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REVIEW

Pharmacotherapy of Insomnia with Ramelteon: Safety, Efficacy and Clinical Applications

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Abstract: Ramelteon is a tricyclic synthetic analog of melatonin that acts specifically on MT_1 and MT_2 melatonin receptors. Ramelteon is the first melatonin receptor agonist approved by the Food and Drug Administration (FDA) for the treatment of insomnia characterized by sleep onset difficulties. Ramelteon is both a chronobiotic and a hypnotic that has been shown to promote sleep initiation and maintenance in various preclinical and in clinical trials. The efficacy and safety of ramelteon in patients with chronic insomnia was initially confirmed in short-term placebo-controlled trials. These showed little evidence of next-day residual effects, withdrawal symptoms or rebound insomnia. Other studies indicated that ramelteon lacked abuse potential and had a minimal risk of producing dependence or adverse effects on cognitive or psychomotor performance. A 6-month placebo-controlled international study and a 1-year open-label study in the USA demonstrated that ramelteon was effective and well tolerated. Other potential off-label uses of ramelteon include circadian rhythm sleep disorders such as shift-work and jet lag. At the present time the drug should be cautiously prescribed for short-term treatment only.

Keywords: circadian rhythms, hypnotic, insomnia, melatonin, ramelteon, sleep

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Introduction

Ramelteon (TAK-375; Rozerem™) is a tricyclic synthetic analog of melatonin (Fig. 1), with the chemical name (S)-*N*-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b] furan-8-yl)ethyl]propionamide. It was approved by the United States Food and Drug Administration (FDA) in 2005 for the treatment of insomnia. In Europe, the marketing authorization application was withdrawn in 2008. Unlike other melatonergic agonists, such as agomelatine, ramelteon is a specific agonist that acts via MT_1 and MT_2 receptors without any known clinically relevant affinity for other receptors.[1–8] Ramelteon has a very low affinity for the serotonin receptor 5-HT_{1A} (K_i = 5.6 μM),[8] a property which is apparently clinically irrelevant.

Several reasons have given rise to the development of ramelteon. Classic hypnotics acting via $GABA_A$ receptors, such as benzodiazepines, cause various undesired side effects, including next-day hangover, transitory cognitive and memory impairments, rebound

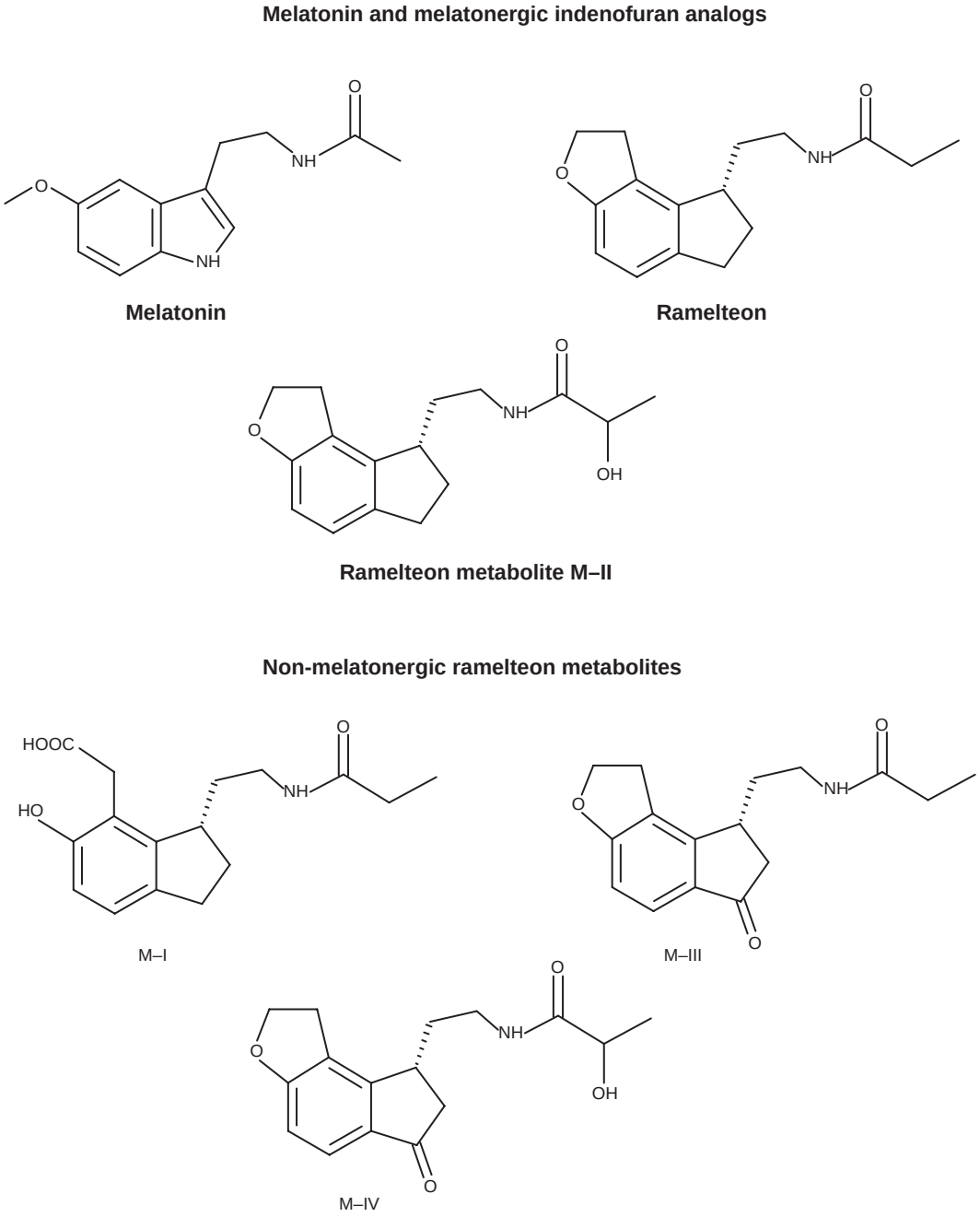

Figure 1. Chemical structures of melatonin, ramelteon and its metabolites.

