edition*, defines CRSWDs as persistent or recurrent patterns of sleep disturbance due primarily to one of the following: alterations of the circadian rhythm system or misalignment between the endogenous circadian rhythm and exogenous factors that affect the timing or duration of sleep.[17] The circadian-related sleep disruption leads to insomnia, excessive daytime sleepiness, or both. These sleep disturbances are associated with impairment of social, occupational, and/or other areas of functioning.[17] CRSWDs can be broadly divided into exogenous and endogenous subgroups. Exogenous CRSWDs include jet lag disorder and shift work disorder

that result from externally mediated (i.e., behavioral) disruptions to an otherwise properly functioning circadian system.[3] Conversely, endogenous CRSWDs involve abnormalities within the circadian system itself that impair proper alignment to the external environment. Whereas endogenous disorders typically involve genetic or biological disruption to the system, behavioral or environmental factors, such as maladaptive exposure to light cues, may contribute to the development of these disorders.[2] This subgroup includes advanced sleep-wake phase disorder (ASWPD), delayed sleep-wake phase disorder (DSWPD), non-24, and irregular sleep-wake rhythm disorder (ISWRD).[17] Table 1 provides a brief summary of CRSWDs.[17] More extensive descriptions of the etiology, symptoms, and prevalence of these disorders are beyond the scope of this review but are available elsewhere.[2, 3, 18, 19]

Treatment of CRSWDs

Nonpharmacologic options for the treatment of CRSWDs include light therapy and behavioral strategies that may be used alone or in conjunction with pharmacotherapy. Review articles covering these topics are available elsewhere.[19, 20] In this review, we evaluate the therapeutic potential of pharmacologic treatment options, specifically melatonin receptor agonists, for CRSWDs.

The Endogenous Melatonin System

Targeting the melatonin receptors for the purpose of shifting and stabilizing the circadian phase represents a compelling pharmacologic approach for the treatment of CRSWDs. Melatonin secretion by the pineal gland is considered to be a reliable and predictable marker of the central pacemaker's circadian phase,[21] which is controlled through a multisynaptic pathway originating from the SCN.[22] In healthy individuals, the duration of melatonin secretion is a faithful representation of the period of darkness[23] and is thought to influence the circadian clock reciprocally through feedback to melatonin receptors in the SCN.[24] Although the exact role of endogenous melatonin in humans is unclear,[25] pharmacologic administration of supraphysiologic doses of melatonin during discrete time windows has been shown to phase-shift the circadian clock and potentially promote sleep.[26] These effects are mediated through two melatonin receptors, MT_1 and MT_2, which are expressed in the SCN of mammalian species including humans.[27] Although the exact role of each receptor is an area of ongoing research, preclinical studies suggest that the MT_2 receptor is critical for phase-shifting the clock,[28] whereas MT_1 activation inhibits SCN activity,[29] potentially affecting the downstream sleep circuits.[30] Activation of MT_1 versus MT_2 results in unique, G-protein–coupled second-messenger cascades that provide a molecular basis for the different functions of these two receptors.[31, 32]

Dietary Supplements Containing Melatonin

Melatonin, marketed as a dietary food supplement in the United States, is available in multiple formulations and doses. Because dietary supplements containing melatonin are a heterogeneous group of products supported by limited efficacy and safety data, drawing conclusions about the use of melatonin to treat conditions or disorders

Table 1. Circadian Rhythm Sleep-Wake Disorders[17]

Disorder	Brief description
Exogenous	
Jet lag disorder	Endogenous sleep-wake cycle is temporarily misaligned with the customary destination sleep-and-wake pattern following rapid travel across multiple time zones
Shift work disorder	Symptoms of insomnia or excessive sleepiness that occur in association with work hours that overlap with the typical sleep period
Endogenous	
Advanced sleep-wake phase disorder	Sleep-and-wake timing is advanced (i.e., earlier), usually by ≥ 2 hr, than required or desired times
Delayed sleep-wake phase disorder	Sleep-and-wake timing is delayed, usually by ≥ 2 hr, relative to what is typically considered normal
Irregular sleep-wake rhythm disorder	No clearly defined circadian rhythm; sleep-wake pattern varies from day to day
Non–24-hr sleep-wake disorder	The intrinsic circadian pacemaker is not entrained to a 24-hr light-dark cycle, and the endogenous sleep-wake timing oscillates in and out of phase with the typical 24-hr sleep-wake pattern

is challenging. As a dietary supplement, it has not been evaluated or approved by the U.S. Food and Drug Administration (FDA) to prevent or treat any disease or condition. Based on their review of the available literature, the American Academy of Sleep Medicine (AASM) clinical guidelines have determined an array of recommendations for the use of melatonin in CRSWDs.[33] They specifically indicate "weak" for use (vs no therapy) of dietary melatonin for DSWPD, non-24 in blind adults, and children with ISWRD. In addition, they list "no recommendation" for ASWPD, non-24 in sighted patients, and "weak against" for elderly patients with ISWRD and dementia. A previous version of these guidelines recommended use in shift work disorder and jet lag disorder.[34] As a caveat, the AASM guidelines note concerns regarding the substantial variability in potency, purity, dissolvability, and safety between lots and brands of dietary supplements containing melatonin, with some brands determined to have no available melatonin present.[35–37]In addition, to our knowledge, no well-controlled, large-scale, long-term clinical trials assessing clinical efficacy and safety of these dietary supplements have been published.[38]

