(left margin) **Journal of Pineal Research** — **Molecular, Biological, Physiological and Clinical Aspects of Melatonin**

REVIEW ARTICLE
Melatonin and its analogs in insomnia and depression

Abstract: Benzodiazepine sedative-hypnotic drugs are widely used for the treatment of insomnia. Nevertheless, their adverse effects, such as next-day hangover, dependence and impairment of memory, make them unsuitable for long-term treatment. Melatonin has been used for improving sleep in patients with insomnia mainly because it does not cause hangover or show any addictive potential. However, there is a lack of consistency on its therapeutic value (partly because of its short half-life and the small quantities of melatonin employed). Thus, attention has been focused either on the development of more potent melatonin analogs with prolonged effects or on the design of slow release melatonin preparations. The MT_1 and MT_2 melatonergic receptor ramelteon was effective in increasing total sleep time and sleep efficiency, as well as in reducing sleep latency, in insomnia patients. The melatonergic antidepressant agomelatine, displaying potent MT_1 and MT_2 melatonergic agonism and relatively weak serotonin $5HT_{2C}$ receptor antagonism, was found effective in the treatment of depressed patients. However, long-term safety studies are lacking for both melatonin agonists, particularly considering the pharmacological activity of their metabolites. In view of the higher binding affinities, longest half-life and relative higher potencies of the different melatonin agonists, studies using 2 or 3 mg/day of melatonin are probably unsuitable to give appropriate comparison of the effects of the natural compound. Hence, clinical trials employing melatonin doses in the range of 50–100 mg/day are warranted before the relative merits of the melatonin analogs versus melatonin can be settled.

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Introduction

Circulating melatonin (*N*-acetyl-5-methoxytryptamine, Fig. 1) originates mainly from the pineal gland in all mammals. In humans, the circadian rhythm of pineal melatonin release is highly synchronized with the habitual hours of sleep, and the daily onset of melatonin secretion is well correlated with the onset of the steepest increase in nocturnal sleepiness. Serum melatonin levels were reported to be significantly lower (and the time of peak melatonin values was delayed) in elderly subjects with insomnia compared with age-matched normal controls [1–3].

Measurements of melatonin in body fluids in elderly subjects have convincingly demonstrated an age-related impairment of nocturnal pineal melatonin synthesis [3–5]. Several studies have shown the importance of melatonin both for the initiation and for maintenance of sleep [6]. In all diurnal animals and in human beings, the onset of melatonin secretion coincides with the timing of increase in nocturnal sleep propensity [7]. As melatonin exhibits both hypnotic and chronobiotic properties, it has been used for the treatment of age-related insomnia as well as of other primary and secondary insomnia [5, 8]. A recent consensus of the British Association for Psychopharmacology on evidence-based treatment of insomnia, parasomnia, and circadian rhythm sleep disorders concluded that melatonin is the first-choice treatment when a hypnotic is indicated in patients over 55 yr [9].

Melatonin has also been used successfully for the treatment of sleep problems related to perturbations of the circadian time keeping system like those caused by jet-lag, shift-work disorder, or delayed sleep phase syndrome [8, 10–12]. The high density of melatonin receptors in the hypothalamic suprachiasmatic nuclei (SCN) [13, 14] suggests that melatonin affects sleep and the sleep-wakefulness cycle by acting on these receptors.

Because melatonin has a short half-life (< 30 min), its efficacy in promoting and maintaining sleep has not been uniform in the studies undertaken so far. Thus, the need for the development of prolonged release preparations of melatonin or of melatonin agonists with a longer duration of action on sleep regulatory structures in the brain arose [15]. Slow release forms of melatonin (e.g., Circadin®, a 2-mg preparation developed by Neurim, Tel Aviv, Israel,
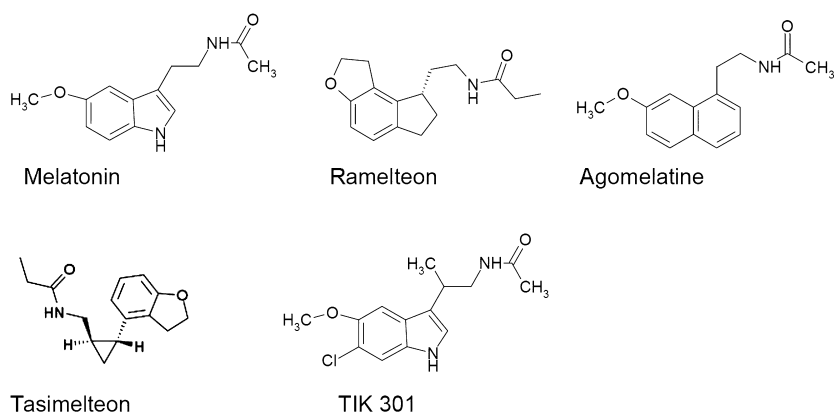
Fig. 1. Formulas of melatonin and related compounds discussed in the text.

and approved by the European Medicines Agency in 2007) and the melatonin analogs ramelteon, agomelatine, tasimelteon, and TK-301 are examples of this strategy.

