Ramelteon, a novel treatment for the treatment of insomnia

Richard Wurtman

Ramelteon, a potent agonist for the melatonin MT1 and MT2 brain receptors, has recently been granted approval by the US FDA for the treatment of insomnia associated with sleep onset. The drug has not exhibited potential for abuse or dependency in laboratory tests, nor does it interact with neurotransmitter receptors most associated with these phenomena, hence it has the great advantage of being a nonscheduled drug. Little data have been published in peer-reviewed journals describing its efficacy and side effects in patients with insomnia; however side-effects noted to date appear minor. No comparison study has been performed to determine whether the recommended dose of ramelteon 8 mg has any advantage over physiologic doses of melatonin (0.3 mg), particularly for long-term use.

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Melatonin, the pineal gland's nocturnallysecreted hormone [1-3], is an important component of the mechanisms that generate and sustain sleep [3-8]. Given to young adults during the daytime or early evening (for example, to those initiating eastbound travel, or undertaking shift work) it promotes sleep onset [4,9]. Given at bedtime to older adults who suffer from prolonged nocturnal awakenings, it improves sleep efficiency and increases sleep time [6,10]. The effective oral dose of melatonin (0.3 mg [4,6]) is the same for both uses, and is equal to the amount needed to elevate plasma melatonin levels to what they would normally be during the night in young adults (approximately 100-200 pcg/ml, as compared with 2-10 pcg/ml around noon). Among older individuals whose substantially-calcified pineals secrete less of the hormone, nocturnal plasma melatonin levels may only rise to 25-50 pcg/ml [11-14], a deficiency state that apparently contributes to their impairment in sleep efficiency [6].

Melatonin for human consumption is unavailable in most of the world because, to date, no company has solicited regulatory approval to market it as a drug. The hormone is sold in the USA as an unregulated dietary supplement [3], usually in doses substantially higher that the 0.3 mg needed to promote sleep. These supraphysiologic doses elevate plasma melatonin levels well beyond their normal range (e.g., to 960–2440 pcg/ml after a 3 mg dose [6,13]), and can cause hypothermia. Moreover by desensitizing the MT1 [15] and MT2 [16] receptors they lose their ability to promote sleep. Hence, the contribution of melatonin to the treatment of sleep disorders remains a disappointment.

Recently, a synthetic analog of melatonin, ramelteon, has been approved by the US FDA, for the treatment of insomnia characterized by difficulty with sleep onset [101]. Since ramelteon, like melatonin itself, neither interacts with receptors for γ aminobutyric acid (GABA) or other neurotransmitters, nor predisposes to substance abuse or dependence [17–19], it has the great advantage, compared with most other sleep-promoting drugs, of not being a scheduled compound [20–21]. Thus, if future clinical experience affirms the efficacy of ramelteon's and it's benign side-effect profile, use of this drug may expand rapidly.

Unfortunately, only two peer-reviewed publications are available to help clinicians and practitioners decide whether to recommend

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Massachusetts Institute of Technology, Department of Brain & Cognitive Sciences, 46–5023B; 43 Vassar Street, Cambridge, MA, 02139, USA Tel.: 1 I 617 253 6731 Fax: +1 617 253 6882 dick@mit.edu

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ramelteon to patients with insomnia [22,23]. In one of these [22] healthy, noninsomniac subjects received single doses of the drug and in the other [23] insomniacs received the ramelteon for just two consecutive days. There have also been a handful of abstracts describing 35-day studies in insomniacs or shorter studies in healthy subjects required to sleep in a laboratory [24-27], and a US FDA report [101], which briefly summarized two unpublished 35-day polysomnographic studies performed on insomniacs. The drug was described as significantly reducing latency to persistent sleep, compared with placebo, however no actual data or experimental details were provided. Apparently no study has examined the effects on sleep of administering ramelteon for more than 35 days, even though nothing in the drug's package insert precludes its likely use by aged insomniacs for months or even years. In addition no study has compared the efficacy and safety of ramelton with that of melatonin, the hormone that the drug was designed to replace [19]. Such comparative data would almost certainly have been required before a novel analog of any other hormone, for example testosterone or thyroxine, would have been granted regulatory approval.

