Melatonin agonists and insomnia


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The ability of melatonin to shift biological rhythms is well known. As a result, melatonin has been used in the treatment of various circadian rhythm sleep disorders, such as advanced and delayed sleep phase disorders, jet lag and shiftwork disorder. The current evidence for melatonin being efficacious in the treatment of primary insomnia is less compelling. The development of agents that are selective for melatonin receptors provides opportunity to further elucidate the actions of melatonin and its receptors and to develop novel treatments for specific types of sleep disorders. The agonists reviewed here – ramelteon, tasimelteon and agomelatine – all appear to be efficacious in the treatment of circadian rhythm sleep disorders and some types of insomnia. However, further studies are required to understand the mechanisms of action, particularly for insomnia. Clinical application of the agonists requires a good understanding of their phase-dependent properties. Long-term effects of melatonin should be evaluated in large-scale, independent randomized controlled trials.

Keywords: circadian rhythm sleep disorders • insomnia • melatonin • melatonin agonists • sleep

Background
Melatonin was identified in 1958 by Aaron Lerner [1]. Since that time, a vast number of research studies have been published examining the role of the hormone in the control and manipulation of biological rhythms, its impact on the initiation and maintenance of sleep and its antioxidant and anticarcinogenic properties. In 1994 the receptors at which melatonin has its actions were characterized and cloned in the human [2]. Inevitably, the application of agents that can activate these receptors is of interest for the potential treatment of a range of circadian and sleep disorders. At this point in time, however, there remains ongoing debate about the application of melatonin in the treatment of chronic (insomnia) and transient (e.g., jet-lag) sleep disorders. Discussion continues around issues such as efficacy, appropriate dose and timing of the treatment, route of administration and the specific patient populations for whom melatonin may be most useful. Notwithstanding some debate about the efficacy of melatonin for sleep disorders, recent attention has turned to the clinical use of a number of melatonin analogs.

The field of research examining the application of melatonin receptor agonists to treatment of sleep and circadian disorders is a relatively novel one. The first publications reporting effects of melatonin agonists in animal models appeared in the early 1990s, but the last 5 years have seen rapid growth in the study of other melatonin agonists along with review articles on this topic. To date there is a relative lack of substantive research into the mechanisms by which melatonin receptor agonists affect sleep and little of the published research has been supported by independent funding agencies.

The development of melatonin agonists and the growth in research surrounding their actions raises some challenging questions. The current review focuses on the potential uses of melatonin receptor agonists in the treatment of particular sleep disorders. Comparisons are made, where possible and appropriate, to melatonin.

Melatonin elicits circadian- and sleep-related responses. The hormone has chronobiotic properties, which means it acts on the central circadian clock to influence the timing of endogenous rhythms under the control of the clock. Endogenous rhythms can be advanced or delayed depending on the timing of the administration. In addition, melatonin is reported to have sleep-promoting properties in diurnal (day-active) animal models and in humans. As our focus is on melatonin agonists and insomnia, both the chronobiotic and sleep-promoting properties are important and relevant to the discussion. In some cases, both of these properties may be desirable in the management of
Introduction to the circadian timing system

The daily rhythm of life for most organisms reflects an interaction between an internally-generated rhythm and the external environmental cycle of day and night [4]. A central clock, located in the suprachiasmatic nuclei (SCN) of the anterior hypothalamus, controls the body’s daily, or circadian (circadian rhythm), timing of production and secretion of melatonin is one of the circadian rhythms under the control of the SCN. Moreover, the hormone melatonin. Light–dark (or entrained) conditions, melatonin is secreted into the bloodstream during the night, with undetectable amounts present during the daylight hours. Light exposure during the dark phase acts to acutely suppress melatonin secretion via a pathway passing through the SCN.

The effects of melatonin on both sleep and circadian rhythms are well described [14, 15]. Melatonin’s effects on sleep and circadian rhythms are mediated at the level of the biological clock by two receptors, MT1 (or Mel1a) and MT2 (or Mel1b), which are colocalized in the SCN [16]. Synthetic melatonin receptor agonists are now under development by the pharmaceutical industry, with the aim of modulating sleep and circadian rhythms via action at the melatonin receptors.

Melatonin receptor agonists

Agonists are defined as agents that bind to and change the activity of a receptor. A number of agonists have been developed on the basis of their action at the melatonin receptors, three of which are described below. Their chemical structures are provided in Figure 1. In this review, we focus on three agonists: agomelatine, tasimelteon and ramelteon.

Agomelatine (N-[2-(7-methoxy-1-naphthyl)ethyl]acetamide), formerly referred to as S-20098, binds both MT1 and MT2 receptors, as well as having antagonistic properties at the serotonergic 5-HT_{2A} and 5-HT_{2C}. The ratio of binding affinities of agomelatine for the MT1 and MT2 receptors is Ki_{MT1}/Ki_{MT2} = 0.3 [17]. Agomelatine is approved in Europe for the treatment of major depression.

Tasimelteon ((1R-trans)-N-[2-(2,3-dihydro-4-benzofuranyl) cyclopropyl[methyl]propionamide], also known as VEC-162 (and previously BMS-214778) has high affinity for both the MT1 and MT2 receptors in humans and appears to be under development for treatment of sleep and mood disorders. Binding affinities for the melatonin receptors are reported as MT1: pKi = 9.45 ± 0.004 [0.35 nM]; and MT2: pKi = 9.8 ± 0.07 [0.17 nM] [18].