Insomnia and pharmacotherapy

Insomnia is most common among elderly people and is a major cause for the impairment of physical and mental health [16, 17]. Nearly 30–40% of the adult population suffers from mild to severe insomnia [18]. The sequels of insomnia include fatigue and reduced alertness, irritability, and impaired concentration, all these symptoms having a major negative impact on the quality of life [19–21]. Because of its broad psychological and physiological impact, insomnia has social consequences like increased risk of accidents and reduced productivity at work [22]. Appropriate treatment of insomnia includes lifestyle modifications like relaxation and cognitive therapies, behavioral techniques like sleep hygiene [23] and pharmacologic interventions that employ sedative-hypnotics of both benzodiazepine and non-benzodiazepine type [9].

Benzodiazepines exert sedative actions through the activation of BZ_1 and BZ_2 receptor subtypes of the γ-aminobutyric acid $(GABA)_A$ complex, the activation of BZ_1 accounting for their specific hypno-sedative, anxiolytic, and anticonvulsant activities [24]. The α_1-subunit of the $GABA_A$ receptor mediates the sedative and anxiolytic effects of benzodiazepines [25]. The efficacy of benzodiazepines in treating insomnia was supported by a meta-analysis that included 22 studies, revealing that benzodiazepines increased total sleep time (TST), improved total sleep quality, and reduced sleep onset latency (SOL) [26]. However, benzodiazepines also exert significant adverse effects like cognitive and psychomotor impairment, anterograde amnesia, next-day hangover, and rebound insomnia. Because of their adverse effects, the use of benzodiazepines for treatment of insomnia has become controversial [24, 27, 28].

Non-benzodiazepine drugs like zolpidem, zaleplon, and zopiclone all have high affinity and selectivity for the α_1-subunit of the $GABA_A$ receptor complex [29, 30]. Zolpidem in doses of 10 mg/day improves sleep maintenance shortly after administration, but the effect disappears at a later stage [9, 27, 31]. Zolpidem use may cause many adverse effects like daytime drowsiness, dizziness, headache, and nausea [32].

Zaleplon, a pyrazolopyramidine derivative which is administered in a dose of 10 mg/day to adults and 5 mg/day to elderly patients, has been found effective in decreasing sleep latency and in improving sleep quality [33]. Zaleplon increases nocturnal melatonin secretion in human subjects [34]. Because of its efficacy and safety, zaleplon is advocated for treating subjects with sleep initiation difficulties [35]. Because of its short duration of action, zaleplon has been suggested as beneficial for shift workers in need of a short sleep period prior to next night work [35]. Zopiclone and its active stereoisomer eszopiclone have demonstrated their efficacy and safety in patients with primary insomnia [30, 36–38].

In general, non-benzodiazepine sedative-hypnotics, although effective in reducing SOL, are only moderately effective in increasing sleep efficiency (SE) and TST [39]. Indeed, an ideal hypnotic drug should not only decrease sleep latency but should also increase TST and SE [15, 40, 41]. In addition, the ideal hypnotic should not produce undesired side effects such as impairment of memory, cognition, next psychomotor retardation and day hangover effects, or potentiality of abuse.

Melatonin and insomnia

The role of melatonin in the control of sleep has been investigated in both diurnal and nocturnal species. Local injection of pharmacological amounts of melatonin (1–50 μg) in the medial preoptic area of the rat hypothalamus during daytime increased TST in a dose-dependent manner, mainly by increasing non-rapid eye movement (NREM) sleep [42]. Melatonin has been shown to induce sleep by altering the functions of the $GABA_A$-benzodiazepine receptor complex [43, 44]. In diurnal species, suppression of electrical activity in the SCN is suggested as the possible mechanism by which melatonin regulates sleep [45]. This effect is absent in MT_1 knockout mice showing thereby the importance of MT_1 receptors in melatonin's acute inhibitory effects on SCN electrical activity [46]. The MT_1 and MT_2 melatonin receptor subtypes are complementary in their actions and to some extent mutually substitute for each other [14]. The suppression of neuronal activity by melatonin is one of the possible mechanisms by which this hormone contributes to the regulation of sleep (see for a recent review [47]).