insomnia after withdrawal, and have the potential for tolerance development, dependence and drug abuse.[9] These problems are less severe with the later developed z-drugs, which are, however, not entirely devoid of side effects[10] and can sometimes induce behavioral changes.[11] Trazodone, a triazolopyridine antidepressant and sedating agent, frequently prescribed for the treatment of insomnia, has been shown to cause cardiac rhythm disturbances and orthostatic hypotension.[12] Since various forms of insomnia are related to circadian rhythm dysfunction, none of these drugs can be expected to have causal treatment efficacy in cases of reduced circadian functionality, whereas the pineal hormone melatonin can directly readjust the circadian oscillator system owing to its chronobiotic properties. Moreover, melatonin is directly involved in the circadian phasing of sleep, and, in diurnally active mammals, including humans, especially in the initiation of sleep. However, melatonin has the disadvantage of having an extremely short half-life in the circulation, which is frequently below 30 min.[13,14] Taken together, these considerations provided a significant justification for the development of longer acting melatonergic agonists, such as ramelteon.

Pharmacokinetic Profile of Ramelteon versus Melatonin

Ramelteon, which is usually administered orally in a dose of 8 mg, is rapidly absorbed and reaches peak serum concentrations of 5700 pg/ml within 0.5 to 1.5 h.[7] By contrast, a comparable dose of melatonin decreases over the same time period from peak values to less than 1000 pg/ml. In serum, 82% of the ramelteon is bound to plasma proteins and, like melatonin,[15] 70% of circulating ramelteon is bound to plasma albumin. In humans, ramelteon has been tested in doses ranging from 4 to 64 mg.[7] The absorption of orally administered ramelteon is at least 84%, but its absolute bioavailability is only about 1.8% because of extensive first-pass metabolism, and also, presumably, because of uptake by tissues. Intravenously administered ramelteon has been shown to reach a distribution volume of 73.6 L.[7]

Ramelteon's unique molecular structure (Fig. 1), ie, a propionyl group instead of acetyl group, two hydrocarbon atoms in a furan ring instead of a methoxy group, and its lack of nitrogen in 5-atom ring, are factors that particularly facilitate its tissue distribution. Compared with melatonin, which itself enters tissues with ease, ramelteon has even greater lipophilicity, and consequently it penetrates and is absorbed more easily into tissue. The half-life of circulating ramelteon is in the range of 1–2 h, depending on the dose,[7] which is considerably longer than that of melatonin. Moreover, one of ramelteon's metabolites, the bioactive compound M-II (Fig. 1), is much more slowly eliminated, so that the functional half-life of the drug including M-II is extended to about 5 h. This might be regarded as a decisive advantage for sleep promotion, because the relatively poor efficiency of melatonin in supporting sleep maintenance is presumed to result from its rapid decay. As outlined above, ramelteon shows a high affinity for MT_1 and MT_2 receptors and displays very low affinity for other CNS receptor binding sites (eg, GABA receptors).

Based on pharmacokinetic studies, four metabolites of ramelteon have been identified: M-I, M-II, M-III and M-IV (Fig. 1).[7] Metabolite M-I is formed by cleavage of the furan ring, which leads to replacement of the oxygen atom with a hydroxyl group. Ring cleavage takes place through formation of a carboxyl group, which is reminiscent of a dioxygenation step. Whether such a reaction can be attributed to a cytochrome P_{450} (CYP) enzymatic activity remains to be clarified.

The M-II metabolite of ramelteon (2-hydroxy-*N*-[2-(2,6,7,8-tetrahydro-1*H*-indeno[5,4-*b*]furan-8-yl) ethyl]propanamide) (Fig. 1), exerts selective actions on MT_1 and MT_2 receptors, as does the parent compound, but it is only about 10% as potent as ramelteon itself. Of these, only M-II can be explained by a single enzymatic hydroxylation step. This compound, which represents the major metabolite, carries a hydroxyl group at C2 of the propionyl residue. The affinity of M-II for melatonin receptors is not surprising in view of its similarity to ramelteon. M-II circulates at much higher concentrations, however, resulting in a 20–100 fold greater mean systemic exposure, so it is likely to contribute to ramelteon's biological effects.[7] Metabolite M-IV differs from M-III by the presence of an aliphatic hydroxyl group as in M-II, and might be formed from either M-II or M-III.[7] The metabolites M-III and M-IV carry a carbonyl group in a position that would be impossible for melatonin, because the relevant carbon atom in ramelteon corresponds to the indolic nitrogen atom in melatonin. Again, the introduction

of the carbonyl group cannot be explained by a single hydroxylation step, but would require an additional oxidation. It might be assumed that the monohydroxylated indene formed by CYP is a reactive intermediate, which readily undergoes further oxidation. The possible significance of a reactive intermediate has, however, never been addressed in either pharmacological or toxicological terms. The metabolism and oxidation chemistry of ramelteon are thus entirely different from those of melatonin. Although ramelteon and melatonin are both substrates of hepatic P_{450} monooxygenases—mainly CYP1A2 and, to a minor extent, CYP2C subforms and CYP3A4—the sites of oxidation of ramelteon are different from those of the melatonin molecule.