Ramelteon ((S)-N-[2-(1,6,7,8-tetrahydro-2H-indeno-[5,4-b]
furan-8-yl)ethyl]propionamide), also known as TAK-375, is a selective MT1 and MT2 receptor agonist and shows 3–16-times higher affinity at these receptors compared with melatonin [19]. Furthermore, ramelteon has ten-times greater affinity for the MT1 receptor than the MT2 receptor and 17-times higher affinity than melatonin at the MT1 receptor [17, 19]. The ratio of binding affinities (Ki_{MT1}/Ki_{MT2}) is 0.13 [17]. While a number of clinical trials report efficacy of the compound in the treatment of insomnia, supporting its approval in the USA for the treatment of insomnia, a recent report also supports its use as a chronobiotic.

Both the chronobiotic and sleep-promoting properties of these agonists will be examined in the following sections.

Melatonin

The hormone melatonin (5-methoxy-N-acetyltryptamine) is endogenously synthesized and secreted by the pineal gland. The timing of production and secretion of melatonin is one of the circadian rhythms under the control of the SCN [11]. Under normal light–dark (or entrained) conditions, melatonin is secreted into the bloodstream during the night, with undetectable amounts present during the daylight hours. Light exposure during the dark phase acts to acutely suppress melatonin secretion via a pathway passing through the SCN.

Melatonin is known to play an important role in reproduction in seasonal breeding animals [12]. While its precise roles in sleep and circadian regulation are not known, one hypothesis is that melatonin acts as a physiological signal of darkness for the circadian timing system [11]. A feedback mechanism exists such that the SCN controls the timing of melatonin production and melatonin also acts directly on the SCN. One possible role of melatonin may be to transmit central timing signals from the SCN to peripheral physiological systems in order to organize behavior and physiological processes according to the temporal niche of the organism [13].

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Chronobiotic properties of melatonin & its analogs

*How melatonin (& its agonists) shifts the clock*

The mechanisms by which melatonin exerts its phase-shifting properties are not fully understood but the melatonin receptors in the SCN are fundamental to the process. As described, melatonin binds to two receptors colocalized in the SCN (MT1 and MT2) [16]. While the specific functional roles of each receptor are not yet defined, there is some evidence that the MT2 receptor may be more important in the phase-shifting actions of melatonin and the MT1 receptor in sleep-related actions (see section entitled ‘How melatonin and its agonist influence sleep’). Current knowledge of the actions of the melatonin receptors comes from data collected in both *in vitro* and *in vivo* studies (for review see [17]).

Melatonin administration shifts the timing of the rat and mouse SCN neuronal firing rhythm *in vitro* [20,21]. In mutant mice lacking the MT1 receptor, the phase shift was only marginally reduced, indicating that the lack of a functional MT1 receptor did not have a large inhibitory influence on the phase shift caused by melatonin. However, the administration of a MT2 receptor antagonist resulted in blocking of the phase advance caused by melatonin. Together, these data provide some evidence that the MT2 receptor may be the primary mediator of the phase-shifting effects of melatonin on the SCN [21,22].

*In vivo* studies are yet to provide clarification, although the MT1 receptor is reported to be necessary for melatonin-induced phase shifts in the whole animal [17]. Phase shifts in activity (wheel-running) induced by melatonin were not observed in MT1-deficient mice [22]. The manner in which the MT1 and MT2 receptors interact also remains unclear and such interaction may be critical in their actions. It has also been proposed that the receptors display differential responses to varying concentrations of melatonin [17], but further work is required. For example, exposure of the MT1 receptor to physiological levels of melatonin does not alter receptor density or affinity, whereas exposure of the MT2 receptor resulted in a desensitization of the receptor. Supra-physiological levels were required for the same result in the MT1 receptor (for review see [17]). At present, it is not known if the receptors are even expressed in the same populations of cells within the SCN [17]. Thus, while the precise mechanisms of action are not yet known, it is clear that melatonin does have direct effects on the SCN that result in phase shifts in the circadian timing system, that is, chronobiotic properties.

**Chronobiotic effects in preclinical models & healthy volunteers**

Melatonin’s chronobiotic properties

Melatonin administered exogenously shifts the phase of the circadian timing system and, therefore, physiological rhythms under the control of the SCN both in humans and in nonhuman animal models (for review see [23,24]). The phase-shifting effects of melatonin are highly dependent on the timing of administration. Phase response curves are used to describe the differential response of the circadian system to a stimulus (e.g., light, melatonin) across all phases of the cycle (Figure 2) [25]. Phase response curves to melatonin indicate that, in humans, administration in the early morning causes phase delays, whereas administration in the afternoon or evening causes phase advances [26–28]. Single-dose studies of melatonin have also been shown to result in phase-dependent shifts of various circadian rhythms [29–32], although the magnitude of the phase shift is low when compared with other stimuli or zeitgebers, such as light [28], in addition to being approximately 12 h out of phase [33].

Table 1 summarizes the studies investigating the chronobiotic properties of melatonin receptor agonists.

Ramelteon’s chronobiotic properties

The phase-shifting properties of ramelteon have been reported in laboratory-based animal and human studies. Using a preclinical model of time-zone shift similar to that used by Redman and Armstrong to examine the effects of melatonin [34], Rats exposed to an 8-h advance of their light–dark cycle were treated with ramelteon (0.1 or 1.0 mg/kg), melatonin (1 or 10 mg/kg) or vehicle solution for 14 days following a shift to the light–dark cycle [35]. The degree of circadian adaptation or re-entrainment was assessed by calculating the amount of activity that occurred during the dark hours as a percentage of total activity. In this

![Figure 1. Melatonin and three melatonin receptor agonists.](image-url)
paradigm, the adaptation to the new light–dark cycle can be measured as a function of the amount of activity that occurs at the appropriate phase of the light–dark cycle (i.e., the dark phase for rats). The time taken for animals to reach a threshold of 85% nocturnal activity was 10.9 days for the vehicle-treated group and 7.9 days for the ramelteon-treated group. Although mean data were not provided for the melatonin group, interpolating from the published data, it appears that the vehicle-treated group took between 8 and 9 days to reach 85% nocturnal activity, compared with 6–7 days for the melatonin group. As noted by the authors, the vehicle-treated groups responded very differently in the two studies. Thus, it is difficult to make any direct comparison of the effects of ramelteon and melatonin. Regardless, these findings suggest that, compared with vehicle, both ramelteon and melatonin hasten circadian adaptation to a new light–dark schedule in rats.