Melatonin Receptor Agonists

The pharmaceutical development of melatonin receptor agonists has yielded a collection of compounds that, by virtue of the approval process, have the benefit of well-characterized pharmacologic profiles and extensive safety data (Table 2). Two of these compounds, ramelteon and tasimelteon, are approved by the FDA and available commercially in the United States, and three compounds—agomelatine, prolonged-release melatonin, and tasimelteon—are approved by the European Medicines Agency and are commercially available in Europe. These melatonin receptor agonist compounds have distinct pharmacokinetic and pharmacodynamic characteristics that

Table 2. Indications and Dosing of Commercially Available Melatonin Receptor Agonists

Agonist	Location	Indication	Dosage	Common adverse events[a]
Agomelatine (Valdoxan or Thymanax; Servier Pharmaceuticals, Neuilly-sur-Seine, France)[40]	Europe	Treatment of major depressive episodes in adults < 75 yrs of age[b]	25 mg/day at bedtime; dose may be doubled if symptoms do not improve after 2 wks	Nausea, dizziness, headache, somnolence, insomnia, migraine, diarrhea, constipation, abdominal pain, vomiting, hyperhidrosis, back pain, fatigue, anxiety, increases in AST and ALT levels[c]
Prolonged-release melatonin (Circadin; Neurim Pharmaceuticals, Tel Aviv, Israel)[39]	Europe South Africa South Korea	Short-term (daily for up to 13 wks) treatment of primary insomnia characterized by poor sleep quality in patients > 55 yrs of age	2 mg/day, 1–2 hr before going to bed and after food	Headache, nasopharyngitis, back pain, arthralgia[d]
Ramelteon (Rozerem; Takeda Pharmaceuticals, Deerfield, IL)[43]	United States Japan	Treatment of insomnia characterized by difficulty with sleep onset[e]	8 mg/day within 30 min of going to bed and without food	Somnolence, dizziness, fatigue, nausea, exacerbated insomnia[f]
Tasimelteon (Hetlioz; Vanda Pharmaceuticals, Washington, DC)[41, 42]	United States Europe	Treatment of non–24-hr sleep-wake disorder in adults	20 mg/day just prior to going to bed and without food	Headache, increased ALT level, nightmares or unusual dreams, upper respiratory infection, urinary tract infection[g]

ALT = alanine aminotransferase; AST = aspartate aminotransferase.
[a]As reported in the product prescribing information or summary of product characteristics.
[b]Treatment may continue for at least 6 months following signs of improvement.
[c]Incidence of ≥ 1/100 to < 1/10, not corrected for placebo.
[d]Common according to the Medical Dictionary for Regulatory Activities definition;not corrected for placebo.
[e]Patients should be reevaluated for comorbid diagnoses if insomnia symptoms do not remit after 7–10 days of treatment.
[f]Incidence ≥ 3% and more common than with placebo.
[g]Incidence ≥ 5% and at least twice as high as with placebo.

differentially modulate the melatonin system.[39–43] Although only tasimelteon is indicated for the treatment of a CRSWD (non-24 in adults), all four have been investigated for potential use in the management of CRSWDs. We review the differences and commonalities of these compounds with emphasis on their respective data for the treatment of CRSWDs.

Aligning the circadian system to the external environment requires the circadian clock to be reinforced or shifted in different directions, depending on the disease subtype. Therefore, the optimal use of a melatonin receptor agonist as a therapeutic agent is not necessarily achieved by replicating the amplitude or duration of endogenous melatonin but may be better reached by phase-shifting the SCN activity during discrete time windows of maximum effectiveness, such as dawn and dusk.[44] Sensitivity of the clock to melatonin administration changes dramatically during the day, with peak sensitivities occurring just before bedtime and wake time.[45] In addition, the direction of the response from melatonin receptor activation (i.e., phase advance vs phase delay) changes across the phase-response curve, and the same melatonin receptor activation can have opposing effects on phase changes at different times of day or night.[45] In both preclinical and human studies, timed pulsatile melatonin administration was more efficacious than prolonged administration for phase-shifting the circadian clock.[46, 47] Because the response of the endogenous clock is time dependent,[45] the timing of administration as well as the pharmacokinetic parameters (Table 3)[39, 48–52] of a given melatonin agonist will likely play a key role in its overall effects on the circadian system.

