Melatonin and Its Agonists in Sleep Disorders

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Abstract

Exogenous melatonin reportedly induces drowsiness and sleep and may ameliorate sleep disturbances, including the nocturnal awakenings associated with old age. Daytime administration of exogenous melatonin (when it is not present endogenously) promotes sleep in humans and results in sleeplike brain activity patterns at specific areas such as the precuneus and hippocampus. However, existing studies on the hypnotic efficacy of melatonin have been highly heterogeneous in regard to inclusion and exclusion criteria, measures to evaluate insomnia, doses of the medication, and routes of administration.

The inconsistent reports about the effectiveness of exogenous melatonin in the treatment of insomnia brought about the development of more potent melatonin analogs with prolonged effects and the design of slow-release melatonin preparations. The melatonergic receptor ramelteon is a selective melatonin-1 (MT1) and melatonin-2 (MT2) receptor agonist with negligible affinity for other neuronal receptors, including gamma-aminobutyric acid and benzodiazepine receptors. It was found 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 MT1 and MT2 melatonergic agonism and relatively weak serotonin 5-HT2C receptor antagonism, reportedly is effective in the treatment of depression-associated insomnia. A review of the currently available evidence regarding the effects of these compounds on sleep quality is presented in this chapter.

Keywords

Melatonin • Melatonin agonists • Sleep • Insomnia • Ramelteon • Agomelatine

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V. Srinivasan et al. (eds.), *Melatonin and Melatonergic Drugs in Clinical Practice*,
DOI 10.1007/978-81-322-0825-9_18, © Springer India 2014

Introduction

In humans, the circadian rhythm of melatonin release from the pineal gland 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 ("sleep gate") [1, 2]. 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 subjects with no insomnia [3]. Exogenous melatonin reportedly induces drowsiness and sleep and may ameliorate sleep disturbances, including the nocturnal awakenings associated with old age [4, 5]. However, existing studies on the hypnotic efficacy of melatonin have been highly heterogeneous in regard to inclusion and exclusion criteria, measures to evaluate insomnia, doses of the medication, and routes of administration. Adding to this complexity, there continues to be considerable controversy over the meaning of the discrepancies that sometimes exist between subjective and objective (polysomnographic) measures of good and bad sleep [6].

Thus, attention has been focused either on the development of more potent melatonin analogs with prolonged effects or on the design of prolonged-release melatonin preparations [7]. The MT1 and MT2 melatonergic receptor ramelteon was effective in increasing total sleep time and sleep efficiency, as well as in reducing sleep latency, in insomnia patients [8–10]. The melatonergic antidepressant agomelatine, displaying potent MT1 and MT2 melatonergic agonism and relatively weak serotonin 5-HT2C receptor antagonism, was found effective in the treatment of depression-associated insomnia [11–15]. Other melatonergic compounds are currently developed [16, 17].

Exogenous Melatonin

Melatonin's two well-established physiological effects—promotion of sleep and entrainment of circadian rhythms—are both mediated by two specific receptor proteins in the brain, and not by the gamma-aminobutyric acid (GABA) receptors through which most hypnotic agents act. This difference probably explains why, unlike the GABA-agonist drugs, which are true "sleeping pills," exogenous melatonin does not suppress rapid eye movement (REM) sleep nor, in general, affect the distribution of sleep stages [18].

Measurements of melatonin in body fluids in elderly subjects have convincingly demonstrated an age-related impairment of nocturnal pineal melatonin synthesis [19–21]. Several studies have shown the importance of melatonin both for the initiation and for maintenance of sleep [22]. In all diurnal animals and in human beings, the onset of melatonin secretion coincides with the timing of increase in nocturnal sleep propensity [23].

In 2005 a meta-analysis of 17 studies, involving 284 subjects that satisfied inclusion criteria, demonstrated that melatonin treatment significantly decreased sleep latency and increased sleep efficiency and total sleep duration [24]. The inclusion criteria were that a study includes at least six subjects, all adults, be randomized and double blinded, involves placebo-controlled clinical trials, and uses objective measures of sleep evaluation. Studies could utilize crossover or parallel group designs; however, case reports were excluded. Statistical significance was obtained in spite of considerable variations among the studies in melatonin doses and routes of administration, 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 relation to the onset or offset of endogenous melatonin secretion.

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 decreases sleep latency at any time in the afternoon or evening and that this effect is independent of an action on sleep rhythms (since no treatment can immediately shift the phase of a circadian rhythm by 8–10 h).

In others, the hormone was given close enough to the onset of darkness for blood melatonin levels to still be elevated when nocturnal melatonin secretion started. 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 who needed to start sleeping earlier.