As melatonin deficiency is suggested as a cause rather than a marker for insomnia in the elderly, melatonin replacement therapy has been advocated for treating insomnia at the old age. Because melatonin is a natural hypnotic, it is suitable for long-term use in elderly people because of its low toxicity and limited side effect profile. Indeed, melatonin replacement therapy has been found beneficial in treating elderly insomniacs by significantly improving TST and quality and by reducing SOL [3–5, 48–52].

Reduced endogenous melatonin production seems to be a prerequisite for effective exogenous melatonin treatment of sleep disorders in the elderly [5]. A meta-analysis on the effects of melatonin in sleep disturbances at all age groups (including young adults with presumably normal melatonin levels) failed to document significant and clinically meaningful effects of exogenous melatonin on sleep quality, efficiency, and latency [53]. However, another meta-analysis involving 17 controlled studies has shown that melatonin was effective in increasing SE and reducing SOL in old subjects [54].

The relationship between sleep disturbances and low nocturnal melatonin production was investigated in a large population of insomniacs aged 55 yr or more [5]. Elderly insomniacs with sleep problems excreted 9.0 ± 8.3 μg of the urinary melatonin metabolite 6-sulfatoxymelatonin per night, whereas age-matched healthy controls excreted 18.1 ± 12.7 μg per night, and younger subjects excreted 24.2 ± 11.9 μg of 6-sulfatoxymelatonin per night. It was also observed that half of the elderly insomniacs excreted < 8.0 μg of a 6-sulfatoxymelatonin per night. Within this subpopulation of 372 subjects, 112 had urinary 6-sulfatoxymelatonin values lower than 3.5 μg per night [5].

Studies carried out using 0.3–1 mg doses of melatonin, that produced physiological melatonin levels in the circulation, have shown that melatonin reduced SL and increased SE when administered to healthy human subjects at the evening [48, 50, 51]. However, in most studies, higher amounts of melatonin (2–6 mg) need to be given to obtain effects. Brain imaging studies in awake subjects have revealed that melatonin modulates brain activity pattern to one resembling that of actual sleep [55]. Despite all these studies, the general efficacy of melatonin as a sleep promoting substance has been a subject of debate [56]. A possible explanation for this is that administered melatonin doses are too low as suggested by the relative potencies of the recently developed melatonin analogs (discussed below).

The fact that the reported lack of efficiency of melatonin could be related to the extremely short half-life of fast release melatonin preparations, prompted the development of active slow release formulations [57]. Circadin® is a 2-mg controlled-release preparation of melatonin, approved by EMEA as a monotherapy for short-term treatment of primary insomnia of elderly subjects. Circadin® was reported to improve the quality of sleep and morning alertness, to reduce SOL and to ameliorate quality of life in middle-aged and elderly insomniacs [58–60]. Generally, the poor melatonin excretors responded better to melatonin replacement therapy.

Ramelteon

Ramelteon (Rozerem®; Takeda Pharmaceuticals, Osaka, Japan) is a melatonergic hypnotic analog that has been demonstrated to be effective and safe in clinical trials. It is a tricyclic synthetic analog of melatonin with the chemical name of (S)-N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)-ethyl]propionamide (Fig. 1). In 2005, ramelteon was approved by the USA Food and Drug Administration (FDA) for treatment of insomnia. It is a selective agonist for MT_1/MT_2 receptors without significant affinity for other receptor sites [61, 62]. In vitro binding studies have shown that ramelteon affinity for MT_1 and MT_2 receptors is 3–16 times higher than that of melatonin. The selectivity of ramelteon for MT_1 has been found to be greater than that of MT_2 receptors. The selectivity of MT_1 receptors by ramelteon suggests that it targets sleep onset more specifically than melatonin itself [63].

Ramelteon is administered usually by the oral route and is absorbed rapidly by the gastrointestinal tract [64]. The half-life of circulating ramelteon is in the range of 1–2 hr which is much longer than that of melatonin. The influence of age and gender on the pharmacokinetics and the pharmacodynamics of ramelteon was evaluated in healthy volunteers (young, 18–34 yr; elderly 63–79 yr) after administration of a single dose of ramelteon. Compared with young individuals, the clearance of ramelteon was significantly reduced in elderly individuals. No significant effect of gender was observed [64].

Ramelteon is metabolized mainly in the liver via oxidation to hydroxyl and carbonyl groups and then conjugated with glucuronide [65]. Cytochrome P450 (CPY) 1A2 is the major hepatic enzyme involved in ramelteon metabolism. Four principal metabolites of ramelteon (M-I, M-II, M-III, M-IV) have been identified [65]. Among these, M-II has been found to occur in a much higher concentration with systemic levels of 20- to 100-fold greater than those of ramelteon itself. Although the activity of M-II is 30-fold lower than that of ramelteon, its exposure exceeds that of ramelteon by a factor of 30. Hence, it is suggested that M-II may contribute significantly to the net clinical effect of ramelteon intake.