Pharmacokinetics

As with any approved and regulated compound, consistent absolute bioavailability is considered a critical pharmacokinetic parameter for the development of melatonin agonists.[53] One of the primary drawbacks of dietary supplement melatonin is its documented poor and highly variable bioavailability from person to person due to high first-pass metabolism in the liver, poor gut absorption, or possibly a combination of both factors.[54, 55] The four approved melatonin receptor agonists exhibit a wide range of absolute bioavailability parameters, with an average of 3.3% for agomelatine,[51] 15% for prolonged-release melatonin,[52, 55, 56] 1.8% for ramelteon,[49] and 38.3% for tasimelteon.[48] It is notable that, in the absence of bioavailability data for the approved prolonged-release melatonin formulation, the estimate provided for the approved product is based on immediate-release formulations.[39] The applicability of immediate-release melatonin data to prolonged-release melatonin is unclear, given the slower absorption rate of the prolonged-release formulation. The absolute bioavailability information

Table 3. Pharmacokinetic Parameters of Commercially Available Melatonin Receptor Agonists

Parameter	Agomelatine[51]	Prolonged-release melatonin[52]	Ramelteon[49, 50]	Tasimelteon[48]
Absolute bioavailability	3.3 ± 1.1%	15% (range 10–56%)[a]	1.8% (range 0.5–12%)	38.3% (range 26.94–54.33%)
$T_{1/2}$, mean ± SD or range, hrs	0.9 ± 0.4	3.5–4.0	1.36 ± 0.49	1.3 ± 0.4
T_{max}, range, hrs	1.0–2.0	0.75–3.0	0.5–1.5	0.5–3.0
Metabolic pathways	CYP1A1 CYP1A2 CYP2C9	CYP1A1 CYP1A2 CYPC19 (possible)	CYP1A2 (primary) CYP2C CYP3A4 (secondary metabolism produces glucuronide conjugates)	CYP1A2 CYP3A4
Protein binding	95%	In vitro: ~60%, mainly to albumin, α_1-acid glycoprotein, and high-density lipoprotein	82%, mostly to serum albumin	89.1%
Volume of distribution (L)	35	Not reported	73.6	56–126

CYP = cytochrome P450; $T_{1/2}$ = half-life; T_{max} = time to reach maximum concentration;
[a]This calculation was not derived from studies of the approved compound itself but was taken from various reports on dietary supplement melatonin.

provided for agomelatine is also unclear. The estimate provided was calculated from pooled population data from a phase I clinical study comparing oral versus intravenous administration, rather than by the more conventional method of comparing area under the curve values after oral and intravenous administration in the same subject.[51] Interindividual and intraindividual variability was high (on the order of 160% and 104%, respectively).[51]

The sensitivity and direction of the response of the circadian clock to melatonin receptor activation is time dependent.[44, 45] Parameters affecting duration of exposure, including half-life ($T_{1/2}$), should be taken into consideration because treatment strategies will involve shifting the clock in different directions depending on the disorder subtype. Prolonged-release melatonin has the longest $T_{1/2}$ of the melatonin agonist compounds, with a range of 3.5–4 hours.[39] The remaining melatonin agonists have $T_{1/2}$ values within a comparable range (0.9–1.36 hours). The active metabolite of ramelteon, M-II, has a mean $T_{1/2}$ of 2.27 hours that is believed to contribute to the circadian response to this compound.[57]

Pharmacodynamics

Given the proposed functional specificity of the two melatonin receptors (MT_1 and MT_2),[24] the precise binding characteristics of a given agonist will likely play a role in determining its therapeutic action. Whereas all of these compounds bind to both melatonin receptors, their differential binding affinities to MT_1 versus MT_2 are distinctive. Table 4 summarizes the pharmacodynamic characteristics of these agonists.[48, 52, 58, 59]

Agomelatine binds to MT_1 and MT_2 receptors with approximately equal affinity and is distinctive in that it has additional antagonist properties at the serotonin receptor subtype (5-HT_{2c}).[40] Ramelteon exhibits a 10-fold greater affinity for MT_1 than MT_2,[59] and prolonged-release melatonin exhibits an 8-fold greater affinity for MT_1 than MT_2.[39] Tasimelteon is the only one of these four compounds that shows a greater affinity for MT_2 than MT_1, with the difference being 4-fold.[58]

The primary metabolites of both agomelatine and prolonged-release melatonin are biochemically inactive; therefore, the timing and duration of the activity of these drugs fully depend on the properties of the parent compounds. The primary metabolite of ramelteon, M-II, is active and exhibits significantly higher systemic exposure than the parent compound.[45, 47] M-II exhibits approximately a tenth and a fifth the binding affinity of the parent molecule for the human MT_1 and MT_2 receptors, respectively. Although the binding affinity for M-II is lower