A 5-h advance of the sleep–wake and light–dark cycles imposed on human subjects (n = 75) in the laboratory was used to test the ability of ramelteon (1, 2, 4 or 8 mg) to facilitate re-entrainment of the circadian system. Ramelteon was shown to phase advance the melatonin rhythm (assessed by dim light melatonin offset) by approximately 90 min when administered daily for 4 days prior to the new bedtime [36]. The highest dose (8 mg) did not produce significant phase advances. One possible explanation for this finding is that high concentrations of ramelteon or its metabolites remained at the target sites for longer following the highest dose. This may have resulted in the circadian pacemaker (i.e., SCN) being exposed to the drug at a time when phase-delays would be induced, thereby counteracting any phase-advancing effect that was initially induced. This hypothesis remains to be confirmed. Taken together however, evidence from studies in animal models and in humans suggests that ramelteon provides a strong phase-shifting signal to the circadian timing system.

Figure 2. Schematic representation of a phase response curve to light and melatonin.
Adapted from [25].

Tasimelteon’s chronobiotic properties
There are no published original reports of the phase-shifting properties of tasimelteon in animal studies. One report (data not shown) indicates that tasimelteon shifts the wheel-running activity rhythm of rats to a comparable degree to that seen with melatonin [37].

In humans, tasimelteon improves sleep initiation and maintenance following a 5-h advance of the light–dark and sleep–wake cycles (see also section entitled ‘Tasimelteon and sleep’) [18]. At the highest dose (100 mg) the agonist produced large (2–3-h) phase shifts in the timing of the endogenous melatonin rhythm compared with placebo within hours of administration of the first dose (n = 7–9 per group). A significant dose–response relationship was observed, but only the highest dose differed significantly from placebo. Interestingly, effects on sleep parameters were apparent at lower doses (see section entitled ‘Tasimelteon and sleep’). Further studies with larger samples are required to confirm the dose–response function for phase-shifting by tasimelteon.

Agomelatine’s chronobiotic properties
The melatonin receptor agonist agomelatine (previously S-20098) has been under investigation for a number of years. In preclinical studies, agomelatine was shown to entrain the rhythm of running activity in rats [38,39], to cause phase advances in rhythms similar in magnitude to those seen with melatonin [40] and to re-entrain rhythms following phase shifts [41]. These early animal studies provided clear evidence that agomelatine does have chronobiotic properties.

In one of the few studies directly comparing the actions of melatonin with one of the melatonin agonists in human participants, agomelatine and melatonin were administered to healthy, young, good sleepers at 1800 h and the subjects were maintained in a controlled, laboratory environment, in a crossover, placebo-controlled design. Agomelatine advanced both the onset of melatonin and the nocturnal decline in core body temperature to a similar degree to melatonin and both did so significantly more than placebo (melatonin 5 mg – 89 min; agomelatine 5 mg – 70 min) [31]. Furthermore, the phase advance was maintained on the post-treatment day and both melatonin (5 mg) and agomelatine (100 mg) produced phase shifts of similar magnitude (~50 min). Phase advances of approximately 2 h were also seen following administration of agomelatine to eight older men for 15 days at 1830 h, although a melatonin condition was not included [42]. Thus, the evidence for agomelatine as a chronobiotic is quite compelling, especially in relation to the ability to elicit phase advances and to provide an entraining signal.

As a group of compounds acting at the melatonin receptors, these agonists do appear to have chronobiotic properties. This makes them potential candidates for treatment of circadian
rhythm sleep disorders. However, in some cases, the degree to which they might be useful clinically also depends on their sleep-promoting capacities.

**Sleep-promoting properties of melatonin & its analogs**

A discussion of the sleep-promoting effects of melatonin and its agonists needs to be prefaced with an introduction to current common treatments for insomnia. At present, the benzodiazepines remain the primary treatment agent for insomnia. Benzodiazepines are described as hypnotics. Melatonin, on the other hand, is not a traditional hypnotic and it is therefore inappropriate to directly compare the effects of melatonin with those of the benzodiazepines as its mechanism of action on sleep is different [9]. In reviewing the evidence of the sleep-promoting effects of melatonin and, in particular, the melatonin receptor agonists, we have therefore refrained from making direct comparisons with benzodiazepines.

**How melatonin (& its agonists) influence sleep**

Melatonin is not essential for sleep as demonstrated by studies of patients without a pineal gland who do sleep [43], but it is reported to facilitate sleep onset/maintenance in some subject populations under some circumstances (see section entitled ‘Melatonin and insomnia’) [44,45]. Sleep-promoting effects can be defined as a demonstrated capacity to elicit positive outcomes in sleep parameters, such as shorter latency to sleep onset, increased total sleep time or increased sleep efficiency. The sleep-promoting effects of melatonin and its agonists are thought to be mediated via a mechanism-of-action involving the MT1 receptor, although as mentioned earlier, the precise contribution of the MT1 and MT2 receptors to this effect is still not clear. Melatonin is reported to inhibit neuronal firing in the SCN in vitro [46], and it has been suggested that melatonin may facilitate sleep by attenuating the wake-promoting signal from the SCN. An additional (or possibly associated) pathway via the thermoregulatory system has been described for melatonin, but not yet for the agonists. In a normally entrained individual, the nightly secretion of melatonin into the bloodstream occurs prior to the decrease in core body temperature (facilitated by a reduction in heat production and an increase in heat loss at the periphery) [47–51]. Thus, the sleep-promoting effects of melatonin in humans may be associated with the reduction in core body temperature and increased heat loss at the periphery [52–54].