Given the paucity of information currently available concerning ramelteon, plus the fact that it and melatonin apparendy interact with the same MT1 and MT2 receptors, our ability to anticipate ramelteon's clinical effects may be enhanced if we also consider those of melatonin itself. Melatonin does differ from ramelteon in that it also binds to a third protein, termed the MT3 receptor but actually a detoxifying enzyme, described below. However this binding has not been demonstrated to produce functional or behavioral consequences. Hence, it seems unlikely that ramelteon's failure to bind to MT3 sites differentiates its clinical effects from those of melatonin.

Effects of ramelteon

Pharmacokinetics & metabolism

When ramelteon [(S)-N-[2-(1,6,7,8-tetrahydro-2H-indeno-[5,4-b]furan-8-yl)ethyl] propionamide; MW 259.34] is administered in its recommended 8 mg oral dosage the drug is rapidly absorbed, serum concentrations peaking after 0.5–1.5 h, at 5,700 pg/ml [101,18] or approximately 20–30 times nocturnal plasma melatonin levels [3,4]. Although at least 84% of the drug is actually absorbed (because of extensive first-pass metabolism) its oral bioavailability is substantially lower (only 1.8%) [101]. Approximately 82% of the drug in human serum is proteinbound, 70% of this to albumin [101]. Intravenous ramelteon exhibits a high mean volume of distribution in humans (74 liters) [101], suggesting that it readily enters most tissues.

Ramelteon is metabolized by oxidation to hydroxyl and carbonyl derivatives, and rapidly eliminated, principally as urinary metabolites, within 96 h of oral administration. Its elimination half-life is short, (i.e., 1.0 - 2.6 h) [18], suggesting that the drug may not accumulate in the brain after repeated daily dosings, however no data are available on its actual brain levels in animals dosed repeatedly. If the brain does accumulate ramelteon, this would increase the likelihood that

the drug – like pharmacologic concentrations of melatonin itself – will desensitize the receptors on which it acts to promote sleep [15,16,28–32]. One ramelteon metabolite, designated M-II, exhibits biological activity, binding both to melatonin MT1 and MT2 receptors and to serotonin-2B receptors [101]. Its affinities for human MT1 and MT2 receptors are approximately one-tenth and one-fifth those of unmetabolized ramelteon. Although this metabolite is 17–25-fold less potent than ramelteon in *in vitro* functional assays, it also circulates at much higher concentrations, producing 20–100-fold greater mean systemic exposures. Thus it may contribute to ramelteon's biological effects. The consequences, if any, of M-II's binding to serotonin receptors await characterization, but could also be important given the known involvement of serotonin in sleep.

Elderly subjects metabolize ramelteon significantly less rapidly than younger subjects, causing their total exposure to a dose (area under the curve) to be almost twice as great [101]. Such total exposure is also increased in patients with mild or moderate hepatic impairment (by four-to tenfold), but not by renal disease [101]. A single dose of ramelteon did not reduce arterial oxygen saturation nor cause respiratory depression in patients with chronic obstructive pulmonary disease, nor did it exacerbate mild-to-moderate sleep apnea [101].

Neurochemical effects

The ability of ramelteon to bind to brain receptors for melatonin or to numerous other brain proteins (e.g., neurotransmitter receptors; ion channels; neurotransmitter transporters) was examined using, for melatonin receptors, cultured Chinese ovary (CHO) cells cloned to contain MT1 or MT2 receptors or brain homogenates containing MT3 receptors [17]. Ramelteon binding to other proteins was assessed using commercial assay protocols. Since the binding of authentic melatonin to MT1 or MT2 receptors was known to suppress cyclic AMP production, this effect was also assessed in the cloned CHO cells.

As described below, the putative MT3 receptor is actually a detoxifying enzyme – quinine reductase 2 - [33] with can bind melatonin but which otherwise has no known involvement in melatonin's physiological effects nor in the side effects (e.g., hypothermia) produced by melatonin megadoses. Ramelteon failed to bind significantly to this MT3 receptor, however no physiological significance can at present be attributed to this nonresponse.