Although MT_1 and MT_2 receptors are widely distributed in the brain outside of the SCN [66–70], the high density of melatonin receptors in the SCN and their relationship to the circadian pacemaker function are highly suggestive of a SCN melatonin receptor role in sleep regulation. Ramelteon specificity for MT_1 and MT_2 melatonin receptors indicates that its probable sleep related site of action is in the SCN.

Ramelteon's efficacy as hypnotic drug was evaluated in a group of freely moving monkeys (*Macaca fascicularis*) in comparison with that of melatonin and zolpidem [71]. Ramelteon and melatonin were administered in doses of 0.003, 0.03, and 0.3 mg/kg and 0.3, 1, and 3 mg/kg, respectively, to independent groups of animals. Zolpidem was administered in doses 1, 3, 10, or 30 mg/kg to a third group of monkeys. All drugs were administered orally at 18:00 hr, and the polysomnographic (PSG) recording of sleep was continuously taken from 17:00 to 7:00 hr. Ramelteon at a dose of 0.03 or 0.3 mg/kg significantly reduced SOL for both light sleep and NREM sleep as

compared to controls. Both doses of ramelteon increased TST, whereas the lowest dose employed (0.003 mg/kg) was ineffective. Melatonin administration at a 0.3 mg/kg dose significantly reduced latency to SOL for light sleep but not for NREM sleep [71]. At a dose of 1 mg and 3 mg/kg, melatonin tended to shorten SOL and increased TST, but these changes were marginally significant. The administration of zolpidem (1–30 mg/kg) did not produce any significant effect on SOL or TST at any of the doses tested. From these results, it was concluded that ramelteon has a potent sleep inducing effect not shared by either melatonin or zolpidem [71]. In another study conducted in rhesus monkeys, ramelteon did not induce either abuse or dependence after administering daily at a dose of 10 mg/kg for 1 yr [72].

A 'sleep-switch' model to describe the regulation of sleep-wakefulness was originally proposed by Saper and his colleagues [73, 74]. It consists of 'flip-flop' reciprocal inhibitions among sleep-associated activities in the ventro-lateral preoptic nucleus and wakefulness-associated activities in the locus coeruleus, dorsal raphe, and tuberomammilary nuclei. The SCN has an active role both in promoting wakefulness as well as in promoting sleep, and this depends upon a complex neuronal network and a number of neurotransmitters released (GABA, glutamate, arginine vasopressin, somatostatin, etc.) [75, 76].

Ramelteon may accelerate sleep onset by influencing the hypothalamic sleep switch downstream the SCN in the same way as melatonin [77, 78]. Ramelteon promotes sleep onset through the inhibition of SCN electrical activity and the consequent inhibition of circadian wake signal thereby activating the specific sleep-circuit pathway.

In a double-blind study including 829 insomniac patients (mean age 72.4 yr), ramelteon, at a dose of 4–8 mg/day, brought about a significant 16–35% reduction in SOL [79]. TST was increased by both doses of ramelteon. In another randomized, multicenter double-blind, placebo-controlled crossover study including 107 patients followed by PSG, ramelteon was administered in doses of 4–32 mg/day [80]. The treatment decreased latency to first sleep (LPS) and increased TST significantly.

A short-term evaluation of the efficacy of ramelteon was performed in 100 elderly subjects by administering 4 and 8 mg doses in a two night/three day period crossover design [81]. LPS decreased, and TST and SE augmented as compared to placebo. Likewise, the efficacy of ramelteon in reducing SOL and in increasing TST and SE was evaluated in 405 patients administered with 8 mg or 16 mg of ramelteon for 5 wk in a double-blind placebo-controlled study [82]. The results confirmed the effect of ramelteon to reduce SOL and to increase SE and TST [82].

Ramelteon's hypnotic action (at an 8 mg dose) was so rapid that it caused significant reductions in SOL within a week (63% for ramelteon versus 39.7% for placebo, $P < 0.001$) [83]. This reduction in LPS was sustained throughout the 5 wk of study (63% and 65.9% ramelteon versus 41.2% and 48.9% placebo at the end of the 3rd and 5th wk, respectively) [83]. Reduction in LPS after ramelteon was also noted in healthy human subjects in a 6-wk-long study using an 8 mg dose; in this study on healthy human subjects, ramelteon also increased TST [84].