In yet others, the hormone was given at the end of the light period 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 these situations, oral 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 higher doses, particularly when the hormone was administered for several days [18]. This dose had no effect on body temperature, affirming that, while pharmacologic doses can 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 (e.g., REM time). Its effects differed from those of most hypnotic drugs, since after receiving melatonin, subjects could readily keep from falling asleep if they chose so, and their cognitive abilities the next morning were unchanged or improved.

In a study of 30 people who were 50 years old or older and did or did not suffer from clinically significant insomnia (i.e., sleep efficiencies of 70–80 % in the insomniacs versus 92 % in controls), melatonin was found to produce statistically and clinically significant improvements in sleep efficiency among insomniacs [18].

In yet another meta-analysis published on the same year (2005), the authors found that melatonin decreased sleep onset latency (−11.7 min; 95 % confidence interval [CI]: −18.2, −5.2); it was decreased to a greater extent in people with delayed sleep phase syndrome (−38.8 min; 95 % CI: −50.3, −27.3; $n=2$) compared with people with insomnia (−7.2 min; 95 % CI: −12.0, −2.4; $n=12$) [25]. The former result appears to be clinically important. However, they conclude that melatonin is not effective in treating most primary sleep disorders with short-term use (4 weeks or less) but that there was evidence to suggest that melatonin was effective in treating delayed sleep phase syndrome with short-term use.

A meta-analysis published in 2009 focused on exogenous melatonin for sleep problems in individuals with intellectual disability [26]. Nine studies (including a total of 183 individuals with intellectual disabilities) showed that melatonin treatment decreased sleep latency by a mean of 34 min ($P<0.001$), increased total sleep time by a mean of 50 min ($P<0.001$), and significantly decreased the number of wakes per night ($P<0.05$). The authors concluded that melatonin decreases sleep latency and number of wakes per night and increases total sleep time in individuals with intellectual disabilities.

It should be noted that very recently, an official regulatory—the European Food Safety Authority (EFSA)—has evaluated the available evidence that melatonin can reduce the time it takes for normal sleepers and patients with insomnia to fall asleep [27]. It concluded that there is evidence that "a cause and effect relationship exist…between the consumption of melatonin and reduction of sleep onset latency…" and that "… 1 mg of melatonin should be consumed close to bedtime…"

Also, 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 years [28].

Melatonin Receptors Agonists

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 [29]. In accordance with this idea, slow-release forms of melatonin were developed (e.g., Circadin^{R}, a 2-mg preparation developed by Neurim, Tel Aviv, Israel, and approved by the European Medicines Agency in 2007) [7]. Their efficacy in treatment of sleep disorders in various populations was recently reported [7, 30].

A "sleep-switch" model to describe the regulation of sleep wakefulness was originally proposed by Saper and his colleagues [31, 32]. It consists of "flip-flop" reciprocal inhibitions among sleep-associated activities in the ventrolateral preoptic nucleus and wakefulness-associated activities in the locus coeruleus, dorsal raphe, and tuberomammillary nuclei. The SCN has an active role both in promoting wakefulness and in promoting sleep, and this depends upon a complex neuronal network and a number of neurotransmitters released (GABA, glutamate, arginine vasopressin, somatostatin, etc.) [33, 34].

The high density of melatonin receptors in the hypothalamic suprachiasmatic nuclei (SCN) may suggest that melatonin affects sleep and the sleep-wakefulness cycle by acting on these receptors [35, 36]. Thus, the need arose for the development of melatonin receptors agonists with a longer duration of action, and hopefully more potent in affecting sleep quality. The melatonin analogs ramelteon, agomelatine, tasimelteon, and TK-301 are examples of this strategy.

Ramelteon

Ramelteon (Rozerem^{R}; Takeda Pharmaceuticals, Osaka, Japan) is a melatonergic hypnotic analog that has been demonstrated to be effective in clinical trials. It is a tricyclic synthetic analog of melatonin with the chemical name of (*S*)-*N*-[2-(1,6,7,8-tetrahydro-2*H*-indeno[5,4-b] furan-8-yl)-ethyl]propionamide (Fig. 18.1). In 2005, ramelteon was approved by the US Food and Drug Administration (FDA) for treatment of insomnia. It is a selective agonist for MT1/MT2 receptors without significant affinity for other receptor sites [9, 36]. In vitro binding studies have shown that ramelteon affinity for MT1 and MT2 receptors is 3–16 times higher than that of melatonin. The selectivity of ramelteon for MT1 has been found to be greater than that of MT2 receptors. The selectivity of MT1 receptors by ramelteon may suggest that it targets sleep onset more specifically than melatonin itself [37].