A binding protein was considered responsive to ramelteon if, at a 10 μ M concentration, the drug failed to inhibit by 50% or more the protein's binding to its true ligand. Using this criterion, ramelteon effectively inhibited the binding of radiolabeled melatonin to brain MT1 or MT2 receptors, but not to the quinone reductase 2 enzyme (MT3 binding site). Furthermore, like melatonin itself, ramelteon inhibited the production of cyclic AMP in cloned CHO cells containing the melatonin receptors. Ramelteon failed to suppress by more than 50% the receptor binding of the other ligands tested, except for the binding of serotonin to its 5HT-1A receptors, for which the inhibition constant (Ki) value was 5.6μ M. Brain receptors failing to respond to ramelteon included the GABA receptors, which mediate the therapeutic actions and side effects of most other hypnotic agents, and also the receptors for opioids, benzodiazepines, dopamine, and other monoamines (excluding the 5HT-1A receptor). This neurochemical specificity probably explains the drug's low abuse potential [101] and its relatively good side-effect profile described below.

The affinities of ramelteon for the MT1 and MT2 receptors are at least as great as for melatonin itself. For the MT1 receptor the Ki's for ramelteon and melatonin are, respectively 14×10^{-12} and 80×10^{-12} , and for the MT2 receptor they are 112×10^{-12} and 383×10^{12} [17,18]. Peak plasma ramelteon levels after a therapeutic (8 mg) dose (i.e., 57,000 pg/ml [18]) are, however, hundreds of times greater than those generated by nocturnal melatonin secretion in younger individuals, or by administering a therapeutic (0.3 mg) dose of the hormone to anyone (i.e., 250 pg/ml or less [13]). Since supraphysiologic concentrations of melatonin markedly desensitize the MT1 receptor thereby affecting physiological responses, following activation of MT1 melatonin receptors [15], and cause a similar long-lasting down-regulation of MT2 receptors in suprachiasmatic nucleus (SCN) neurons [16], it seems likely that significant receptor desensitization will develop among patients taking ramelteon for more than a few days - perhaps even exacerbating their insomnia. Therefore, the drug probably should not be used for prolonged periods, particularly by older individuals having difficulty staying asleep, until the risk of desensitization has been evaluated.

Clinical effects

A single publication [23] has presented data on the effects of ramelteon on patients with insomnia (n = 107; mean age 37.7 years). Subjects received the drug (4, 8, 16, or 32 mg, separated by 5- or 12-day washout periods) on two consecutive evenings, 30 min prior to their habitual bedtime, and were monitored polysomnographically for 8 h. All doses significantly reduced sleep latency by approximately 13 min; increased total sleep time by approximately 12 min (i.e., from 400 to 412 min); and increased sleep efficiency (from 83.5 to 86% for the 8 mg dose). No residual next-day pharmacological effects were noted. Two unreviewed abstracts have also described studies on ramelteon in insomniacs, including two in which patients received the drug for 5 weeks. In the 2005 study by Zammit and coworkers, 405 patients (mean age 39.3 years) receiving ramelteon 8 or 16 mg of exhibited significantly decreased sleep latency, assessed polysomnographically, after 2, 16, or 30 days [25]. Moreover, total sleep time and sleep efficiency were increased after 2 days of treatment, and no rebound insomnia or withdrawal effects were noted after cessation of treatment. Roth, and colleagues describing 829 elderly patients (mean age 72.4 years) receiving ramelteon 4 or 8 mg and evaluated by a questionnaire, found significant reductions in sleep latency (by 8 min, from 78.5 to 70.2 min) and

increases in total sleep time (by 8–10 min) after 1 week of treatment [26]. The reductions in subjective sleep latency persisted for the 5 weeks of treatment. Abstracts have also described sleep-promoting effects of ramelteon among noninsomniac subjects in which transient insomnia had been induced by having them sleep in a sleep laboratory [27].

A laboratory study on ramelteon's abuse potential, performed on 14 subjects with a history of sedative/hypnotic or anxiolytic drug use, uncovered no differences in subjective test responses between those receiving ramelteon and those on placebo; the positive control drug used in the study, triazolam, did consistently demonstrate differences from placebo [34].