In another 6-month-long study performed in 451 adults suffering from chronic insomnia drawn from different centers across the globe (mainly USA, Europe, Russia and Australia), ramelteon consistently reduced LPS when compared with placebo [85]. The baseline LPS decreased from 70.7 to 32.0 min at week 1 (with ramelteon) and this reduction in LPS was maintained at months 1, 3, 5, and 6. No adverse effects, like next morning residual effects, rebound insomnia, or withdrawal effects, were noted [85].

In a double-blind placebo-controlled study involving a large number of Japanese patients with chronic insomnia (N = 1130), the efficacy and safety of 4 and 8 mg ramelteon were evaluated [86]. At a 4 mg dose of ramelteon, no statistically significant differences were found in subjective SOL as compared to the placebo group, while with 8 mg of ramelteon, a significant increase in TST and a decrease in SOL were observed.

The same investigators evaluated the efficacy and safety of ramelteon in 190 Japanese adults with chronic insomnia treated for a period of 24 wk [87]. TST significantly increased with an 8 mg/day dose of ramelteon, and this was maintained for 20 wk. In this study, ramelteon was well tolerated and did not cause residual effects, rebound insomnia, withdrawal symptoms, or dependence after 24 wk of continuous treatment [87].

Therefore, in all clinical studies undertaken so far to evaluate the efficacy and safety of ramelteon in various doses ranging from 4 mg to 32 mg/day in patients with chronic insomnia, the drug reduced SOL and increased sleep duration [77, 88]. Besides acting as a sedative-hypnotic drug, ramelteon also exhibited chronobiotic properties. In a study conducted on 75 healthy human subjects, the administration of ramelteon at doses of 1, 2, 4, and 8 mg for 6 days caused significant advancement of dim light melatonin offset [89].

Melatonergic antidepressants: agomelatine

As disturbances in sleep and circadian rhythms are prominent features of depression, antidepressant drugs that are also effective in alleviating sleep disturbances can be of better therapeutic value in treating depressive disorders [90]. It is suggested that an ideal antidepressant should not only decrease sleep onset difficulties and wakefulness after sleep onset but should also promote the feelings of freshness and alertness during daytime [91].

The newly introduced melatonergic antidepressant agomelatine (Valdoxan®; Servier, Neuilly-sur-Seine, France) is endowed with these properties. Agomelatine, a naphthalenic compound chemically designated as *N*-(2-[7-methoxy-1-naphthalenyl]ethyl)acetamide (Fig. 1), acts on both MT_1 and MT_2 melatonergic receptors (IC_{50} 1.3×10^{-10} and 4.7×10^{-10} M, respectively) and also acts as an antagonist to $5\text{-}HT_{2C}$ receptors at a three orders of magnitude greater concentration (IC_{50} 2.7×10^{-7} M) [92]. It does not show any significant affinities for muscarinic, histaminergic, adrenergic, and dopaminergic receptor subtypes [92].

Agomelatine has been licensed by EMEA for the treatment of major depressive disorder (MDD). In several animal models of depression like the forced swimming test [93], the learned helplessness model [94], and the social

stress model [95], agomelatine displayed antidepressant activity.

It has been hypothesized that agomelatine has a unique mechanism of action because its effects are mediated through MT_1/MT_2 melatonergic receptors and 5-HT_{2C} serotonergic receptors, acting differently at different circadian phases of the day/night cycle [96]. Through this dual action, agomelatine may promote and maintain sleep at night and helps to maintain alertness during daytime. Agomelatine given before sleep would have an immediate sleep promoting melatonergic effect that would prevail over its potentially anti-hypnotic $5HT_{2C}$ antagonism [96]. In contrast, during the day, the drug's 5-HT_{2C} antagonism would predominate over the melatonergic action, thus having an alerting action. 5-HT_{2C} receptors are concentrated in frontal cortex, amygdala, hippocampus, and cortico-limbic structures that are involved in the regulation of mood and cognition [97]. They are also present in the SCN [98], and antidepressants, while exerting their therapeutic effects, decrease the number of SCN 5-HT_{2C} receptors in those structures [99].

One criticism of this dual interpretation of agomelatine action is the large differences in affinity for the putative action on serotonergic receptors as compared to the melatonergic one (about three orders of magnitude greater concentration are needed to exert 5-HT_{2C} antagonism) [92]. Moreover, both melatonin and ramelteon have been shown to display antidepressant-like effects even though they are not reportedly known to affect serotonergic activity significantly [100–102].