**Effects on sleep in preclinical studies & healthy volunteers**

Melatonin & sleep

Studies in animal models have demonstrated some sleep-promoting effects of melatonin, including a reduction in latency to sleep onset and an increase in total sleep time. The reader is directed to a recent review specifically focused on the effect of melatonin and melatonin receptor agonists on sleep in animal models [55].

Several studies have examined the sleep-promoting properties of melanin in humans. Despite some studies reporting minimal or no positive effects of melatonin around the time of normal sleep onset (for review see [56]), numerous studies have reported positive effects. The observed changes in sleep-onset latency, sleep maintenance and total sleep time appear to be dependent on a number of factors, including the circadian phase of administration (timing relative to the internal clock), dose (concentration) and route of administration (oral, intravenous, topical) [35,44,52,53,57–59]. For example, morning injections of melatonin did not affect sleep parameters in young adults; however, peripheral hand temperature was reported to increase [52]. Administration of both melatonin and temazepam at 1400 h resulted in decreased sleep-onset latency in young people and concomitant changes in peripheral skin temperature measured at the feet [53]. In that study, sleep-onset latency was assessed using the multiple sleep latency test, a well-established method of assessing sleep propensity during wake time. Compared with placebo, melatonin reduced sleep-onset latency by 4.8 ± 1.49 min and temazepam (a benzodiazepine used to treat insomnia) reduced sleep latency by 6.5 ± 1.62 min. In this crossover, randomized, placebo-controlled study, the degree of change of sleep-onset latency was similar between the benzodiazepine and melatonin. However, as discussed previously,

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**Table 1. Chronobiotic properties of the melatonin receptor agonists.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Agent</th>
<th>Species</th>
<th>Dose</th>
<th>Outcome</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hirai et al.</td>
<td>Ramelteon</td>
<td>Rat</td>
<td>0.1 or 1.0 mg/kg</td>
<td>Hastened re-entrainment of rest/activity cycle compared with vehicle</td>
<td>[35]</td>
</tr>
<tr>
<td>Richardson et al.</td>
<td>Ramelteon</td>
<td>Rat</td>
<td>1, 2, 4 or 8 mg</td>
<td>90-min phase advance compared with placebo</td>
<td>[36]</td>
</tr>
<tr>
<td>Rajaratnam et al.</td>
<td>Tasimelteon</td>
<td>Human</td>
<td>10, 20, 50 or 100 mg</td>
<td>2–3-h phase advance (100 mg)</td>
<td>[18]</td>
</tr>
<tr>
<td>Martinet et al.</td>
<td>Agomelatine</td>
<td>Rat</td>
<td>0.5–10 mg/kg</td>
<td>Entrained the running activity rhythm</td>
<td>[38]</td>
</tr>
<tr>
<td>Armstrong et al.</td>
<td>Agomelatine</td>
<td>Rat</td>
<td>1 or 3 mg</td>
<td>Phase advances similar to melatonin</td>
<td>[40]</td>
</tr>
<tr>
<td>Redman et al.</td>
<td>Agomelatine</td>
<td>Rat</td>
<td>1–3 mg/kg</td>
<td>Changed the direction of re-entrainment compared with vehicle?</td>
<td>[41]</td>
</tr>
<tr>
<td>Käuuchi et al.</td>
<td>Agomelatine</td>
<td>Human</td>
<td>5 or 100 mg</td>
<td>70-min phase advance versus 89 min with melatonin</td>
<td>[30]</td>
</tr>
<tr>
<td>Leproult et al.</td>
<td>Agomelatine</td>
<td>Human</td>
<td>50 mg</td>
<td>2-h advance over 15 days</td>
<td>[42]</td>
</tr>
<tr>
<td>Käuuchi et al.</td>
<td>Agomelatine</td>
<td>Human</td>
<td>5 or 100 mg</td>
<td>Phase advanced the rhythm of core body temperature</td>
<td>[116]</td>
</tr>
</tbody>
</table>
administration occurred at a biologically inappropriate time for sleep, when melatonin is thought to have its strongest effect on sleep parameters.

In an older population, Dawson and colleagues reported no changes in polysomnographic sleep following short-term melatonin administration via a transbuccal patch [60]. Longer treatment periods in the elderly (oral) did result in actigraphically-recorded improvements in sleep parameters, such as sleep efficiency and wake after sleep onset [61]. Furthermore, no cognitive impairment was reported in association with treatment of healthy middle-aged and elderly individuals with prolonged release melatonin on the day after treatment [62].

A study in healthy young adults demonstrated that melatonin significantly improved sleep efficiency, particularly during the time of the so-called wake maintenance zone [63] or forbidden zone for sleep [64]. Melatonin administered in the late afternoon just prior to an advanced and extended sleep opportunity (1600–0800 h), significantly increased the total amount of sleep obtained in the period 1600–2400 h by 2 h (3.37 h in controls vs 5.37 h in the melatonin-treated group) [65]. Thus, melatonin facilitated sleep when the sleep opportunity occurred at a biologically inappropriate time. Supporting these findings, a study of the efficacy of melatonin in healthy volunteers maintained in a forced desynchrony protocol reported that melatonin improved sleep efficiency when it was administered when endogenous melatonin levels are low, but not when endogenous levels are high [66]. These results have implications for shiftworkers and transmeridian travelers who attempt to sleep during the daytime, and also potentially for DSPD patients. Multiple reviews of the melatonin literature have concluded that pharmacological doses (0.5–10 mg) of melatonin are safe at least for short-term use, without associated impairments to performance the following day [67–69].