Some evidence of small, next-day residual effects was observed among insomniac subjects receiving ramelteon for 35 days: at week one those receiving ramelteon (8 mg) had higher Visual Analog Scale scores – a measure of fatigue – than those on placebo, and at week three those on ramelteon exhibited lower immediate word recall [101]. No evidence has been presented suggesting rebound insomnia or withdrawal effects among subjects receiving ramelteon for 35 days. The most common side effects (compared with placebo) noted in Phase I–III studies on ramelteon have been somnolence, fatigue, dizziness and an exacerbation of insomnia [101].

Effects of melatonin

Two likely-physiologic effects have been associated with melatonin administration, the promotion of sleep onset and maintenance [2-10], and the phase-shifting of circadian rhythms, including the rhythm in melatonin itself [35,36]. Both have been shown to be produced by physiologic doses, (i.e., 0.1 - 0.3mg for sleep and 0.3–0.5 mg for phase-shifting). The action of melatonin on sleep reflects both of these effects, a direct action which decreases sleep latency, increases sleep efficiency, and increases total sleep time; and an indirect action on the phasing of sleep onset and offset, mediated by changes in the timing of the sleep rhythm.

Sleep

A 1997 article [5] on melatonin and sleep listed 24 papers, almost all of which described sedation, fatigue, decreased alertness, increased reaction time, shortened sleep latency (i.e., number of min needed to fall asleep), increased sleep efficiency (i.e., percent of the total sleep period actually spent sleeping), and/or increased total sleep time. A 2005 meta-analysis [7] of 17 studies involving 284 subjects who satisfied inclusion criteria, demonstrated a statistically significant decrease in sleep latency (by 4 min; 95% CI: 2.5-5.4) and significant increases in sleep efficiency (2.2%; CI: 0.2-4.2) and total sleep duration (12.8 min; CI: 2.9-22.8) (TABLE 1). The inclusion criteria required that a study include at least six subjects, all adults; be randomized and double-blinded; involve placebo-controlled clinical trials and use objective measures of sleep evaluation. Studies could utilize crossover or parallel group designs, however case reports were excluded. It was perhaps noteworthy that statistical significance was attained in spite of major variations Table 1. Sleep parameters following melatonin (0.1-, 0.3- and 0.3-mg doses) or placebo treatment in subjects with normal sleep or suffering from age-related insomnia.

Diagnosis dose (mg)	Normal sleep				Insomnia			
	0.0	0.1	0.3	3.0	0.0	0.1	0.3	3.0
Sleep period (SP, min)	443 (41)	450 (35)	449 (42)	452 (39)	490 (56)	484 (52)	484 (54)	472 (59)
Total sleep time (TST, min)	408 (39)	411 (40)	410 (42)	413 (41)	390 (91)	402 (45)	409 (49)	398 (56)
Sleep efficiency (TST/SP, %)	92 (4)	91 (3)	91 (3)	91 (4)	78 (15)	84 (8)	88 (7)	84 (8)
Sleep latency (min)	9 (7)	10 (7)	5 (4)	7 (6)	11 (10)	10 (6)	10 (8)	10 (7)
REM latency (min)	74 (48)	60 (17)	70 (36)	61 (20)	99 (80)	68 (29)	54 (27)	52 (22)
Awake (% SP)	8 (4)	9 (4)	9 (4)	9 (4)	21 (16)	17 (9)	12 (7)	16 (8)
Stage 1 (% TST)	16 (7)	17 (5)	19 (6)	16 (7)	22 (9)	21 (8)	18 (9)	20 (8)
Stage 2 (% TST)	46 (12)	46 (8)	44 (9)	45 (8)	45 (9)	44 (8)	45 (13)	45 (9)
Stage 3 (% TST)	15 (7)	13 (6)	16 (9)	14 (7)	11 (6)	13 (6)	13 (7	13 (5)
Stage 4 (% TST)	7 (5)	5 (4)	5 (4)	6 (5)	5 (6)	5 (4)	5 (4)	4 (4)
Stage REM (% TST)	17 (6)	20 (7)	18 (6)	19 (5)	17 (5)	17 (5)	19 (7)	18 (5)

Data are expressed as group mean (standard deviation). SP, interval between first and last epoch of sleep (i.e., time in bed less latency to sleep); TST, amount of actual sleep time during SP (i.e., equal to SP less awake time); sleep efficiency, percent of time spent asleep during SP (i.e., TST/SP [%]; sleep latency, duration of time from bedtime to the onset of sleep; REM latency, interval from the time of sleep onset to the first appearance of REM sleep; awake, percent of time spent awake during SP; stage (1-REM), percent of total sleep time spent in one sleep stage (i.e., stage 1–4 or REM).