Table 4. Pharmacodynamics of Commercially Available Melatonin Receptor Agonists

Parameter	Agomelatine[51]	Prolonged-release melatonin[52]	Ramelteon[59]	Tasimelteon[48, 58]
Mechanism of action	MT_1 and MT_2 agonist; serotonin 5-HT_{2C} antagonist	MT_1, MT_2, and MT_3 agonist	MT_1, MT_2, and selective MT_3 agonist	MT_1 and MT_2 agonist
Receptor binding affinity (Ki values [nM])	MT_1: 0.10 MT_2: 0.12 5-HT_{2C}: 6.15	MT_1: 0.081 MT_2: 0.383	MT_1: 0.014 MT_2: 0.112	MT_1: 0.304 MT_2: 0.0692
Metabolite activity	Primary metabolites: (hydroxylated and demethylated agomelatine) inactive	Principal metabolite (6-sulphatox-y melatonin [aMT6s]) inactive	Four metabolites (M-II, M-IV, M-I, and M-III [in order of prevalence in human serum]); MT-II active at MT_1 (10% affinity of parent) and MT_2 (20% affinity of parent compound), with systemic exposure 20- to 100-fold higher than parent compound and mean terminal $T_{1/2}$ of 2–5 hrs	Primary metabolites: M3, M9, M11, M12, M13, and M14; low binding affinity for MT_1 and MT_2 (< 1/10 of the binding affinity of the parent compound); low activity at melatonin receptors (at least 13-fold less than parent compound); mean terminal elimination $T_{1/2}$ of the main metabolites ranges from 1.3 ± 0.5–3.7 ± 2.2 hrs

$T_{1/2}$ = half-life.

than that of the parent compound, its overall mean systemic exposure is 20- to 100-fold higher than that for ramelteon. As a result of these properties, the active metabolites of ramelteon may be relevant at a clinical level,[47] specifically when being studied in circadian rhythm disorders.[57] For tasimelteon, the primary metabolites (M9, M11, M12, M13, M14, and M3, a glucuronidated metabolite) have binding affinity to the melatonin receptors that is at least 13-fold lower than that of the parent compound.[42, 48] This weak affinity suggests that such metabolites are unlikely to contribute significantly to the observed clinical effects.

These distinctive pharmacodynamic properties, coupled with the theorized function of the MT_1 and MT_2 receptors, are consistent with the approved clinical application for each melatonin agonist. The additional binding and antagonism of the $5\text{-}HT_{2C}$ receptor with the melatonin receptor binding of agomelatine is hypothesized to contribute to its efficacy in treating major depressive disorder.[40] Prolonged-release melatonin and ramelteon, each indicated for insomnia, show a much higher MT_1 binding affinity that may contribute to the reported soporific effects of these drugs.[42, 43] In addition, the increased systemic exposure associated with the active metabolite of ramelteon, MT-II,[49] theoretically provides a functional similarity to prolonged-release melatonin in terms of exposure duration. Tasimelteon, indicated for non-24, preferentially binds the MT_2 receptor, believed to be most critical for phase-shifting the clock.[28, 60]

Evidence for the Use of Melatonin Receptor Agonists in Treating CRSWDs

Melatonin agonists represent compelling pharmacologic treatments for CRSWDs. In an effort to provide a concise summary of available data describing the use of these agents for CRSWDs, we performed a systematic review of published studies.

Literature Search

The assessment of available literature for the treatment of CRSWDs with approved melatonin receptor agonists was conducted in April 2015 and again in December 2015 to include the most recent literature. We conducted a search of the PubMed database using the following keywords: [(DSPD OR delayed sleep phase disorder) OR (ASPD OR advanced sleep phase disorder) OR (ISWR OR irregular sleep-wake rhythm disorder) OR (non-24 OR non–24-hour sleep-wake rhythm disorder OR free-running disorder) OR (jet lag OR jet lag disorder) OR (shift work OR shift work disorder) AND (treatment OR therapy OR medication) OR (melatonin agonist) OR (prolonged-release melatonin OR Circadian) OR (ramelteon OR Rozerem) OR (tasimelteon OR Hetlioz) OR (agomelatine OR Valdoxan)].

Evidence was evaluated according to the evidence grading scale used by the Oxford system for evidence-based medicine (Table 5).[34] The scoring criteria reflect the nature of the experimental design, rather than the specific clinical outcome measures obtained.

These search criteria yielded a total of eight articles, ranging from a single-patient case study to double-blind, placebo-controlled, parallel-group multicenter trials. Table 6 summarizes the eight studies.[57, 61–67] Most of the results (not including small case studies) examined treatment of exogenous CRSWDs including jet lag and shift work disorders.[57, 61–63] These disorders are the most prevalent CRSWDs in the general population.[17] The only results focused on endogenous CRSWDs were studies aimed at treating non-24.[64–67] Overall, the lack of evidence for studies intended to treat any other endogenous CRSWD reflects a significant need for additional research that uses the therapeutic potential of the melatonin system.