One hypothesis for the modest efficacy of melatonin when administered during the biological night to healthy individuals is related to a saturation effect on melatonin receptors at that time. A further increase in hormone concentrations in the system over and above those induced by endogenous production results in no further activation of receptors [70]. Another possible explanation is that during the biological night, ceiling levels occur in sleep-onset latency and sleep efficiency in healthy volunteers without sleep disorders. Finally, it is suggested that oral melatonin may have to be administered at extremely high doses in order to perfuse the necessary brain structures [70,71]. This is considered by some to be one reason to explore the development of specific melatonin receptor agonists. According to this rationale, high specificity receptor agonists may be delivered in lower doses for the same effect. The short half-life of melatonin may also reduce its potential utility as a sleep-promoting agent (particularly for improving sleep maintenance), compared with the agonists that are reported to have longer half-lives.

In nonclinical populations, melatonin appears to have sleep-promoting properties predominantly when administered outside of biologically appropriate times for sleep. That is, at times of the day when the biological drive for sleep is low (e.g., daytime), melatonin is most effective. The other important factor in considering the sleep-promoting capacity of melatonin is that administration to healthy normal sleepers around the time of normal sleep onset is unlikely to result in any significant improvements in sleep due to ceiling effects [42]. Melatonin may, thus, be more effective in clinical populations with disordered sleep (see section entitled ‘Melatonin and insomnia’).

Table 2 summarizes the studies investigating the sleep-promoting effects of melatonin receptor agonists.

Ramelteon & sleep
The effects of ramelteon and melatonin on sleep have been investigated in cats. Sleep-onset latencies were unchanged following both melatonin and ramelteon compared with vehicle-control; however, sleep duration was increased following both treatments [72]. Eight animals were included in each analysis from a group of 14 for each treatment group. It is important to note that there is considerable variation in the sleep parameters for the vehicle-treated groups, making it difficult to compare these findings to others in the area. In monkeys, ramelteon was reported to decrease sleep latency and also to increase total sleep time [73]. In another study in rats, it was associated with increases in rapid eye movement sleep [74]. Together, these studies indicate a consistent sleep-promoting effect of ramelteon across a number of nonhuman species, mostly associated with increased total sleep time, and in some cases reduced sleep latency and altered sleep structure.

Transient insomnia induced by a novel sleeping environment was used to assess the efficacy of ramelteon in improving the initiation of sleep in healthy volunteers without sleep complaints. Shorter latency to persistent sleep (placebo: 24.6 ± 21.9 min vs ramelteon 16 mg: 14.1 ± 15.1 min, and 64 mg: 15.5 ± 15.4 min) and increased total sleep time by approximately 12 min was observed with ramelteon compared with placebo [75]. In another study using a transient insomnia model, ramelteon was again reported to decrease the latency to persistent sleep compared with placebo (by less than 10 min); however, no difference was found between the two doses administered (8 and 16 mg) [76]. The studies to date therefore indicate that, as with melatonin, ramelteon has modest sleep-promoting properties at times of the day when sleep propensity is normally low.

Tasimelteon & sleep
Tasimelteon was tested in two randomized, double-blind, placebo-controlled clinical trials for its effects on transient insomnia induced by a 5-h phase advance of the sleep–wake cycle in healthy individuals. Compared with placebo, tasimelteon improved both the initiation and maintenance of sleep [18,65]. In particular, individuals treated with tasimelteon had 30–104 min (range for all doses) more sleep than did those on placebo. Latency to sleep onset and total sleep time were approximately the same as on the baseline night, when sleep occurred at habitual times, suggesting that the agonist attenuated the transient insomnia caused by sleep time shift. The authors suggested that tasimelteon may improve sleep at least in part due to a shift in the timing of the melatonin rhythm, and may therefore be a good candidate for treatment
of circadian rhythm sleep disorders [58]. It is important to note that transient insomnia is a symptom for which there can be a variety of causes. Based on the proposed mechanism of action of tasimelteon, the compound is likely to be effective for transient insomnia due to circadian misalignment, but not necessarily for insomnia with other causes.

Agomelatine & sleep
A recent study in rats demonstrated sleep-promoting effects of agomelatine in the form of increases in rapid eye movement and slow-wave sleep [74]. In humans, agomelatine was reported to have no significant effects on sleep in a group of older males without sleep complaints [42]. Eight elderly men (age range 51–76 years) received agomelatine or placebo in a double-blind, crossover protocol involving 15 days of administration at 1830 h. It should be noted that in this protocol agomelatine was administered approximately 4 h before bedtime, which may explain the lack of efficacy on sleep parameters. However, it may also be the case, as with melatonin, that the effects on sleep are minimal when the individual is not displaying any sleep disturbance.

Treating clinical populations
Circadian rhythm sleep disorders
Circadian rhythm sleep disorders (CRSDs) are characterised by “a persistent or recurrent pattern of sleep disturbance due primarily to alterations in the circadian timekeeping system or a misalignment between the endogenous circadian rhythm and exogenous factors that affect the timing or duration of sleep” [77]. There are essentially two main ‘classes’ of CRSD – those that arise as a result of disrupted timekeeping mechanisms within the circadian system and those that result from deliberate misalignment of sleep–wake cycle and environmental cues from the internal circadian system. In the former, the individual’s internal circadian phase may be timed earlier (advanced sleep phase disorder) or later (DSPD) than is desirable from a personal or social perspective. The latter class is associated with a temporary misalignment due to transmeridional travel (jet-lag disorder) or nonstandard work patterns (shiftwork disorder). Chronobiotics have been used both as treatments for CRSDs and also to study the underlying mechanisms of the disorder.