Ramelteon is less rapidly eliminated than melatonin, but it is still eliminated at a rate sufficient to avoid accumulation. Less than 0.1% of the radiolabeled drug is excreted non-metabolized; 84% of radioactivity appears in the urine and 4% in the feces.[7] Total elimination is completed within 96 h. It should be noted that the half-life of M-II is 2–5 hours longer than that of the parent compound.[7]

In view of the fact that ramelteon is mainly metabolized by CYP1A2 and CYP2C19, drugs that inhibit these enzymes can considerably increase the levels of the agonist. In human liver microsomes, CYP1A2, CYP2C19 and CYP3A4 contribute 49, 42, and 8.6%, respectively, to the metabolism of the agonist.[16] Consequently, ramelteon should not be used in combination with fluvoxamine, ciprofloxacin, mexiletine, norfloxacin, tacrine or zileuton.[8] The extent of drug-drug interactions can be remarkable: for instance, coadministration of fluvoxamine has been shown to produce more than 100-fold increases of ramelteon plasma concentrations.[16] Substantial increases in ramelteon levels have also been observed when it was administered with the CYP2C9 inhibitor fluconazole and the CYP3A4 inhibitor ketoconazole, whereas compounds affecting various other P_{450} enzymes have not produced meaningful changes. The CYP inducer rifampin has been shown to considerably decrease levels of both ramelteon and its metabolite M-II. To avoid losses in efficacy, this and other strong upregulators of relevant CYP enzymes should be avoided.[8]

Stated more simply, ramelteon, like melatonin, exerts its direct sleep-inducing effects via MT_1 receptors located in the hypothalamic suprachiasmatic nucleus (SCN), while its phase shifting effects may be mediated via MT_2 receptors.[17] In the human SCN, the role of MT_2 remains to be clarified. Since ramelteon's direct soporific effect, as measured by reduction of sleep onset latency (SOL) (but not the phase shifting capacity) is indistinguishable at 4 mg and 8 mg doses, ramelteon seems to promote sleep by regulating the sleep/wake cycle rather than by having a more generalized CNS-depressant effect. This is supported by the observations that ramelteon does not worsen sleep apnea in insomniacs.[17]

Due to the potency of its effects on melatonin receptors in the SCN, ramelteon apparently accelerates sleep onset by influencing the hypothalamic "sleep-switch" downstream from the SCN, essentially in the same way as melatonin, but, owing to its higher receptor affinity, does so more efficiently.[18] The sleep-switch model, originally proposed by Saper and colleagues, describes flip-flop mutual inhibitions among sleep-associated activities in the ventrolateral preoptic nucleus (VLPO) and wakefulness associated activities in the locus coeruleus (LC), dorsal raphe nucleus (DRN) and tuberomammillary nucleus (TMN).[19–22] It has been hypothesized that the prolonged use of ramelteon, like melatonin,[23] could result in desensitization of melatonin receptors in the SCN. From studies of the SCN or immortalized SCN2.2 neurons desensitization and internalization of MT_2 receptors is known to occur following exogenous melatonin administration.[23,24] Whether down-regulation by ramelteon is stronger or longer-lasting or even occurs at all, remains to be demonstrated.

In any event, the studies of its actions to date indicate that ramelteon represents a good pharmacological option for the treatment of sleep initiation in insomnia and thus has a promising future for use with chronic insomnia patients.[6,25–32]

Mechanism of Action

Clinical evidence indicating that ramelteon does not alter sleep architecture and tends to be well tolerated is consistent with what is known about its pharmacokinetic activity. Melatonin receptors (both MT_1 and MT_2) are present in high densities in rodent SCN.[33,34] In human SCN, MT_1 is particularly expressed in vasopressin neurons,[35,36] a finding which is centrally relevant in as much as vasopressin release represents a major circadian output function of the SCN.[37–39]

MT_2 was not detected in an earlier investigation of the human SCN.[40] This receptor subtype is expressed in the SCN of numerous mammals and, where present, is particularly important for circadian phase shifting.[41–44]

The SCN is not the only site where melatonin receptors are found, and because sleep is not exclusively under circadian timing control, but is also influenced by homeostatic factors such as fever, hypothermia and infections, one question that remains to be addressed is whether ramelteon acts also as a chronobiotic, ie, a drug that directly influences circadian mechanisms.[45] In this context it has already been shown that ramelteon has the ability to promote phase shifting in rodents,[46] a capability that can be attributed to its action on the MT_2 receptor.

Activation of SCN MT_1 receptors attenuates the circadian wake-promoting signal, thereby prolonging the homeostatic mechanisms that underpin the sleep process. This suggestion assumes that the principal effect of MT_1 receptor activation is to suppress neuronal firing in the SCN, and that phase effects make only a minor contribution to the process.[41,47] Stimulation of MT_1 receptors inhibits neuronal firing in the SCN of both diurnal and nocturnal animals but suppression of wakefulness via MT_1 can only take place in diurnally active species such as primates.[19–22]

As mentioned above, the sleep-switch model describes the mutual inhibitions among sleep-associated activities in VLPO and wakefulness-associated activities in LC, DRN and TMN, as a system capable of changing in a flip-flop manner.[19–22] The SCN can influence both of these subsystems through projections via the ventral subparaventricular zone to the hypothalamic dorsomedial nucleus, from which numerous circadian functions are regulated. Projections from the dorsomedial nucleus to the VLPO induce sleep, whereas projections to the lateral hypothalamus are associated with wakefulness.