REM: Rapid eye movement; SP: Sleep efficiency; TST: Total sleep time.

among the studies in melatonin doses and routes of administration used, the general health of the subjects, and the measures used to evaluate sleep.

The effects of exogenous melatonin on sleep have been examined under three types of experimental conditions. In some studies the hormone was administered during the daily light period, such that blood melatonin levels would be transiently elevated but would then return to baseline before the initiation of nocturnal melatonin secretion. Such experiments were used to demonstrate that melatonin can decrease sleep latency at any time in the afternoon or evening, and that this effect is independent of any action the hormone might have on sleep rhythms (since no treatment can immediately shift the phase of a circadian rhythm by 8–10 h) [3].

In others the hormone was also given during the light period, but close enough to the onset of darkness so that blood melatonin levels would still be elevated when nocturnal melatonin secretion started [37]. The period during which plasma melatonin levels were continuously elevated would thus be prolonged. Such experiments reflected the use of melatonin to decrease sleep latency and maintain continuous sleep in, for example, a shift-worker or eastbound world traveler required to start sleeping earlier.

Yet others the hormone was given at the end of the light period [6] to older insomniacs with low nighttime plasma melatonin levels. The intent was to prolong the portion of the night during which their plasma melatonin concentrations would be in the same range as those of noninsomniac young adults.

In all of these situations, exogenous melatonin decreased sleep latency and, when tested, increased sleep duration and sleep efficiency. A 0.3 mg dose was either as effective as, or more effective than [6], higher pharmacologic doses, which tended to lose efficacy when administered for several days. This dose had no effect on body temperature, affirming that, while pharmacologic doses do cause hypothermia, melatonin's ability to promote sleep is not mediated by such a change, as had been suggested. The hormone had no consistent effect on sleep architecture, neither increasing nor decreasing the portion of the sleep period during which subjects exhibited rapid eye movement (REM). Its effects were different from those usually associated with hypnotic drugs, since after melatonin subjects could readily keep from falling asleep if they so chose and their cognitive abilities the morning after, receiving the hormone were unchanged or improved [3].

In a relatively large (n = 30) study [6], individuals who were 50 years old or more and did or did not suffer from clinically-significant insomnia (i.e., sleep efficiencies of 70–80% in the insomniacs vs 92% in controls), received each of four randomized doses of melatonin (0; 0.1; 0.3; or 3.0 mg;) orally for a week, with 1-week washout periods. The hormone was found to produce statistically and clinically significant improvements in sleep efficiency among the insomniacs (FIGURE 1), with the 0.3 mg dose causing the greatest effect (p < 0.0001): total sleep time increased by 19 min, and sleep efficiency rose from 78 to 88%. The effect of the melatonin was greatest during the middle portion of the nocturnal sleep



period, when sleep efficiency was increased from 70 to 92% (FIGURE 2). No effects were noted in subjects without insomnia, and among the insomniacs there were no changes in total sleep time, latency to sleep onset (which is not abnormal in this population) or to REM sleep, or percent time spent in any of the sleep stages. Dose-related increases in plasma melatonin levels were observed, the 0.3 mg dose causing peak levels in the range usually observed nocturnally among young adults (FIGURE 3). By 10 h after administration of the 0.1 or 0.3 mg doses, plasma melatonin levels did not differ from those after placebo treatment; however after the 3.0 mg dose plasma melatonin levels remained significantly elevated for much of the following day. This high dose but not the other two also caused significant hypothermia (FIGURE 4). The study concluded that many older individuals with poor sleep efficiency might benefit if their low nocturnal melatonin levels were corrected.