Exogenous CRSWD Treatment

Four studies evaluated approved melatonin receptor agonists as potential treatments for exogenous CRSWDs: three focused on jet lag disorder[57, 61, 62] and one on shift work disorder.[63]

Table 5. Oxford System for Evidence-Based Medicine

Evidence level	Criteria
1	High-quality randomized, controlled trial of well-characterized subjects or patients
2	Cohort study or flawed clinical trial (e.g., small sample size, blinding not specified, incompletely validated reference standards[a], possible nonrandom assignment to treatment)
3	Case-control study
4	Case series (or poor-quality cohort and case-control studies)

[a]Reference standards: polysomnography, sleep logs, actigraphy, phase markers, validated self-reports.
Adapted from reference 34 with permission.

Table 6. Evidence for the Use of Approved Melatonin Receptor Agonists for the Treatment of Circadian Rhythm Sleep-Wake Disorders[a]

	Evidence level[b]	Compound	Study design	Population	Treatment regimen	Key findings
Jet lag disorder						
	2	Tasimelteon	Two randomized, double-blind, placebo-controlled, parallel-group studies (1 phase II study and 1 phase III study)[61]	451 healthy volunteers with experimentally induced jet lag[c]: phase II study (n = 39) and phase III study (n = 412)	Phase II study: tasimelteon 10, 20, 50, or 100 mg/day given 30 min before bedtime for 3 days Phase III study: tasimelteon 20, 50, or 100 mg/day given 30 min before bedtime for 3 days	Phase II study: • Significantly higher sleep efficiency with tasimelteon 50 mg (85.5%, p=0.02), and 100 mg (89.3%, p=0.02) vs placebo • Significantly greater total sleep time with tasimelteon 20 mg (+71.4 min, p=0.03), 50 mg (+85.7 min, p=0.013), and 100 mg (+104.2 min, p=0.01) vs placebo • Significantly decreased mean latency to sleep onset with tasimelteon 10 mg (−11.6 min, p=0.025), 20 mg (−11.8 min, p=0.023), 50 mg (−10.2 min, p=0.018), and 100 mg (−15.0 min, p=0.01) vs placebo • Significantly decreased mean latency to persistent sleep with tasimelteon 10 mg (−13.7 min, p=0.03), 50 mg (−13.9 min, p=0.019), and 100 mg (−19.1 min, p=0.021) vs placebo • Significantly earlier dim light melatonin onset with tasimelteon 100 mg (2–3 hrs, p=0.01) vs placebo Phase III study: • Significantly higher sleep efficiency with tasimelteon 20 mg (73.2%, p=0.002), 50 mg (76.0%, p<0.001), and 100 mg (72.3%, p=0.005) vs placebo • Significantly greater total sleep time with tasimelteon 20 mg (+33.5 min, p=0.002), 50 mg (+47.9 min, p<0.001), and 100 mg (+30.0 min, p=0.005) vs placebo • Significantly decreased wake after sleep onset with tasimelteon 20 mg (−24.1 min, p=0.002) and 50 mg (−34.0 min, p<0.001) vs placebo • Significantly decreased mean sleep onset latency with tasimelteon 20 mg (−11.9 min, p<0.006), 50 mg (−14.1 min, p<0.001), and 100 mg (−12.2 min, p=0.002) vs placebo • Significantly decreased mean latency to persistent sleep with tasimelteon 20 mg (−21.4 min, p<0.001), 50 mg (−26.1 min, p<0.001), and 100 mg (−22.6 min, p<0.001) vs placebo
	2	Ramelteon	Randomized, double-blind, multicenter, placebo-controlled study[57]	75 healthy volunteers with experimentally induced jet lag[c]	Ramelteon 1, 2, 4, or 8 mg/day given 30 min before bedtime for 4 days following a 5-hr phase shift	• Endogenous melatonin rhythm significantly shifted with ramelteon 1 mg (−88 min, p=0.002), 2 mg (−80.5 min, p=0.003), and 4 mg (−90.5 min, p=0.01) vs placebo • Shifts occurred as early as day 1 (ramelteon 4 mg) and day 2 (ramelteon 1 mg and 4 mg) after the light shift • No significant effects on sleep architecture parameters with ramelteon vs placebo • No significant improvements in subjective measures of sleep with ramelteon vs placebo[d]

(continued)

Table 6 (continued)