Both melatonin and ramelteon should be capable of influencing the switch via MT_1 and MT_2 receptors, thereby accelerating sleep onset. Whether such melatonergic actions would also support sleep maintenance is not known. This would depend on receptor availability throughout the sleep period; that is, the efficiency of sleep maintenance might depend on duration and extent of receptor desensitization and internalization. In this respect, ramelteon's affinity for MT_1 and MT_2 receptors is greater than that of melatonin (Table 1).

Physiological sleep promotion by melatonin also includes effects on core body and skin temperatures. In order to distinguish drug effects from the circadian rhythm of body temperature, one recent study has examined the effects of ramelteon (8 mg) administration during the day. Similar to melatonin, ramelteon has been found to reduce core body temperature and to increase the distal-proximal skin temperature gradient.[48]

Following recommended dose administrations of 8 mg, plasma levels of ramelteon are greater and longer lasting than those of melatonin. Consequently, ramelteon seems more likely to desensitize MT_1 and MT_2 receptors than would melatonin itself.[8] More information is required concerning receptor downregulation by ramelteon.

Primate Studies

The role of the SCN in the control of sleep was first reported in diurnally active squirrel monkeys.[49] In monkeys with SCN lesions, consolidated sleep and wake periods were abolished and the animals slept more. Based on such findings, it was proposed that the circadian signal arising from the SCN promotes wakefulness during the day as well as consolidating sleep during the night.[49]

A study conducted in 22 young adult female monkeys (*Macaca fascicularis*) included various measures based on cortical electroencephalography, electromyography and electrooculography.[48] Individual monkeys received, at 1000 h, different doses of ramelteon (0.003, 0.03 and 0.3 mg/kg) and, correspondingly, other animals were treated, at the same circadian phase, with different doses of melatonin (0.3 mg, 1 mg

Table 1. Receptor affinities of melatonin and ramelteon.[2]

Receptor binding characteristics in CHO cells	Melatonin	Ramelteon
Affinity (k_i) for human MT_1 receptor expressed in CHO cells	80.7 ± 2.1 pM	14 ± 0.5 pM
Affinity (k_i) for human MT_2 receptor expressed in CHO cells	383 ± 5 pM	112 ± 5 pM

and 3 mg/kg). For comparison, zolpidem was administered to additional experimental groups (1, 3, 10 and 30 mg/kg). The study demonstrated that ramelteon, in doses of 0.03 and 0.3 mg/kg, was effective in reducing the time to sleep onset as compared with controls.[50] Ramelteon, in these two doses, also significantly increased the total duration of sleep. Melatonin also tended to increase the total duration of sleep, but without attaining statistical significance. Zolpidem, in none of the doses tested (1, 3, 10, 30 mg/kg), had any effect on the latency to light sleep or slow wave sleep (SWS), nor on total sleep time (TST). The investigators concluded that ramelteon reduced the latency to sleep onset and increased sleep duration in freely moving monkeys without producing any of the side effects often seen with benzodiazepines.[50] In another study in monkeys, ramelteon did not promote physical dependence,[51] a finding of particular importance for judging the clinical usefulness of the drug.

Clinical Studies

The sleep-promoting effects of ramelteon have been studied in several trials having different designs, using models of induced transient insomnia as well as various schedules for treating younger, middle-aged and elderly patients with chronic insomnia (Table 2). A broad spectrum of doses ranging from 4 to 64 mg has been tested, but, in the majority of trials, the finally recommended dose of 8 mg has been applied. Sleep parameters have been objectively determined by polysomnography (PSG) and/or, especially in studies of long duration with high numbers of outpatients, by subjective self-rating measures.

Regardless of type of insomnia, schedule of treatment, age of patients, and evaluation of objective or subjective measures, the most consistently observed effect was a reduction of sleep onset latency, either as latency to persistent sleep (LPS) or as subjective sleep latency (sSL). Despite some variation in significance levels resulting from the number of participants and study design, it can clearly be stated that ramelteon facilitates sleep onset. The conclusion is also supported by a pooled analysis of four large trials.[59] This effect is observed after a single dose as well as daily treatment for several weeks or months (Table 2). Sometimes, the level of significance decreases upon longer duration of treatment, but this is mainly due to progressing sleep improvements in the respective placebo groups. Findings relating to dose dependence do not allow a general conclusion. In some studies, slight increases in efficiency have been observed with higher doses, but, in other cases, the opposite has been found. These divergent results have notably been obtained in trials of similar design (cf. refs. 25 and 26 for LPS, or refs. 6 and 27 for sSL). The differences may be partly explained by the lack of homogeneity within participant groups. Nevertheless, one can state that doses above 8 mg ramelteon usually do not lead to further improvements of substantial value.

Effects on sleep duration, determined either by PSG as total sleep time (TST) or by self-rating as subjective total sleep time (sTST), have been much more variable than those on sleep latency (Table 2). Although several studies reported significant improvements, this was not generally observed, even in larger studies and after prolonged treatment. Nevertheless, it may be concluded that ramelteon leads to improvements in sleep duration, but their extent remains limited. Other sleep parameters, such as wake after sleep onset (WASO), subjective WASO (sWASO) and sleep efficiency (SE), are only slightly influenced by ramelteon (Table 2). The subjective measure of sleep quality, which has also been determined in several of the studies, was not included in the table since a level of significance was never consistently reached.