Ramelteon is administered usually by the oral route and is absorbed rapidly by the gastrointestinal tract [38]. The half-life of circulating ramelteon is in the range of 1–2 h which is much longer than that of melatonin. The influence of

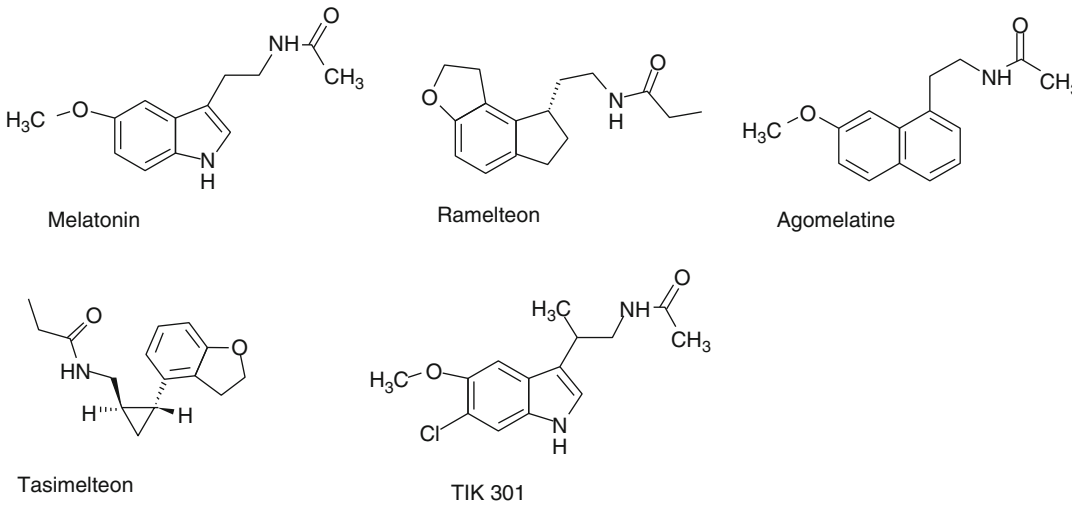

Fig. 18.1 The chemical structure of melatonin and melatonin agonists

age and gender on the pharmacokinetics and the pharmacodynamics of ramelteon was evaluated in healthy volunteers (young, 18–34 years; elderly 63–79 years) 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 [38].

Ramelteon is metabolized mainly in the liver via oxidation to hydroxyl and carbonyl groups and then conjugated with glucuronide [39]. 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 [39]. 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 MT1 and MT2 receptors are widely distributed in the brain outside of the SCN [40–44], the high density of melatonin receptors in the SCN and their relationship to the circadian pacemaker function are highly suggestive of an SCN melatonin receptor role in sleep regulation. Ramelteon specificity for MT1 and MT2 melatonin receptors indicates that its probable sleep-related site of action is in the SCN.

Ramelteon may accelerate sleep onset by influencing the hypothalamic sleep switch downstream from the SCN in the same way as melatonin [10, 45]. 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.

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 [45]. 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 at18:00 h, and the polysomnographic (PSG) recording of sleep was continuously taken from 17:00 to 7:00 h. Ramelteon at a dose of 0.03 or 0.3 mg/kg significantly reduced sleep onset latency (SOL) for both light sleep and NREM sleep as melatonin and its analogs in insomnia and depression compared to controls. Both doses of ramelteon increased total sleep time (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 [46]. 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 [46]. 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 year [47].

In a double-blind study including 829 insomniac patients (mean age, 72.4 years), ramelteon, at a dose of 4–8 mg/day, brought about a significant 16–35 % reduction in SOL [48]. 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 [49]. The treatment decreased latency to first sleep (LFS) 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 [50]. 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 or 16 mg of ramelteon for 5 weeks in a double-blind placebo-controlled study [51].

The results confirmed the effect of ramelteon to reduce SOL and to increase SE and TST[51].

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, $P<0.001$) [52]. This reduction in LPS was sustained throughout the 5 weeks of study (63 and 65.9 % ramelteon versus 41.2 and 48.9 % placebo at the end of the third and fifth weeks, respectively) [52]. Reduction in LPS after ramelteon was also noted in healthy human subjects in a 6-week-long study using an 8 mg dose; in this study on healthy human subjects, ramelteon also increased TST [53].

In yet another 6-month-long study performed in 451 adults suffering from chronic insomnia drawn from different centers across the globe (mainly the USA, Europe, Russia, and Australia), ramelteon consistently reduced LPS when compared with placebo [54]. 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 [54].