	Evidence level[b]	Compound	Study design	Population	Treatment regimen	Key findings
	1	Ramelteon	Randomized, double-blind, placebo-controlled, parallel-group study[62]	110 participants with a history of jet lag–induced sleep difficulty	Ramelteon 1, 4, or 8 mg/day for 5 days given 5 min before lights out, based on each participant's habitual bedtime	• Mean latency to persistent sleep was reduced in the ramelteon 1-mg group (−10.64 min vs placebo, p=0.030) • No significant changes in sleep parameters were observed in the ramelteon 4- or 8-mg groups compared with placebo • Compared with placebo, participants in the ramelteon 1-mg, 4-mg, and 8-mg groups performed significantly lower (p≤0.05 for all comparisons) on immediate memory recall tasks following jet lag (day 4)
Shift work disorder						
	2	Ramelteon	Placebo-controlled, crossover study[63]	10 healthy volunteers	Ramelteon 8-mg single dose given prior to a 2-hr afternoon nap opportunity followed by a simulated night shift	• No significant effect on sleep efficiency during the nap prior to the night shift with ramelteon vs placebo • Significantly lower neurobehavioral performance in the ramelteon 8-mg group on visual analog scale performance (p=0.0013), Karolinska Sleepiness Scale (p=0.0003), and Digit Symbol Substitution Test (p=0.0068) compared with placebo immediately following the nap • Significantly lower neurobehavioral performance in the ramelteon 8-mg group on primary measures including Psychomotor Vigilance Tasks (median reaction time, p=0.013; number of lapses, p=0.0001) and secondary measures including Digit Symbol Substitution Test (p=0.0341), Probed Recall Memory Task (p=0.0432), Visual Analog Scale delta (change from start to end of testing, p=0.0143), and Karolinska Sleepiness Scale delta (change from start to end of testing, p=0.0091) compared with placebo during the simulated night shift
Non–24-hr sleep-wake disorder						
	1	Tasimelteon	Randomized, double-masked, placebo-controlled, parallel-group, multicenter study[64] Study 1: tasimelteon 20 mg vs placebo for 26 wks Study 2: 11-wk, open-label run-in period followed by 8-wk randomized treatment period (withdrawal to placebo or continued treatment)	84 (study 1) and 20 (study 2) totally blind patients with a confirmed diagnosis of non-24	Study 1: tasimelteon 20 mg/day given 1 hr before target bedtime for up to 26 wks Study 2: tasimelteon 20 mg/day given 1 hr before target bedtime for 8 wks	Study 1: • Higher circadian entrainment with tasimelteon vs placebo at month 1 (20% [8/40] vs 2.6% [1/38], p=0.0171; effect size 17.4%) • Significantly higher clinical response (including entrainment at months 1 and 7 plus clinical improvement) with tasimelteon vs placebo (23.7% [9/38] vs 0% [0/34], p=0.0171) • Significantly improved CGI-C score (2.6 vs 3.4, p=0.0028); significantly increased nighttime sleep (56.8 vs 17.1 min/day, p=0.0055), and significantly decreased daytime sleep (−46.5 vs −17.9 min/day, p=0.005) with tasimelteon vs placebo in the worst quartile of study days Study 2: • 50% achieved entrainment during the open-label run-in period • Patients receiving tasimelteon remained entrained at a significantly higher rate (90% vs 20%, p=0.0026), had significantly more nighttime sleep (−6.7 min vs −73.7 min decrease from baseline per day, p=0.0233), and had significantly less daytime sleep (−9.3 min vs +50.0 min from baseline per day, p=0.0026) vs patients switched to placebo during the randomized withdrawal phase

(continued)

Table 6 (continued)

	Evidence level[b]	Compound	Study design	Population	Treatment regimen	Key findings
	4	Agomelatine	Case report[65]	61-yr-old patient with traumatic brain injury and suspected non-24 based on sleep-wake patterns (i.e., no subjective measures or biological assays)	Agomelatine 25 mg/day at 10 P.M. for 60 days before sleep assessment and maintained for up to 18 mo	• Significant improvement in sleep efficiency (40% increase from baseline in time spent asleep between 12 A.M. and 8 A.M., $p<0.00$) • Significant improvement in behavioral outcomes as assessed by the Overt Aggression Scale Modified for Neuro-Rehabilitation following 18 mo of agomelatine administration compared with the 12-mo preintervention assessment ($p=0.008$) • These sleep and behavioral improvements were maintained throughout the intervention period (18 mo at time of publication)
	2	Prolonged-release melatonin	Randomized, double-blind, placebo-controlled study[66]: 2-wk, placebo run-in period; 6-wk double-blind treatment; 2-wk placebo run-out period	13 totally blind subjects reporting periodic sleep difficulties with sleep diary evidence of a phase delay for ≥ 6 wks	Prolonged-release melatonin 2 mg/night for 6 wks	• Mean nightly sleep duration improved in both groups (+43 min in the prolonged-release melatonin group vs +16 min in the placebo group) • Sleep latency, sleep onset and offset times, number and duration of naps, CGI-C score, and WHO-5 scores were not significantly different between groups
	4	Ramelteon	Case series[67]	2 sighted patients with non-24 based on clinical interviews and sleep diary assessments	Patient 1: ramelteon 8 mg/night, with triazolam 0.125 mg/night added after 25 days Patient 2: ramelteon 8 mg/night + methylcobalamin (vitamin B_{12}) 500 µg 3 times/day with meals	Patient 1: • History of delayed sleep phase and depressive symptoms • Sleep onset free-running type over the first 10 days of ramelteon monotherapy, then consistent at 2 A.M. thereafter • Persistent daytime sleepiness occurred throughout ramelteon monotherapy • Ramelteon and triazolam combination therapy normalized the sleep pattern by day 34 Patient 2: • Symptoms of non-24 began during a leave of absence from work during which the patient had a brief psychotic episode and was prescribed olanzapine 5 mg/day and risperidone 1 mg/day for 1 wk; prior to the episode, he had been traveling for work between South America and Japan every few months • Sleep onset stabilized in the first day, and sleep offset stabilized a few days later, which continued for the duration of treatment