In some studies, intra-group heterogeneities may have gradually obscured ramelteon's soporific effects, since the causes of sleep disturbance can be highly divergent and may be associated with chronobiological and mood disorders, which may be a source of differences in symptom tractability. The relevance of distinguishing between subgroups is indicated by a study, in which patients differing in their self-rating depression scale (SDS) score were separately analyzed.[55] Patients with SDS scores below 48 showed stronger and more sustained improvements in sSL than those with higher scores. This finding was, however, based on a subjective measure. Therefore, the possibility should be excluded that dysthymic patients only differ in their self-rating behavior. Another means of eliminating relevant intra-group heterogeneities is to exclude non-compliant patients from the evaluation.[55]

Major differences to classic GABAergic hypnotics exist with regard to next-morning effects and withdrawal. The absence of residual effects by ramelteon

Table 2. Main findings on sleep-promoting effects of ramelteon.

Study [Ref.]	Disorder, population [N: completed only]	Study design,* duration	Dose [mg]*	Objective (PSG) measures** (mean values and significance levels)				Subjective measures** (mean values and significance levels)		
				LPS [min] or [%]	TST [min]	WASO [min]	SE [%]	sSL [min]	sTST [min]	sWASO [min]
[5]	Transient insomnia (first night effect), 375 adults	R, DB, PC; single dose	P 16 64	24.6 14.1••• 15.5•••	411.3 425.4•• 422.4•	42.1 37.4 ns 39.5 ns		31.2 22.2• 25.4 ns	410.6 427.8 ns 419.9 ns	
[52]	Transient insomnia (first night effect), 289 adults	R, DB, PC; single dose	P 8 16	19.7 12.2•• 14.8 ns	419.7 436.8•• 433.1•	38.8 33.8 ns 36.3 ns	87.9 91.1• 90.3 ns	29.5 24.8 ns 27.7 ns	411.8 424.2 ns 413.1 ns	36.7 25.6 ns 38.6 ns
[25]	Chronic insomnia, 107 adults	R, DB, PC, CO; 5 × 2 ni, intervening washouts	P 4 8 16 32	37.7 24.0••• 24.3••• 24.0••• 22.9•••	400.2 411.0• 412.9•• 411.2• 418.2•••	45.5 48.5 ns 47.0 ns 48.3 ns 43.0 ns		57.0 50.9 ns 46.7 ns 43.9• 46.5 ns	360.6 364.1 ns 370.4 ns 370.9 ns 372.8 ns	
[26]	Chronic insomnia, 100 elderly adults	R, DB, PC, CO; 3 × 2 ni, intervening washouts	P 4 8	38.4 28.7••• 30.8••	350.4 359.4• 362.0••		73.1 74.9• 75.5••	58.2 48.2• 50.9 ns	333.9 337.8 ns 337.0 ns	
[6]	Chronic insomnia, 829 elderly outpatients ≥ 65 y	R, DB, PC, 5 wk	wk 1 P 4 8 wk 3 P 4 8 wk 5 P 4 8					 78.5 70.2•• 70.2•• 69.3 64.9 ns 60.3•• 70.6 63.4• 57.7•••	 313.9 324.6•• 321.1 ns 324.3 336.0•• 332.1 ns 330.1 337.5 ns 334.4 ns	
[53]	Severe sleep-onset difficulty, 327 elderly outpatients ≥ 65 y	Post-hoc analysis, from ref. 6	wk 1 P 8 wk 3 P 8 wk 5 P 8					 99.1 92.5•• 86.8 82.0•• 89.5 78.3•••		

(*Continued*)

Table 2. (*Continued*)

Study [Ref.]	Disorder, population [N: completed only]	Study design,* duration	Dose [mg]*	Objective (PSG) measures** (mean values and significance levels)				Subjective measures** (mean values and significance levels)		
				LPS [min] or [%]	TST [min]	WASO [min]	SE [%]	sSL [min]	sTST [min]	sWASO [min]
[27]	Chronic insomnia, 405 adults	R, DB, PC, 5 wk	wk 1							
			P	47.9	375.2	60.4	78.3	70.2	329.6	86.1
			8	32.2•••	394.2•••	58.0 ns	82.3•••	52.9•••	353.8•••	72.3•
			16	28.9•••	397.6•••	55.4 ns	83.4•••	56.3••	352.0••	67.8••
			wk 3							
			P	45.5	382.0	56.8	79.7	65.7	340.1	69.2
			8	32.6•••	387.3 ns	62.6 ns	80.9 ns	47.2•••	360.3••	72.2 ns
			16	27.9•••	393.8•	61.6 ns	82.1 ns	54.3•	349.7 ns	74.1 ns
			wk 5							
			P	42.6	385.9	56.4	80.4	61.5	347.1	71.2
			8	31.5••	391.5 ns	59.9 ns	81.8 ns	44.8•••	365.4•	70.3 ns
			16	29.5••	393.3 ns	61.1 ns	82.0 ns	53.8 ns	358.9 ns	68.0 ns
[54]	Chronic insomnia, 269 adults	Post-hoc analysis, from ref. 27; % of patients with ≥50% improvement	wk 1	[%]						
			P	39.7						
			8	63.0•••						
			wk 3	[%]						
			P	41.2						
			8	63.0•••						
			wk 5	[%]						
			P	48.9						
			8	65.9••						
[29]	Chronic insomnia, 335 adults	R, DB, PC, 6 mo	wk 1							
			P	~46#	365.7			~64#	330.2	91.3
			8	~32•,#	381.1•			~51•,#	337.0 ns	94.2 ns
			mo 5							
			P	~39#	379.1			~57#	347.3	79.5
			8	~31•,#	380.8 ns			~49•,#	351.6 ns	84.7 ns
			mo 6							
			P	~39#	383.0			~56#	349.5	79.5
			8	~30•,#	372.9 ns			~50 ns#	345.4 ns	90.9•
[30]	Chronic insomnia, 460 adults (18–84 y: 356; ≥65 y: 104)	OL, 1 y; patients of 18–684 y: 16 mg ramelteon daily; patients of ≥65 y: 8 mg ramelteon daily	B							
			8					~81#	~304#	
			16					~83#	~310#	
			mo 1							
			8					~59 s#	~340 s#	
			16					~63 s#	~346 s#	