As the first melatonergic antidepressant, agomelatine displays a unique non-monoaminergic mechanism of action, while all other antidepressants act through monoaminergic mechanisms [103]. As agomelatine addresses sleep disturbances as well as depressive symptoms and has early onset of action even in a severely depressed population, it stands unique among the antidepressants for effective management of MDD [104].

The first clinical study of agomelatine on depressive disorders was undertaken on 711 patients drawn from 102 centers located in Belgium, France, and the United Kingdom [105]. Agomelatine was administered in doses of 25 mg/day to MDD patients for a period of 8 wk and its clinical effect was compared with that of the specific serotonin reuptake inhibitor paroxetine (20 mg/day). Both agomelatine and paroxetine caused significantly more remissions than placebo. Responder analysis (50% or more reduction in the Hamilton's depression, HAM-D, score) showed that agomelatine was significantly better (61.5%) than placebo (46.3%). In the severely depressed subgroup of patients (586 patients with HAM-D scores over > 25), agomelatine was found to be significantly better than paroxetine [105].

Similarly, the efficacy and safety of agomelatine was evaluated in 212 patients drawn from the centers in Finland, Canada, and South Africa in a 6-wk double-blind placebo-controlled study [106]. Agomelatine in 25–50 mg doses caused significant improvement in the clinical state of the patients when compared with placebo. In the severely depressed population (with HAM-D score over 25), agomelatine, in doses 25–50 mg/day, caused significant reduc-

tion in depression scores with improvement of the clinical state [106].

Agomelatine was also used in the treatment of bipolar affective disorder I, administered as an adjunctive to either lithium or valpromide for 46 wk [107]. In this study, patients with severe depression of HAM-D score higher than 25 showed clinical responses as early as 1 wk after starting agomelatine therapy; 19 patients opted for extension period up to 211 days (6–325 days) and 11 patients completed a 1 yr extension period of treatment. There was no dropout from the study because of adverse events. Clinical remission was good suggesting that agomelatine at a 25 mg dose is effective for the treatment of bipolar disorder I [107].

Interestingly, a recent randomized, placebo-controlled study suggested that ramelteon can be also beneficial for the treatment of ambulatory bipolar I disorder patients with manic symptoms and sleep disturbance [101]. Twenty-one outpatients with bipolar I disorder with mild-to-moderate manic symptoms and sleep disturbance were randomized to receive either ramelteon (N = 10) or placebo (N = 11) in an 8-wk, double-blind, fixed-dose (8 mg/day) study. Ramelteon and placebo had similar rates of reduction in ratings of symptoms of insomnia, mania, and global severity of illness. However, ramelteon was associated with improvement in a global rating of depressive symptoms. It was also well tolerated and associated with no serious adverse events [101]. These findings underline the interpretation that activation of MT_1/MT_2 receptors alone is sufficient to induce antidepressant activity [100–102].

Agomelatine has low relapse rates (21.7%) when compared with placebo (46.6%) 6 months after continuous treatment [108]. This may well be because agomelatine targets the residual symptoms such as anxiety or sleep disturbances. The early clinical response to agomelatine therapy was confirmed in another open-label study in which 24 patients suffering from MDD received agomelatine 25–50 mg for 8 wk [109]. Agomelatine was found effective in reducing HAM-D scores and improving anhedonia seen in depression. Agomelatine not only has an early onset of action but also exhibits excellent safety and tolerability [110–112].

Because sleep disturbances constitute one of the prominent features of depressive illness and are among the diagnostic criteria of DSM-IV [113], it is not strange that the melatonergic activity of agomelatine or ramelteon could be beneficial for this symptom. Patients suffering from MDD or bipolar disorder exhibit marked difficulties in initiation and maintenance of sleep, poor quality of sleep and frequent nocturnal, and early morning wakening [90]. The NIMH Epidemiological Catchment Area (ECA) study of sleep disturbances and psychiatric disorders identified sleep disturbances as a highly significant risk factor for subsequent development of depression [114].

The effectiveness of agomelatine in reducing the sleep complaints of depressed patients has been evaluated. Altered intra-night temporal distribution of REM sleep with increased amounts of early REM sleep and reduction in SOL to REM sleep is the specific EEG sleep patterns that are associated with depression [115]. Hence, prevention of persistent sleep disturbances would help to reduce the risk

of relapse or recurrence of depressive disorders. The treatment of depressive patients with agomelatine for 6 wk increased the duration of NREM sleep without affecting REM sleep thereby causing improvements in both sleep quality and continuity [116]. In the study that compared the effect of agomelatine (25 mg) with the antidepressant venlafaxine, agomelatine promoted sleep earlier and scored higher on the 'criteria of getting into sleep' as assessed by the Leeds Sleep Evaluation Questionnaire [117]. The improvement in sleep quality was evident from first week of treatment with agomelatine, whereas venlafaxine did not produce any beneficial effect. This can be important clinically in as much as improvement in sleep disturbances often precede that of depressive symptoms [118–120]. Agomelatine has also been shown effective in reducing circadian rhythm disturbances seen in patients with MDD [121].