CGI-C = Clinical Global Impression of Change.
[a]No studies were found for advanced sleep phase disorder, delayed sleep phase disorder, or irregular sleep-wake rhythm disorder.
[b]Using the Oxford system for evidence-based medicine.
[c]Jet lag was experimentally induced with a transient 5-hr phase advance in the light-dark schedule designed to represent eastward travel across five time zones.
[d]Subjective measures included sleep latency, total sleep time, number of awakenings, ease of falling asleep, sleep quality, and the restorative nature of sleep.

Of the three jet lag disorder studies, only one, a placebo-controlled study of ramelteon 1, 4, or 8 mg, was conducted in 110 subjects with a history of jet lag–induced sleep difficulty.[62] Given the chronic disturbance in these patients, this study is most representative of a clinical jet lag disorder population and represents the highest level of evidence (level 1) based on the established criteria. Compared with placebo, of the three dose levels tested, only ramelteon 1 mg was associated with a significant reduction in their primary end point, mean latency to persistent sleep.

The two additional jet lag studies used laboratory-based acute protocols involving phase shifts in the light-dark cycle in healthy volunteers, thus providing less reliable evidence (level 2).[57, 61] The ramelteon study was conducted in 75 healthy volunteers with experimentally induced jet lag.[57] The three lower doses of ramelteon tested (1, 2, and 4 mg) were associated with the primary outcome, namely shifts in the endogenous melatonin rhythm compared with placebo; however, none of the doses tested (1, 2, 4, and 8 mg) significantly affected sleep architecture parameters or subjective measures of sleep relative to placebo. The tasimelteon report included data from two randomized, double-blind, placebo-controlled studies conducted in 451 healthy volunteers with experimentally induced jet lag.[61] The first was a phase II study of tasimelteon 10, 20, 50, or 100 mg conducted in 39 individuals, and the second was a phase III study of tasimelteon 20, 50, or 100 mg conducted in 412 individuals. In the phase II study, tasimelteon 50 and 100 mg significantly increased sleep efficiency, and all doses significantly reduced sleep latency compared with placebo. Subjects in the 20-mg, 50-mg, and 100-mg treatment groups also demonstrated significantly greater total sleep time compared with placebo. The 100-mg dose also shifted the dim light melatonin onset significantly earlier than placebo. In the phase III study, all tasimelteon doses (20, 50, and 100 mg) significantly improved sleep efficiency, total sleep time, and sleep latency relative to placebo. The 20-mg and 50-mg doses also significantly improved sleep maintenance (decreased wake after sleep onset) compared with placebo.

A single study assessed the effects of an approved melatonin receptor agonist (ramelteon 8 mg) in shift work disorder.[63] The placebo-controlled crossover study used a simulated night shift in 10 healthy subjects and thus provided an intermediate level of evidence (level 2). Participants received ramelteon or placebo followed by a 2-hour nap opportunity and then a simulated night shift. Sleep efficiency and neurobehavioral tests were performed the following morning to determine if ramelteon 8 mg, taken before an afternoon nap, would improve sleep and neurobehavioral symptoms following a night shift. No statistically significant differences were seen in sleep efficiency between subjects receiving ramelteon and those receiving placebo during the nap prior to the night shift. Immediately following the nap and during the simulated night shift, subjects scored significantly lower on neurobehavioral performance assessments in the ramelteon arm.

Endogenous CRSWD Treatment

Four articles described the use of approved melatonin receptor agonists for non-24: two were randomized, double-blind, placebo-controlled studies conducted in blind patients with non-24,[64, 66] one was a case report detailing use in two sighted patients with non-24,[67] and another was a case report regarding use in a single patient with traumatic brain injury.[65] Diagnostic criteria for non-24 were not consistent across studies, thus complicating interpretation.

The only publication providing the highest level of evidence (level 1) was a combined report of two clinical efficacy trials for the use of tasimelteon for non-24.[64] These randomized, double-masked, placebo-controlled, parallel-group multicenter trials were completed in totally blind adults with a confirmed diagnosis of non-24. Study 1 assessed the efficacy of tasimelteon 20 mg to entrain the circadian clock (measured by melatonin timing) and improve sleep parameters (changes in nighttime and daytime sleep) compared with placebo over a 26-week period, and study 2 assessed the maintenance effect of tasimelteon 20 mg over 8 weeks following randomized withdrawal to placebo or continued treatment. Circadian period was estimated from rhythms in the urinary melatonin metabolite 6-sulfatoxymelatonin (aMT6s). This metabolite is a faithful representation of circulating melatonin and therefore provides a biomarker that is a reliable proxy of circadian amplitude and phase. In study 1, tasimelteon treatment was associated with higher rates of circadian entrainment (defined by aMT6s acrophase) and improved sleep parameters (defined by significantly reduced daytime sleep and

significantly increased nighttime sleep). In study 2, patients receiving placebo during the randomized withdrawal remained entrained at a significantly lower rate and had significantly decreased nighttime sleep and significantly increased daytime sleep compared with those remaining on tasimelteon.