			mo 4			~52 s[#]	~352 s[#]	
			8			~51 s[#]	~368 s[#]	
			16					
			mo 12			~44 s[#]	~369 s[#]	
			8			~42 s[#]	~380 s[#]	
			16					
[55]	Chronic insomnia, 947 adults (Japanese)	R, DB, PC, 4 wk (ramelteon 8 mg daily during wk 2 and 3)	wk 2					
			P			65.7		
			8			61.2•••	+4.2• (vs. P)	
			wk 3					
			P			59.5		
			8			57.1 ns[‡]	+2.4 ns (vs. P)	
[56]	Chronic insomnia, 190 adults (Japanese)	SB, 26 wk (ramelteon daily during 24 wk)	B			70.5	331	
			wk 1					
			8			54.4•••	347•••	
			wk 20					
			8			33.8•••	378•••	
[57]	Menopause 20 peri- or postmenopausal women	OL, 6 wk	B			46.2	336	38.4
			wk 2					
			8			42.6 ns	378•	25.8 ns
			wk 4					
			8			27.6••	422•••	25.7 ns
			wk 6					
			8			24.0•••	420•••	20.4 ns
[58]	Insomnia in OSA, 21 adults ≥ 60 y	R, DB, PC, 4 wk (data from wk 4)	P	34.4	72.8	18.8		
			8	9.7••	78.6 ns	31.5 ns		

Notes: Significance vs. placebo (or, where indicated, vs. baseline). •$P < 0.05$; ••$P < 0.01$; •••$P < 0.001$; ns, non-significant; s, significant vs. baseline; but no P values provided; [#]Approximate data extracted from figure; [‡]Significant improvements were obtained in a subgroup with self-rating depression scale score below 48.

Abbreviations: *B, baseline; CO, crossover; DB, double-blind; mo, months; ni, nights; P, placebo; PC, placebo-controlled; R, randomized; wk, weeks; y, years; **LPS, latency to persistent sleep; OSA, obstructive sleep apnea; TST, total sleep time; WASO, wake after sleep onset; SB, single-blind; SE, sleep efficiency; sSL, subjective sleep latency; sTST, subjective total sleep time; sWASO, subjective wake after sleep onset.

concerning morning alertness, various cognitive and psychomotor as well as mood parameters has been repeatedly documented.[5,25–27,32,52,56,60] Patients reported feeling refreshed upon arising in the morning.[6] Minor deficits in morning alertness and ability to concentrate were only observed at the very high dose of 64 mg/day,[5] which has not been applied in later studies. At a dose of 8 mg, ramelteon also did not impair memory and motor functions in older adults during the night, such as mobility and middle-of-the-night balance, findings that strongly contrast with those observed with zolpidem.[60] Importantly, ramelteon also does not induce changes in sleep architecture.[27,52] Moreover, no withdrawal symptoms have been observed, especially that of rebound insomnia,[6,27,29,32,54,56,57] which is not uncommon with other hypnotics, in particular, benzodiazepines. Instead, after a treatment for several weeks or longer, discontinuation typically leads to slow increases in sleep latency, but not to an immediate return to baseline.

The usefulness of ramelteon has been also studied in several disorders associated with sleep disturbances. For instance, sleep difficulties have been reported as one of the most troubling manifestations of menopause.[61,62] In older adults, insomnia is frequently associated with sleep apnea (estimated co-morbidity 29%–61%).[58] Data on peri- or postmenopausal women[57] and older patients with obstructive sleep apnea[58] are included in Table 2. In a double-blind, placebo-controlled study on bipolar I disorder with manic symptoms, ramelteon was applied as adjunctive therapy, but no effects on sleep parameters were demonstrable.[63] This negative finding may have resulted from the small number of patients (10 with ramelteon, 11 with placebo). However, a few significant changes were observed in global ratings of depressive symptoms, such as quality of life (according to Pittsburgh Insomnia Rating Scales) and depression (according to Clinical Global Impressions Scale, modified for bipolar illness). This is in contrast to a study in which adjunctive long-acting melatonin had no significant antidepressant action in depressed patients.[64] The findings of the ramelteon study suggest that, similar to agomelatine, ramelteon may be an effective melatonergic antidepressant drug, but unlike agomelatine, its actions are restricted to melatonergic MT_1 and MT_2 receptors, and have no effect on serotonergic receptors. Alternately, the activation of the melatonin receptors may possibly potentiate the effects of antidepressant drugs. On the other hand, interpretations of antidepressant effects in bipolar disorders have to consider the largely chronobiological nature of these diseases, which are characterized by severely disrupted circadian rhythms, in the majority of patients.[65] It should also be pointed out that sleep symptoms are a component of the global ratings for depression so that improvement in these ratings could simply represent an improvement in sleep. Clarification of this issue will depend on further studies aimed at disentangling the symptoms of disrupted sleep and depression, and, more fundamentally, how these symptoms may relate to underlying circadian dysfunctionalities.