Circadian rhythms: phase-shifting & jet lag

The ability of exogenous melatonin to synchronize and to shift the phases of various human circadian rhythms is generally accepted. As little as 0.5 mg of pure melatonin [35], or 0.05 mg of melatonin in corn oil [38] (which causes earlier peaks in, and the more rapid disappearance of, elevated plasma melatonin levels) was able to advance the onset of nocturnal melatonin secretion when administered at 5 pm [38] and larger doses caused greater phase advances. The hormone was also able to shift the core body temperature rhythm, however a statistically significant effect was found only after a dose that elevated plasma melatonin levels well beyond their normal range, (i.e., to 1327 pcg/ml [37]), affirming that the physiologic elevations in plasma melatonin which occur nocturnally, or after submilligram doses, fail to affect body temperature. As described above, melatonin can also control the timing of the sleep and sleepiness rhythms, an effect readily demonstrated among blind individuals with free-running melatonin and sleep rhythms [38] but also among sighted individuals. Moreover physiologic doses (0.3 mg) reportedly entrain a variety of otherwise free-running rhythms in blind individuals [39,40].

The ability of melatonin to phase-shift circadian rhythms underlies its common use to prevent or treat jet lag - particularly that associated with eastbound travel (possibly because the melatonin can be taken while the traveler is still awake): a 1999 review [41] cited nine placebo-controlled field studies on this use, of which seven were successful in that improvements were noted in subjective (and in one case objective) measures of sleep and alertness. Adequate data are not available on the relationship between the efficacies of a particular melatonin dose in treating jet lag and in raising plasma melatonin levels. Some investigators recommend taking the melatonin at a specific time (e.g., at 2 am in the traveler's new geographic environment); others simply propose "a pre-flight early evening treatment before an eastbound flight, followed by treatment at bedtime for 4 days after arrival" [41]. Westbound the traveler is advised to take the melatonin late in the evening, to sustain nocturnal plasma melatonin levels for as long into the night as possible. A 2003 Cochrane Review on melatonin in the prevention and treatment of jet lag' concluded that melatonin is remarkably effective in preventing or reducing jet lag [42]. A more recent 2006 meta-analysis concluded that melatonin has not been shown to be effective in treating sleep disorders, such as jet lag and shift work disorder, nor insomnias secondary to (e.g., neurologic disease) [43]. This review failed to include many publications in which melatonin had been found effective for jet lag, nor to consider the prior meta-analyses,



Figure 2. Sleep efficiency in insomniacs during three consecutive parts (I, II, and III) of the night, following placebo (light bar) or melatonin (0.3 mg, dark bar) treatment. * p = 0.05.

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which concluded that the hormone is efficacious. Moreover almost all of the studies it did cite had utilized very high, probably desensitizing melatonin doses.

Other reported effects

It has been suggested [44,45] that melatonin is a potent antioxidant, and that melatonin supplements may protect against such age-related diseases as atherosclerosis, cancer and Alzheimer's disease. None of these proposed uses has been tested in a controlled clinical trial nor, of course, has any been approved by the US FDA. All still remain questionable because of their lack of confirmations; the enormous melatonin concentrations or doses needed to produce the effect; the failure of the investigators to provide data on actual blood or tissue melatonin concentrations after treatment and the lack of studies comparing melatonin's effects with those of known antioxidants like vitamins C or E. It has usually been possible to demonstrate antioxidant or free-radical scavenger effects in vitro [44], however, such demonstrations generally have required melatonin concentrations 1000-100,000 times those ever occurring in vivo [46]. Similarly, while high doses of melatonin (10-450 mg/kg body weight parenterally) have sometimes been shown to elicit antioxidant effects in experimental animals in vivo, neither their long-term safety nor their effects on the animals' blood melatonin levels have been characterized. In humans such megadoses might ultimately be expected to impair sleep or various circadian rhythms by desensitizing melatonin receptors.

In several small studies melatonin was found to reduce blood pressure when given to normotensive men or women during the daytime or early evening, [47], or to patients with essential hypertension. This possible effect should be explored further in subjects given ramelteon, as should whether therapeutic doses of the drugs cause hypothermia.







Figure 4. Core body temperature profiles following melatonin or placebo treatment. Orange, placebo; green, 0.1 mg; blue, 0.3 mg, black, 3 mg. *p = 0.05.