Other compounds

Tasimelteon, [VES-162] N-([(1R,2R)-2-(2,3-dihydro-1-ben-zofuran-4-yl)cyclopropyl]methyl) propanamide (Fig. 1), is a MT_1/MT_2 agonist developed by Vanda Pharmaceuticals that completed phase III trial in 2010. In animal studies, tasimelteon exhibited the circadian phase shifting properties of melatonin [122]. In clinical studies on 39 healthy human subjects with transient insomnia after 5-hr phase advance, tasimelteon was administered randomly at doses of 10, 20, 50, or 100 mg against placebo [123]. A decrease in SOL, an increased in SE, and a shift in melatonin rhythm were noticed. In a further extended study involving 411 healthy human subjects after a 5-hr phase advance, the administration of tasimelteon improved SE and reduced SOL and wake after sleep onset [123]. In both these phase II and phase III clinical trials, the side effects of tasimelteon did not differ from that of placebo. Long-term studies are needed to establish the effectiveness and safety of tasimelteon in treating insomnia [124]. The FDA granted tasimelteon orphan drug designation status for blind individuals without light perception with non-24-hr sleep-wake disorder in 2010.

TIK-301 (formerly LY-156,735) has been in a phase II clinical trial in the USA since 2002. Originally, it was developed by Eli Lilly and Company and called LY-156,735. In 2007, Tikvah Pharmaceuticals took over the development and named it TIK-301. It is a chlorinated derivative of melatonin with MT_1/MT_2 agonist activity and $5HT_{2C}$ antagonist activity. Its formula, *N*-[2-(6-chloro-5-

methoxy-1*H*-indol-3-yl)propyl]acetamide, is shown in Fig. 1. TIK-301 pharmacokinetics, pharmacodynamics, and safety have been examined in a placebo-controlled study using 20, 35, 50, and 100 mg/day doses in healthy volunteers [125]. Unlike melatonin, TIK-301 induced sleepiness at all doses studied and did not because of unwanted effects like hypothermia, hypotension, or bradycardia. In another double-blind study on 40 patients with chronic insomnia, TIK-301 was administered at doses of 20, 40, and 100 mg with placebo on two nights with 5 days washout period between treatments [126]. TIK-301 produced significant improvement in subjective and objective measures of SOL at higher doses with a trend of improvement at 20 mg doses. The FDA granted TIK-301 orphan drug designation in 2004, to use as a treatment for circadian rhythm sleep disorder in blind individuals without light perception and individuals with tardive dyskinesia.

Conclusions

Although both benzodiazepines and non-benzodiazepines have been in use for more than 40 yr for the management of insomnia, their adverse side effects (e.g., cognitive and memory impairment, psychomotor retardation, and next-day hangover) discourage the usage of these drugs especially for prolonged time. Non-benzodiazepine drugs reduce SOL but are not very effective in increasing TST.

Melatonin exhibits both hypnotic and chronobiotic properties and thus has been tried for inducing sleep and treating sleep disorders of children, adults, and elderly people. The results of endogenous melatonin's action in insomnia have not been consistent probably due to its short half-life and ready metabolism after oral administration of fast release preparations. Hence, a prolonged released melatonin preparation (Circadin®) was introduced and has shown good results in treating insomnia. According to a recent consensus report of the British Association for Psychopharmacology on evidence-based treatment of insomnia, melatonin should be tried first in insomnia patients over 55 yr [9].

Another reason for the erratic effect of melatonin on sleep disturbances is probably the inadequate doses employed. As shown by the binding affinities, half-life, and relative potencies of the different melatonin agonists (Table 1), it is clear that studies using 2 or 3 mg melatonin are probably unsuitable to give appropriate comparison with the effect of ramelteon, agomelatine, tasimelteon, or TIK-301, which in addition to being generally more potent

Table 1. Some properties of melatonin and melatonergic agonists

	Melatonin	Circadin® (melatonin)	Ramelteon	Agomelatine	Tasimelteon	TIK-301
Binding affinity	MT_1: 0.085 nM MT_2: 0.263 nM	MT_1: 0.085 nM MT_2: 0.263 nM	MT_1: 0.014 nM MT_2: 0.112 nM	MT_1: 0.062 nM MT_2: 0.268 nM	MT_1: 0.35 nM MT_2: 0.17 nM	MT_1: 0.081 nM MT_2: 0.042 nM
Half-life	45 min	3.5–4 hr	1–2 hr	1–2 hr	–	–
Protein binding	70%	70%	82%	95%	–	–
Relative potency	MT_1: 1 MT_2: 1	MT_1: 1 MT_2: 1	MT_1: 8 MT_2: 3	MT_1: 1 MT_2: 1	MT_1: 0,25 MT_2: 1	MT_1: 1 MT_2: 5
Recomended daily dose	3 mg	2 mg	8–16 mg	25–50 mg	50 mg	40–100 mg

than the native molecule are employed in considerably higher amounts.