The action of melatonin at its receptors in the SCN is thought to be the main mechanism by which the hormone alleviates circadian misalignment associated with CRSDs [78–83]. However, there remains some debate in the literature as to the effectiveness of melatonin in the treatment of symptoms associated with jet lag and shiftwork disorder (see section entitled ‘Melatonin and sleep’ – a single review questions the efficacy of melatonin). To date, studies have variously demonstrated significant effects of melatonin, and also a lack of effect in relieving symptoms associated with CRSDs (e.g., [81,84,85]). Given that laboratory studies in healthy volunteers have demonstrated convincingly that melatonin can act as a chronobiotic and a sleep-promoting agent, it is likely that subject selection criteria and appropriate (circadian) timing of administration are critical factors for consideration in both the design and interpretation of the previous findings in CRSD patients [86].

Melatonin is often recommended for the treatment of CRSDs, taking into account preceding caveats about appropriate timing of the treatment [44,57]. Such conclusions are based on laboratory simulation studies and field studies. For example, jet-lag-related symptoms have been shown to be alleviated by treatment with melatonin. More than 300 people were studied in a randomized, double-blind, placebo-controlled study of melatonin or placebo, which demonstrated the ability of melatonin to alleviate symptoms of jet-lag [84]. Furthermore, a Cochrane review concluded that melatonin is an effective treatment for jet-lag based on changes recorded using a jet-lag global visual analogue scale (four studies) and measurement of sleep parameters, such as sleep-onset latency and total sleep time [68]. Finally, an earlier placebo-controlled, double-blind study also reported improvements in jet-lag symptoms with appropriately timed melatonin treatment [87].
In contrast to these reports, a meta-analysis of the efficacy of melatonin in the treatment of ‘secondary sleep disorders and sleep disorders accompanying sleep restriction’ concluded that melatonin is not effective in treating disorders such as jet-lag or shiftwork [67]. The selection of studies for inclusion in the analysis is contentious [86]. Inclusion criteria did not extend to simulated studies in which sleep schedules were manipulated and a number of published studies were excluded based on methodological reasons. Furthermore, the inclusion criteria did not take account of the assessment of phase in the study population.

Studies of CRSDs, such as DSPD, were part of a separate meta-analysis by the same authors focused on primary sleep disorders. The authors concluded that melatonin is probably an effective treatment for DSPD [69]. Specifically, a randomized, double-blind, crossover study reported that melatonin treatment reduced sleep-onset latency in DSPD patients by approximately 40 min compared with placebo (melatonin 20.2 ± 17.7 min; placebo 58.9 ± 30.3 min) [85]. Advances in the timing of sleep onset and offset were also reported with melatonin treatment in the range of 80–110 min [81]. Similar findings have been reported by others [83,88].

Daily administration of melatonin to blind individuals with non-24-h sleep–wake disorder entrains endogenous circadian rhythms and improves sleep [89,90]. Blind individuals who lack light perception often experience symptoms similar to those reported by shiftworkers, international travellers and others suffering from CRSDs. Strong evidence to date suggests that melatonin is an appropriate and effective treatment for such individuals.

To our knowledge, to date there have been no published studies reporting efficacy of the melatonin agonists in the treatment of chronic sleep–wake disturbances associated with CRSDs.

Primary insomnia
Melatonin & insomnia
The literature reporting treatment of the insomnia disorder with melatonin remains inconclusive. Melatonin has been reported to improve sleep parameters, such as latency to sleep and sleep efficiency, in chronic insomnia and age-related insomnia [61,91–93]. However, other studies have demonstrated no significant effects in insomnia patients [94,95]. Although the mechanism(s) through which melatonin improves sleep in insomnia patients is not well understood, one possibility is that it involves the hypothermic effects discussed earlier. Recent work provides evidence that slow-release formulae are efficacious in treating insomnia [96].

Ramelteon & insomnia
A recent review of the clinical efficacy of ramelteon reported moderate efficacy in reducing sleep latency, similar in magnitude to traditional hypnotics. Studies reviewed included patients with primary insomnia as well as healthy volunteers undergoing experimentally-induced transient insomnia. Reports of eight clinical trials were reviewed, four of which were reported in abstract form only. Sateia and colleagues describe difficulties with interpreting the results of these studies due to different definitions and measurement of the primary outcome [97]. For example, sleep-onset latency is reported in some studies as percentage change from baseline and in others as absolute values.

One of the cited studies reported reduced latency to persistent sleep and increased total sleep time in 103 insomnia patients (diagnosis of primary insomnia according to the Diagnostic and Statistical Manual, Fourth Edition – Text Revision) aged 18–64 years [98]. These authors also reported improvements in subjective ratings of sleep latency, total sleep time and self-reported complaints of disturbed sleep. Another study examined 829 patients aged 64–93 years with the diagnosis of primary insomnia. Nightly administration of ramelteon (4 or 8 mg) occurred in a randomized, double-blind, placebo-controlled design. Self-reported sleep latency was reduced with ramelteon treatment compared with placebo [99]. Large-scale trials such as these, using objectively recorded sleep as well as patient-reported outcomes suggest that ramelteon may be a useful treatment for primary insomnia.

Older subjects with primary insomnia (n = 100) were reported to have shorter latencies to sleep onset (8–10 min) when administered ramelteon, together with longer total sleep time (10 min) measured using polysomnography [100]. While statistically significant, the clinical relevance of such improvements is not known (in particular, the modest increase in total sleep time). By comparison, the nonbenzodiazepine hypnotic indiplon produced a reduction in sleep-onset latency of 13–17 min [101] and 15 min [102], in addition to an increase in total sleep time of more than 30 min. A review by Neubauer highlights the fact that, at present, ramelteon primarily acts on sleep latency, without significant impact on sleep maintenance [103]. Given the high percentage of insomnia patients who complain of sleep initiation as a major symptom, a reduction in sleep onset is important. It would be interesting to explore the mechanisms associated with this effect, perhaps through concurrent assessment of circadian phase as well as core and peripheral temperature.