The second randomized, double-blind, placebo-controlled study evaluating prolonged-release melatonin use in an endogenous CRSWD was conducted in 13 totally blind subjects who reported periodic sleep difficulties and who had sleep diary evidence of a phase delay for at least 6 weeks.[66] Because no formal diagnosis of non-24 was required, the study provided a lower level of evidence (level 2). The study included 2 weeks of a placebo run-in period, a 6-week randomized (1:1) treatment period with patients given nightly prolonged-release melatonin 2 mg or placebo, and finally a 2-week placebo run-out period. Outcome measures included a daily voice-recorded sleep diary, Clinical Global Impression of Change (CGI-C) score, WHO-Five Well-being Index (WHO-5) score, and safety measures. Efficacy was defined as a change in sleep duration of more than 20 minutes. This predefined primary clinical end point was achieved; however, the improvement in the melatonin group was not statistically significantly different from that observed in the placebo group. The authors alluded to the fact that none of these end points were powered to demonstrate a statistically significant effect given the sample size of this study. Sleep latency, sleep onset and offset times, number and duration of naps, CGI-C scores, and WHO-5 scores were also not significantly different between groups.

The two case reports provide the lowest level of evidence (level 4). One described nightly administration of agomelatine 25 mg to a 61-year-old man with traumatic brain injury and non-24.[65] The authors postulated that the patient's circadian clock was damaged as a result of a large subarachnoid hemorrhage. Inspection of the patient's sleep pattern over ~1 year indicated a free-running period of about 25 hours with no discernible pattern found for weekly or monthly analyses. The authors found a significant increase in sleep efficiency after 60 days of agomelatine 25 mg taken at 10 P.M., and a significant improvement in behavioral outcomes (as assessed by the Overt Aggression Scale Modified for Neuro-Rehabilitation) assessed after 18 months of the nightly agomelatine dose.

The second report described the efficacy of ramelteon as part of a combination regimen for the treatment of non-24 in two sighted patients.[67] These individuals were determined to have non-24 based on clinical interviews and sleep diary assessments that led the authors to believe a free-running pattern had persisted for a number of months prior to their entering the clinic. Patient 1 was given nightly ramelteon 8 mg, and after 25 days was additionally given a 0.125-mg dose of the hypnotic triazolam. The patient exhibited a free-running sleep onset over the first 10 days of ramelteon treatment alone and then switched to a consistent sleep onset at 2 A.M. Persistent daytime sleepiness occurred throughout ramelteon monotherapy. Ramelteon and triazolam combination therapy normalized the sleep pattern by day 34. Patient 2 was given ramelteon 8 mg at night and methylcobalamin (vitamin B_{12}) 500 μg 3 times/day with meals. The patient's sleep onset stabilized in the first day and sleep offset stabilized a few days later, which continued for the duration of his treatment. The authors listed a number of limitations for their non-24 diagnoses in these sighted individuals, including no biomarker or actigraphy-based analysis and a loss of the patients' sleep diaries without providing further description. The results of these case reports should be interpreted with caution, given the diagnostic limitations of these data for patients.

Conclusion

The currently approved melatonin receptor agonists exhibit distinct pharmacologic profiles that may underlie their clinical characteristics, approved indications, and potential for use in treating CRSWDs. Effective treatment for these disorders will adjust the circadian system and align endogenous rhythms to the external environment. This requires the circadian clock to be shifted in different directions, depending on the disease subtype. Given that the sensitivity and direction of the circadian response changes based on time of day, timing of administration and duration of systemic exposure should be taken into consideration with the treatment of these disorders. When reviewing the available data for the use of melatonin receptor agonists for the treatment of CRSWDs, a relative paucity of evidence clearly remains regarding these disorders, including the most prevalent endogenous disorder, the delayed sleep phase type.

Intervention for the exogenous disorders—jet lag disorder and shift work disorder—have only been assessed in a handful of cases, despite accounting for the vast majority of individuals with CRSWDs, with an estimated prevalence in the millions worldwide.[46] In addition to the relatively limited number of studies for the treatment of CRSWDs, there are no approved therapies for almost all of these disorders. Accordingly, there is a tremendous opportunity for additional research that uses the therapeutic potential of the melatonin system and takes into consideration the distinctive properties of these diverse melatonergic compounds to address this unmet medical need.

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