There are two melatonin agonists on the market today, ramelteon (Rozerem®) and agomelatine (Valdoxan®). Additionally, two melatonin agonists, tasimelteon and TIK-301, have been granted orphan drug designation and are going through clinical trials in the USA. Ramelteon has shown promising results in the treatment and management of insomnia. Similarly, agomelatine, although developed for treatment of MDD, has also been found effective in treating sleep problems associated with depressive disorders. Both these melatonergic drugs, acting through MT_1 and MT_2 melatonergic receptors in brain, particularly the SCN, are found effective and promising for promoting sleep quality and efficiency without adverse side effects as compared to benzodiazepine and non-benzodiazepine drugs.

It must be noted that neither ramelteon nor agomelatine can display the full spectrum of effects given by a very pleiotropic signaling molecule like melatonin [127]. Restriction of these agonists to membrane-bound receptors can be regarded as an advantage in terms of specificity. However, one should not neglect the fact that MT_1 and MT_2 receptors are also present outside the SCN and in the periphery. Indeed, the MT_1/MT_2-dependent effects of ramelteon and agomelatine in other brain areas as well as in peripheral tissues, like the immune and the vascular systems, have been poorly addressed.

Safety of ramelteon and agomelatine has been addressed in several publications but this issue refers only to the absence of immediately detectable adverse effects associated with patients' complaints [79, 128]. Evidently, these subjective criteria are not sufficient. Although precautions have been listed concerning interference with drugs changing CYP monooxygenase activities, hepatic and renal impairment, alcohol, high fat diet, and pregnancy, additional information is required on long-term hepatotoxicity and mutagenicity, especially with regard to ramelteon's metabolite M-II, which attains considerably higher concentrations than the parent compound.

In comparison to ramelteon, the corresponding data on agomelatine are much scarcer. Although the compound was very well tolerated according to subjective ratings, the issue of long-term toxicity has not been yet fully addressed. Although the metabolism of agomelatine has been partially studied with regard to CYP1A1, CYP1A2, and CYP2C9 [128], there are no reports on the toxicity of the hydroxylated naphthalenic metabolites. Moreover, all precautions concerning CYP-modulating drugs, hepatic and renal impairment, alcohol, puberty, and pregnancy mentioned for ramelteon are likewise applicable to agomelatine.

Melatonin has a high safety profile and it is usually remarkably well tolerated, e.g., very high doses (300 mg melatonin/day) were given orally for up to 2 yr to amyotrophic lateral sclerosis patients and found to be safe [129]. Hence, further studies employing melatonin doses in the 100 mg/day or higher range, comparable on the basis of affinity and bioavailability to those of ramelteon (up to 32 mg/day), agomelatine (up to 50 mg/day), or tasimelteon (up to 50 mg/day) are needed to clarify the potential implication of the native melatonin compound to treat sleep disorders. From animal studies, it is clear that a number of potentially useful effects of melatonin, like those in neurodegenerative disorders or in the metabolic syndrome, need high doses of melatonin to become apparent. If one expects melatonin to be effective in improving health, especially in aged people, it is likely that the low doses of melatonin employed so far will not be very beneficial.

Another important point when dealing with the effect of melatonin and its analogs on sleep is to understand that they are different from benzodiazepines and their derivatives in that they exert a promoting effect on sleep by amplifying day/night differences in alertness and sleep quality and displaying a modest sleep inducing effect, quite mild as compared to that seen with the benzodiazepine drugs. Certainly because of the long time in the market and on the lack of new alternatives for treatment of insomnia, the preconception that the consumer has for a sleeping pill is that of a strong sleep inducer, something that the melatonin family of compounds will hardly accomplish. Therefore, a very important educational goal is to change this view because of the lack of negative effects (addiction, dependence, etc.) the melatonin analogs have in face of the well-known complications of benzodiazepines. In the meantime, it seems probable that the drop-out rate with melatonin and melatonin analogs in treating insomnia will continue to be high.

Acknowledgements

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