The same review by Neubauer concludes that ramelteon is both safe and efficacious for the treatment of insomnia in young adults and elderly individuals. Neubauer also suggests that the lack of abuse potential, lack of cognitive and psychomotor impairment and sedating effects add to the appeal of ramelteon, although we note that a number of studies relied upon were preclinical or presented in abstract form. Trials with ramelteon have reported no difference in safety measures between the agonist and placebo. One published laboratory study recruited 14 individuals with a history of sedative abuse. Placebo, three doses of ramelteon and three doses of triazolam were administered in random order over 7 consecutive days [104]. No difference was found between ramelteon and placebo treatments on measures of cognitive performance, motor performance or mood.

Depression
Melatonin & depression
Melatonin does not appear to alleviate depressive symptoms, and in one older study was reported to make symptoms worse [105]. In a study of eight patients with major depression, melatonin treatment
over an 8-week period was reported to improve insomnia and fatigue measures; however, sleep data were not reported [106]. No improvement was seen in depressive symptoms. A similar study of melatonin treatment for 4 weeks in conjunction with fluoxetine, an antidepressant of the selective serotonin-reuptake inhibitor class, also reported improvements in subjective sleep quality but no change in symptoms of depression [107]. In animal models, melatonin has been reported to induce antidepressant-like effects in a number of standard paradigms (forced swim test and elevated plus maze) [108,109].

### Agomelatine & depression

Agomelatine appears to have been initially developed as a potential phase-shifting agent. However, because it also acts as an antagonist at the 5-HT$_2c$ receptor, its clinically utility as an antidepressant and an anxiolytic have also been vigorously pursued (Table 3). For example, agomelatine has been tested in some animal models of depression. Agomelatine reduced the time spent immobile in a forced swim test in rats (and in mice to a lesser degree) [108]. The results observed with serotonin receptor agonists or antagonists administered concurrently with agomelatine indicate that agomelatine does indeed have action at both melatonergic and serotonergic receptors. Agomelatine, melatonin and the tricyclic antidepressant desipramine were all administered to a transgenic mouse and produced the same positive outcomes in the forced swim test [109].

Agomelatine is also reported to improve sleep quality in subjects with major depression and depressive symptoms [110–113]. It has been suggested in relatively short-term studies that agomelatine does not have the same negative tolerance and hangover effects as some other antidepressants, and two of the cited studies confirmed this suggestion by comparing agomelatine to other common treatments.

One hypothesis for the reported efficacy of agomelatine in treating depression is that agomelatine realigns the sleep pattern with other circadian rhythms [114,115]. Correction of the misalignment results in sleep being attempted at a more biologically appropriate time thereby increasing sleep propensity. However, as already discussed, melatonin also acts to realign circadian rhythms, but does not appear to alleviate depressive symptoms. Therefore, the available evidence does not support the argument that such a mechanism in and of itself is sufficient to alleviate depressive symptoms. The other proposed mechanism of action is through antagonism of the 5-HT$_2c$ receptor by agomelatine, which has been associated with mood regulation [114]. Agomelatine may be a novel treatment for depression and lack of side effects indicate significant potential in this regard.

### Expert commentary

Despite decades of research with melatonin, the mechanisms by which it affects sleep and the circadian system are still not completely understood. In particular, the specific roles of the melatonin receptors in mediating the effects of melatonin remain unclear. The development of melatonin agonists with varying affinities for these receptors may help to elucidate the specific roles of the receptor subtypes. The agonists discussed in this review (ramelteon, tasimelteon and agomelatine) act through both the MT1 and MT2 receptors, and in some cases have higher binding affinities for melatonin receptors than melatonin does. Furthermore, one of these compounds is also an antagonist at the serotonin 5-HT$_2c$ receptor. The 5-HT$_2c$ antagonism and/or a synergistic relationship between the MT agonist properties and 5-HT$_2c$ antagonist properties may be the mechanism by which efficacy in the treatment of depression is achieved.

Effects of the melatonin agonists on neurobehavioral performance should be assessed. We suggest that more studies should focus on whether administration of these compounds during the daytime would result in impaired neurobehavioral performance, and conversely whether nocturnal administration results in improvement in neurobehavioral performance on the subsequent day, secondary to improved sleep.

In general, the class of compounds known as chronobiotics is able to phase advance the human circadian system when administered using traditional phase shifting protocols. Melatonin and the agonists reviewed here do have such properties. There is now