In a double-blind placebo-controlled study involving a large number of Japanese patients with chronic insomnia ($N=1{,}130$), the efficacy and safety of 4 and 8 mg ramelteon were evaluated [55]. 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 weeks [56]. TST significantly increased with an 8 mg/day dose of ramelteon, and this was maintained for 20 weeks. In this study, ramelteon was well tolerated and did not cause residual effects, rebound insomnia, withdrawal symptoms, or dependence after 24 weeks of continuous treatment [56].

Summarizing Ramelteon's studies, it seems that in all clinical studies undertaken so (in various doses ranging from 4 to 32 mg/day) in patients with chronic insomnia, the drug reduced SOL and increased sleep duration [10, 57] without significant adverse effects.

Agomelatine

Disturbances in sleep 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 [58]. 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 [59].

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, acts on both MT1and MT2 melatonergic receptors and also acts as an antagonist to 5-HT_{2C} receptors at a three orders of magnitude greater concentration [11]. It does not show any significant affinities for muscarinic, histaminergic, adrenergic, and dopaminergic receptor subtypes [60] (Fig. 18.1).

Agomelatine has been licensed by European Medicines Agency (EMEA) for the treatment of major depressive disorder (MDD). In several animal models of depression like the forced swimming test, the learned helplessness model [61], and the social stress model [62], agomelatine displayed antidepressant activity. It has been hypothesized that agomelatine has a unique mechanism of action because its effects are mediated through MT1/MT2 melatonergic receptors and 5-HT_{2C} serotonergic receptors, acting differently at different circadian phases of the day/night cycle [63]. 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 antihypnotic 5-HT_{2C} antagonism [63]. 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 the frontal cortex, amygdala, hippocampus, and cortico-limbic structures that are involved in the regulation of mood and cognition [64]. They are also present in the SCN [65], and antidepressants, while exerting their therapeutic effects, decrease the number of SCN 5-HT_{2C} receptors in those structures [66].

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) [11]. 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 [67–69].

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 [12]. Because sleep disturbances constitute one of the prominent features of depressive illness and are among the diagnostic criteria of DSM-IV [70], 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 [58].

The American National Institute of Mental Health (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 [13].

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 pattern that is associated with depression [71]. 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 weeks increased the duration of NREM sleep without affecting REM sleep, thereby causing improvements in both sleep quality and continuity [14]. 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 [72]. 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 [73–75]. Agomelatine has also been shown effective in reducing circadian rhythm disturbances seen in MDD [76].

Other Melatonin Agonists

Tasimelteon, [VES-162] *N*-([(1R,2R)-2-(2,3-dihydro-1-benzofuran-4-yl)cyclopropyl]methyl) propanamide, is a MT1/MT2 agonist developed by Vanda Pharmaceuticals that completed phase III trial in 2010 (Fig. 18.1). In animal studies, tasimelteon exhibited the circadian phase shifting properties of melatonin [77]. In clinical studies on 39 healthy human subjects with transient insomnia after a 5-h phase advance, tasimelteon was administered randomly at doses of 10, 20, 50, or 100 mg against placebo [16]. 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-h phase advance, the administration of tasimelteon improved SE and reduced SOL and wake after sleep onset [16]. 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 [78]. The FDA granted tasimelteon orphan drug

designation status for blind individuals without light perception with a non-24-h 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 MT1/MT2 agonist activity and 5-HT2C antagonist activity. Its formula is *N*-[2-(6-chloro-5-methoxy-1*H*-indol-3-yl)propyl] acetamide (Fig. 18.1). 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 [79]. Unlike melatonin, TIK-301 induced sleepiness at all doses studied and did not cause 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 [17]. 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.

Summary

The data presented above clearly indicate that exogenous melatonin and its various analogs promote and maintain sleep. However, there is inconsistency and discrepancy among the large number of reports regarding the degree of efficacy and the clinical significance of these effects. The results of endogenous melatonin's action in insomnia have not been consistent probably because the studies described in existing publications on melatonin's efficacy have utilized different inclusion and exclusion criteria, different outcome measures to evaluate insomnia, different doses of the hormone, and different routes and timing of its administration. There also continues to be considerable controversy over the meaning of the discrepancies that sometimes exist between subjective and objective (polysomnographic) measures of good and bad sleep. Adding to this complexity is melatonin's short half-life and ready metabolism after oral administration of fast-release preparations. Hence, prolonged-release melatonin preparations and melatonin agonists were introduced and have shown good results in treating insomnia.

It is noteworthy that most of the trials that examined the efficacy of melatonin in people with primary sleep disorders were of relatively short trial duration (4–6 weeks or less), as were the trials examining the safety of melatonin in this population (3 months or less). Therefore, the reported efficacy and safety of melatonin may reflect only the short-term effects of melatonin. Long-term safety and efficacy studies are needed for melatonin and especially for melatonin's agonists, particularly considering the pharmacological activity of their metabolites.

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