The effectiveness and tolerability of ramelteon was also examined in an open label study of 27 adult patients who met DSM-IV diagnostic criteria for generalized anxiety disorder (GAD) and who had disturbed sleep.[66] After 12 weeks, a significant symptom reduction was observed on all scales of clinical global impression indices, with subjects falling asleep faster and sleeping longer. Ramelteon may be an effective treatment for insomnia symptoms in patients with GAD.[66] However, the data obtained cannot be easily compared with sleep parameters of other studies, not only because of the clinical scales used, but mainly because of the continued medication with escitalopram or other antidepressants/anxiolytics.

Since sleep is also controlled by the circadian oscillator system and since phase shifts cause sleep disturbances, the effects of the melatonergic drug ramelteon was also of interest in this context. In 110 healthy adults with a history of jet lag, ramelteon (1, 4 or 8 mg) was given before bedtime following an eastward travel across five time-zones from Hawaii to the east coast of US.[67] Reductions of LPS were only demonstrable at low significance levels and not under any condition, presumably because of the small number of participants in the respective subgroups. More pronounced effects on LPS were obtained in a subset of participants who were kept in dim light throughout the study.

Delayed sleep phase syndrome (DSPS) is a circadian rhythm sleep disorder (CRSD) in which sleep onset latency is delayed, in some cases by as much as 2 to 6 hours. It is characterized by chronic inability to fall asleep at the desired clock time.[68,69] There is

compelling evidence to implicate changes in the endogenous melatonin pattern as an important factor in the pathophysiology of CRSD.[69] In fact, the administration of 5 mg melatonin was reported to advance sleep onset time by an average of 82 min (range 19–124 min) and waking time by 117 min in patients with DSPS.[70]

The therapeutic potential of ramelteon for treating CRSD has been indicated by studies on the phase-shifting capacity of varying doses of the compound in healthy subjects.[71] Ramelteon, at doses of 1, 2, 4, and 8 mg, was administered to 75 adults of the age group 18–45 years for 6 days. Administration of 1, 2, or 4 mg of ramelteon for a period of 4 days was found to cause significant phase advance shifts, as assessed by determining the dim light melatonin offset effect, ie, the time point when salivary melatonin decreases to below 3 pg/mL (normally after morning awakening). Shifts of −7.1 ± 18.6, −88 ± 16.6 ($P = 0.002$), −80.5 ± 14.8 ($P = 0.003$) and −90.5 ± 15.2 min ($P = 0.001$) were determined for placebo, and 1, 2 and 4 mg ramelteon, respectively. Surprisingly, a higher dose of ramelteon (8 mg/day) did not cause significant changes as compared to placebo [−27.9 ± 16.4 min ($P = 0.392$)], an unexpected divergence between the soporific effect and phase shifting.

Safety and Adverse Effects of Ramelteon

In comparison to the safety of other newly introduced drugs, ramelteon appears to be well tolerated, at least during short-term treatment. Although the extent and duration of melatonin receptor desensitization following ramelteon therapy are unknown, these effects may be limited. Moreover, clinical studies of ramelteon carried out to date have shown little evidence of next-day hangover, withdrawal symptoms or rebound insomnia.[5,6]

Toxicological data have sufficed for US FDA approval. Interference with other drugs—in particular, those changing CYP activities—and precautions concerning the use of alcohol, high-fat meals, hepatic and renal impairment and pregnancy have been documented.[8,25,72]

The reported incidence of adverse effects of ramelteon, as inferred from subjects' complaints and neurological parameters, has been similar to that of placebo. In a study by Erman et al the incidence of treatment-emergent adverse events ranged from 8.4 to 10.7% among the ramelteon groups and was 8.7% in the placebo group.[25] The most commonly reported adverse events were headache, somnolence, dizziness and sore throat.

In as much as all currently available benzodiazepines and non-benzodiazepine hypnotics cause either addiction, withdrawal symptoms or trigger rebound insomnia, the relative absence of symptoms following the use of ramelteon is noteworthy and underscores its specific advantages for the treatment of insomnia. Ramelteon's efficacy and favorable side effect profile have been further confirmed in a recent open label study, in which subjects with primary insomnia received ramelteon nightly for 1 year.[30] Subjects aged 65 or more years received ramelteon 8 mg (n = 248) while those aged 18 to 64 years received ramelteon 16 mg (n = 965). Ramelteon was associated with sustained improvements in subjective sleep latency, subjective TST, and in the Clinical Global Impression rating scale. A total of 40.8% of subjects reported at least 1 adverse event possibly associated with ramelteon use. The adverse events reported varied considerably, the incidence of individual adverse events was low, and the frequencies of adverse events were similar at months 6 and 12.[30] In contrast to zolpidem, ramelteon did not impair middle-of-the-night balance, mobility nor memory recall of elderly patients.[60] There were no noteworthy changes in vital signs, physical examinations, clinical chemistry, hematology, nor urinalysis values. Further, no electrocardiogram changes suggested the occurrence of adverse cardiac effects. Endocrine values remained within the normal range throughout treatment, although consistent statistically significant decreases in free thyroxine (in adults) and free testosterone (in older men) were detected. The duration of menses increased by approximately 1 day.[30]

In a double-blind, placebo-controlled trial of adults (18–45 years) with chronic insomnia, the effects of nightly 16 mg doses for 6 months of either ramelteon or placebo on endocrine function were evaluated.[73] There were no consistent statistically significant differences between treatments on measures of thyroid function (total or free thyroxine, TSH, total T3), adrenal function (AM cortisol and ACTH), nor on most reproductive endocrine measures [LH, FSH, estradiol (women), total and free testosterone (men)].