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**Table 3. Agomelatine and depression.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Species</th>
<th>Dose</th>
<th>Outcome</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bourin et al.</td>
<td>Rat/mouse</td>
<td>4–64 mg/kg</td>
<td>Decreased time spent immobile in forced swim test (mice to a lesser degree)</td>
<td>[108]</td>
</tr>
<tr>
<td>Papp et al.</td>
<td>Rat</td>
<td>10 and 50 mg/kg</td>
<td>Reversed the chronic mild stress-induced decrease in sucrose consumption</td>
<td>[117]</td>
</tr>
<tr>
<td>Barden et al.</td>
<td>Mouse</td>
<td>10 mg/kg</td>
<td>Decreased time spent immobile in forced swim test</td>
<td>[109]</td>
</tr>
<tr>
<td>Loo et al.</td>
<td>Human</td>
<td>1, 5 or 25 mg</td>
<td>Depressive symptoms improved</td>
<td>[110]</td>
</tr>
<tr>
<td>Kennedy et al.</td>
<td>Human</td>
<td>25 or 50 mg</td>
<td>Depressive symptoms improved</td>
<td>[111]</td>
</tr>
<tr>
<td>Olie et al.</td>
<td>Human</td>
<td>25 mg (up to 50 mg)</td>
<td>Depressive symptoms improved, sleep improved</td>
<td>[112]</td>
</tr>
<tr>
<td>Lemoine et al.</td>
<td>Human</td>
<td>25–50 mg</td>
<td>Depressive symptoms improved, sleep improved</td>
<td>[113]</td>
</tr>
<tr>
<td>Quera-Salva et al.</td>
<td>Human</td>
<td>25 mg</td>
<td>Increased sleep efficiency, decreased wake after sleep onset and increased slow-wave sleep</td>
<td>[118]</td>
</tr>
</tbody>
</table>
compelling evidence that phase advances may be achieved by the melatonin agonists, when they are administered in the late afternoon or early evening. However, the effects of melatonin are phase-dependent such that the phase shift is dependant on when in the circadian cycle melatonin is administered. To date, the phase-shifting effects of the agonists have not been evaluated at all phases of the circadian cycle. This information is important to inform clinical practice; the desired direction of the phase-shift (i.e., advance or delay) will vary depending on the particular type of CRSD being treated (e.g., advanced sleep phase disorder or DSPD). Differences in the pharmacokinetic properties of the melatonin agonists may result in differences in their phase response characteristics.

Based on the available evidence, melatonin and its agonists appear to improve sleep primarily by modulating the circadian system. Maximal efficacy occurs when treatment occurs towards the end of the light phase of the daily light and dark cycle (late afternoon/evening), when endogenous melatonin levels are naturally low. For melatonin, the thermoregulatory system may be involved in the observed sleep-promoting effects and again such effects are phase-dependent. Ramelteon and tasimelteon improve sleep parameters in healthy individuals. In patients with primary insomnia, melatonin has not been consistently shown to improve sleep, whereas ramelteon significantly improved sleep in these patients.

The mechanisms by which improvements in sleep are induced in insomnia patients are not clear. To our knowledge, there are no published studies reporting on the effects of the melatonin agonists on thermoregulation. Another hypothesis that remains to be tested is whether the reported improvements in sleep in insomnia patients are a consequence of a phase-advance induced in at least a subgroup of patients with delayed circadian rhythms. Finally, acute inhibition of SCN activity by melatonin may be another mechanism by which sleep propensity is increased. The longer half-life of some of the agonists compared with melatonin may prove to be an important feature in their ability to treat insomnia, in particular sleep-maintenance insomnia.

A hallmark characteristic of CRSDs is that the desired sleep time occurs at an adverse circadian phase, when the circadian system is promoting wakefulness. Based on the findings that melatonin and its agonists can advance the timing of the circadian system and promote sleep at adverse circadian phases, the use of these compounds in the treatment of some CRSDs has sound justification. It would appear that melatonin and its agonists can be used to realign the sleep and circadian systems in CRSDs, such as jet-lag and shiftwork disorder, and there is strong evidence supporting the use of melatonin in blind individuals who lack light perception. Ramelteon has been shown to alleviate jet-lag-related symptoms, such as sleep disturbance, and tasimelteon improved sleep parameters when bedtime was advanced by several hours in a laboratory setting.

The complex relationship that exists between depression and sleep is receiving increasing attention. The possibility remains that agomelatine may have efficacy in depression through a combination of its effects on melatonin and 5-HT2c receptors. Agomelatine appears to be well tolerated, but at this time it is not clear whether its efficacy is greater than that of the traditional antidepressants as no direct comparisons have been made.

Although the agonists may be more potent than the naturally occurring compound, few studies have directly compared their effects to those of melatonin. One study reported that agomelatine produced phase advances of similar magnitude to melatonin [31]. In a study of the phase-shifting effects of tasimelteon, the largest dose induced a phase shift of 2–3 h on average on the first day of treatment [18]. Although this is considerably larger than the advances expected from melatonin, a melatonin group was not included in that study and hence direct comparisons are not possible.

The available safety data on melatonin and the agonists reviewed here suggest that these compounds are well tolerated, at least in short-term use. However, one important caveat is that melatonin preparations are available over-the-counter in the USA and their safety and purity are not regulated by the US FDA. Long-term assessments of safety are needed.

Five-year view
At this stage it is reasonable to conclude that the synthetic melatonin agonists reviewed here (ramelteon, tasimelteon and agomelatine) are efficacious in the treatment of CRSDs and insomnia. Only agomelatine has been shown to be effective in the treatment of depression. The physiological mechanisms of action have not yet been well elucidated, in particular for primary insomnia. One would expect clinical utility to be enhanced through a better understanding of the underlying mechanisms of action.

We suggest that the next generation of studies on the synthetic agonists should evaluate mechanisms of action through concurrent assessment of circadian rhythm phase and sleep, and also thermoregulatory changes. Criteria and methodologies used to classify and select patients should be important considerations for future studies, in particular baseline assessment of circadian rhythm phase. Large-scale, long-term randomized controlled trials are warranted in the appropriate patient populations, with direct comparisons to melatonin.

Additional work should also focus on optimal dose and time of administration. We suggest that a better understanding of how these compounds work at the molecular and physiological levels, including the roles of the MT1, MT2 and possibly 5-HT2c receptors in mediating the circadian and sleep-promoting effects, will substantially increase their clinical utility.

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insomnia, clinical application requires an understanding of chronobiology. While there is some evidence that the agonists may be effective treatments for circadian rhythm sleep disorders, and some types of circadian disruption.

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