Conclusions

Ramelteon, a potent agonst for the melatonin MT1 and MT2 receptors, shares with melatonin the ability to reduce sleep latency, and is approved for this use by the US FDA. It is not an agonist for benzodiazepine or GABA receptors, nor for those of other neurotransmitters thought to mediate the hypnotic effects or addictive potential of most hypnotic drugs; moreover, ramelteon has not manifested abuse potential in laboratory tests. Hence, probably unique among prescription hypnotics, ramelteon is a nonscheduled drug. The longest, still-unpublished studies on the use of ramelteon in insomniacs have lasted only 35 days, and in the longest such study described in a peer-reviewed publication the drug was administered for only 2 days. Hence, it is not yet possible to conclude that, with chronic administration, ramelteon will retain its efficacy and propensity for causing only benign side effects. That ramelteon might indeed lose efficacy with repeated use by its relatively high peak blood levels (compared with those of melatonin) after a standard therapeutic dose and by the tendency of the MT1 and MT2 receptors to become desensitized when exposed to supraphysiologic levels of their agonist.

Expert commentary

It is not yet apparent that ramelteon manifests clinically-relevant advantages over melatonin, the hormone it is designed to replace. A further, long-term study directly comparing the two compounds is sorely needed. The effects of ramelteon 8 mg on sleep efficiency, duration and latency among individuals with abnormal values seem to be no greater than those of melatonin 0.3 mg. However, the affinity with which ramelteon binds to the MT1 and MT2 receptors is substantially greater than that of melatonin itself, and plasma ramelteon levels after the 8 mg dose are at least an order of magnitude greater than those of melatonin after its standard 0.3 mg dose. Hence, ramelteon seems more likely than melatonin to desensitize the MT1 and MT2 receptors – with a consequent loss of hypnotic activity. Unlike physiologic doses of melatonin, but like supraphysiologic quantities, ramelteon 8 mg can apparently induce prolactin secretion in some subjects; it also needs to be determined whether recommended doses of ramelteon cause hypothermia.

The one clear advantage of ramelteon over melatonin is likely to be its ready availability in much of the world. No company has introduced melatonin as a drug for sleep anywhere in the world, probably because this use lacks patent protection outside the USA, and paradoxically, the presence of such protection seems to have worked against the marketing of a useful melatonin preparation within the USA. This is because it was initially assumed that melatonin would be regulated as a drug, and that the US FDA would require that it, like all drugs, be sold at the lowest fully-effective dosage. On this basis patent protection was sought only up to the 1 mg dose level. However, melatonin was subsequently classified as a dietary supplement, and thus not regulated by the US FDA, whereupon companies were free to sell it at any dose they chose - even ultimately-ineffective megadoses of 3 mg or greater. Many Americans started using the available megadoses of melatonin, for example to treat age-related insomnia, but may have stopped doing so when receptor desensitization rendered those doses ineffective. Perhaps there might be some mechanism, at least in Europe, through which, because melatonin lacks patent protection, the first company that completed a regulatory dossier on the hormone's hypnotic effects could be granted marketing exclusivity for a certain number of years. At that point, having comparison data on the efficacy and safety of ramelteon versus melatonin would become essential.

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Five-year review

Perhaps melatonin receptors will emerge as especially useful targets for sleep-promoting drugs. This possibility is suggested by the apparent lack of abuse potential or dependency associated, to date, with ramelteon, the first such drug. But it will only happen if receptor agonists are found, which are at least as effecive as native melatonin itself; do not cause significant receptor desensitization; and do not produce, with chronic use, side effects perhaps related to enhanced prolactin secretion. The discovery that just one group of melatonin receptors mediates its hypnotic effects, and the identification of an agent that interacts selectively with just that one receptor, could tip the odds in favor of melatonin-related hypnotic drugs

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Key issues

- Do currently-prescribed doses of ramelteon continue to promote sleep if they are taken daily for extended periods (e.g., by older individuals who have difficulty staying asleep during the night), or does significant desensitization occur?
- Is ramelteon more effective than physiologic doses of melatonin in decreasing sleep latency and enhancing sleep efficiency with repeated use?
- Is withdrawal from ramelteon after prolonged use associated with rebound insomnia?
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Affiliation

Richard Wurtman, MD Green Distinguished Professor, Massachusetts Institute of Technology, Department of Brain & Cognitive Sciences, 46–5023B; 43 Vassar Street, Cambridge, MA, 021.39, USA Tel.: +1 617 253 6731 Fax: +1 617 253 6882 dick@mit.edu