Prolactin concentrations were increased overall in women in the ramelteon group compared with placebo ($P = 0.003$). However, no clinical effects of elevated prolactin were reported. Average menstrual cycle length, duration of menses, and ovulation probability did not differ between groups.[73]

Objective criteria in relation to metabolism, other diseases, hepatotoxicity, etc. have also been investigated by Takeda Pharmaceuticals, with relevant testing showing that ramelteon clearly met the safety requirements which had been fundamental for approval by the FDA. Nevertheless, it cannot be overemphasized that MT_1 and MT_2 receptors are also located outside the SCN and do not only regulate the circadian pacemaker.[74] Additional effects via these receptors have to be expected, eg, in cerebral vasomotor control, in immunomodulation, and other hormonal systems, including those involved in reproduction. Reasons for concern in this regard have been discussed elsewhere,[14,18,32,75] and may become especially relevant for long-term treatment with the drug.

One final point of concern relates to the possible mutagenic and carcinogenic potential of ramelteon. According to the information provided by Takeda,[76] the no-effect level for induction of hepatic tumors in male mice was only three times the concentration of the metabolite M-II measured after the therapeutic dose. Moreover, micronuclei formations were observed in Chinese hamster lung cells after metabolic activation.[76] The same information sheet mentions no mutagenicity in the Ames test, but does not refer in this case to metabolic activation, which should also be routinely done with this assay. It seems advisable that toxicity studies should be continued with ramelteon and its metabolites, in particular, M-II, which attains concentrations more than an order of magnitude higher than the parent compound and which is much more slowly removed from the circulation.[7]

In summary, the suitability of ramelteon for long-term treatment requires further substantiation. With good reason, Wurtman critically noted the paucity of available information on extended treatment with ramelteon.[77] For the present, the drug should be cautiously prescribed, and only for short-term treatment.

Place in Therapy

While ramelteon appears to be safe for short-term treatment, a major question for future scientific investigation is whether ramelteon is safe for extended therapeutic use. Moreover, its applicability in older individuals, including those with age-related diseases, requires further investigation. In this context, we would like to draw attention to the fact that MT_1 and MT_2 receptors are not only present in the SCN, but are widely distributed throughout the body. It seems important to know the consequences of desensitization of these receptors in the cerebral vascular system, in leukocytes and in peripheral organs, especially if ramelteon should cause longer lasting receptor downregulation compared with melatonin. Should this phenomenon occur, it could be a factor of concern for cerebral vascular tone and immune functions, especially in elderly people after long-term application. There is clearly an urgent need for a timely investigation of these issues.

Other melatonergic agonists, such as agomelatine (Servier) and tasimelteon (Vanda), are now on the market or are in the process of being approved by the American FDA and other non-US regulatory bodies. Moreover, Circadin™ (Neurim), a slow release preparation of melatonin has been approved by EMEA (The European Medicines Agency, London) for use in elderly patients with sleep disorders. A final important point to be considered is that melatonin-like compounds generally display a modest sleep inducing effect, quite mild as compared to BZP. Certainly because of their long established availability in the marketplace, and also due to the lack of new alternative insomnia treatments, "sleeping pills" are often perceived by consumers to be strong sleep inducers. This is a product characteristic which agents in the family of melatonergic compounds do not share, and, in terms of their actions, will never accomplish.[78] Therefore an emphasis on the fairly benign side effect profile (its lack of negative effects, eg, addiction, dependence, etc.) should be a central part of the associated message imparted to medical consumers. This is particularly relevant in view of the complications of benzodiazepines, which are well known to a major portion of insomnia sufferers.

Conclusions

Preclinical (rats and monkeys) and clinical evidence suggest that ramelteon is a good candidate of choice and a safe hypnotic drug for clinical use in chronic primary insomnia. It has been shown to reduce the

latency for sleep onset and to increase the TST in all the clinical studies undertaken. During treatments lasting several weeks, the reported incidence of adverse effects with ramelteon has been similar to that of placebo. In all clinical studies carried out up to the present time, there have been no reports that ramelteon is associated with any physical dependence or abuse liability issues. The hypnotic and chronobiotic actions of ramelteon are attributed to its effects on G potein-coupled melatonergic receptors present in the SCN. Ramelteon's effectiveness in promoting phase advances of sleep/wake rhythms in humans has also been demonstrated, thus suggesting that it has potential therapeutic value not only in primary insomnia but also in CRSD. In addition, adverse drug effects such as withdrawal and rebound effects, drug effects on learning and memory, impaired motor co-ordination, and its abuse potential appear to be minimal.[28,51,79]

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and not under consideration by any other publication and has not been published elsewhere. S.R. Pandi-Perumal is a stockholder and the President and Chief Executive Officer of Somnogen Inc., a New York Corporation. He declares that he has no competing interests that might be perceived to influence the content of this article. J.C. Verster is a consultant/advisor to Sepracor, Red Bull GmbH, and Transcept, and has received research support from Wyeth Ayerst Research, Takeda Pharmaceuticals, UCB Pharma, and Red Bull GmbH. All remaining authors declare that they have no proprietary, financial, professional, nor any other personal interest of any nature or kind in any product or services and/or company that could be construed or considered to be a potential conflict of interest that might have influenced the views expressed in this manuscript. The peer reviewers report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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