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Melatonin agonists in primary insomnia and depression-associated insomnia: are they superior to sedative-hypnotics?

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Abstract

Current pharmacological treatment of insomnia involves the use of sedative-hypnotic benzodiazepine and non-benzodiazepine drugs. Although benzodiazepines improve sleep, their multiple adverse effects hamper their application. Adverse effects include impairment of memory and cognitive functions, next-day hangover and dependence. Non-benzodiazepines are effective for initiating sleep but are not as effective as benzodiazepines for improving sleep quality or efficiency. Furthermore, their prolonged use produces adverse effects similar to those observed with benzodiazepines. Inasmuch as insomnia may be associated with decreased nocturnal melatonin, administration of melatonin is a strategy that has been increasingly used for treating insomnia. Melatonin can be effective for improving sleep quality without the adverse effects associated with hypnotic-sedatives. Ramelteon, a synthetic analog of melatonin which has a longer half life and a stronger affinity for MT1 and MT2 melatonergic receptors, has been reportedly effective for initiating and improving sleep in both adult and elderly insomniacs without showing hangover, dependence, or cognitive impairment. Insomnia is also a major complaint among patients suffering from depressive disorders and is often aggravated by conventional antidepressants especially the specific serotonin reuptake inhibitors. The novel antidepressant agomelatine, a dual action agent with affinity for melatonin MT1 and MT2 receptors and 5-HT2c antagonistic properties, constitutes a new approach to the treatment of major depressive disorders. Agomelatine ameliorates the symptoms of depression and improves the quality and efficiency of sleep. Taken together, the evidence indicates that MT1 / MT2 receptor agonists like ramelteon or agomelatine may be valuable pharmacological tools for insomnia and for depression-associated insomnia.

Abbreviations:

5-HT2c (serotonin 2c receptor)

CYPA2 and CYP1A (cytochrome P450 monooxygenases)

EMEA (European Medicines Agency)

GABA (gamma-aminobutyric acid)

LY 156735 (beta-methyl-6–chloromelatonin)

LPS (latency to persistent sleep)

MASSA (melatonin agonist and selective serotonin antagonist)

MDD (Major depressive disorder)

MT1 and MT2 (melatonin receptors)

PSG (polysomnography)

SCN (suprachiasmatic nucleus)

SSRI (selective serotonin reuptake inhibitor)

TST (total sleep time)

US FDA (Food and Drug Agency USA)

1. Introduction

Insomnia is a common disorder seen in nearly 30 - 35% of the adult population becoming chronic in about 10% of the population (Summers et al. 2006). The risk of insomnia is greatest in the elderly. Symptoms of insomnia include poor sleep quality, difficulty in falling asleep, frequent awakenings during the night and early morning awakenings. The sequelae of insomnia, which include fatigue and reduced alertness, have a major negative impact on the quality of life of affected individuals (Cricco et al. 2001; Vgontzas and Kales 1999), causing daytime symptoms such as fatigue, irritability and impaired concentration (Walsh et al. 2000)

Because of its broad physiological and psychological impact, insomnia has social consequences, including reduced productivity and an increased risk of accidents, both at home and in the workplace.

The overall economic burden of insomnia has been estimated to be $13.9 billion annually in the USA, with a large majority of the costs attributable to nursing home care (Stoller 1994; Walsh 2004).

Insomnia is not only a leading cause of mental impairment, it is also a major symptom of both short term psychological stressors as well as long standing psychiatric illness (Drake et al. 2003; Lam 2006). Since insomnia can reduce human effectiveness in dealing with everyday life pressure, and can even compromise the immune system (Irwin et al. 2003), it is not surprising that it has been reported to be associated with increased human mortality (Kamel and Gammack 2006).

Appropriate treatment of insomnia involves pharmacologic interventions as well as lifestyle changes to improve sleep quality. Non pharmacologic interventions include behavioral techniques such as sleep hygiene, relaxation therapies, stimulus control, sleep restriction and cognitive therapies (Montgomery and Dennis 2004; Morin et al. 1999; Morin et al. 1999).

2. Pharmacologic interventions for insomnia

Pharmacotherapy has been the most useful intervention for treating both primary and secondary insomnia. Currently used sedative-hypnotic agents include both benzodiazepines and non-benzodiazepine drugs that act mainly through gamma-aminobutyric acid (GABA)A receptors. It is thought that GABAergic neurons in the brain play a major role in sleep-induction and maintenance systems (Fuller et al., 2006).

Since reports of a significant correlation between low melatonin production and insomnia (Haimov et al., 1994; Leger et al., 2004; Rodenbeck et al., 1998), there has been a continuous interest in the possible therapeutic use of melatonin in primary and secondary insomnia. Because of its low toxicity and lack of adverse effects, melatonin could be an ideal pharmacological agent (Zhdanova, 2005). However the very short half life of exogenously administered melatonin has hampered its application. To overcome this drawback, a slow release preparation of melatonin (CircadinTM, Neurim) was introduced in the market, being recently approved by the European Medicines Agency (EMEA) for its use in elderly insomniac patients (Garfinkel et al., 1995; Leger et al., 2004; Wade et al., 2007). Another strategy has been the development of melatonin analogs of longer half-life and more potent action on receptors. Ramelteon, a melatonin MT1/MT2 receptor agonist, one of these compounds, has been approved by the US FDA for treating insomnia and is presently used successfully (Richardson et al., 2009). Compared to exogenously administered melatonin, ramelteon and its active metabolites has a longer half-life, a more rapid onset of action and produce a greater clinical response (Miyamoto, 2009; Pandi-Perumal et al., 2007). Agomelatine is a unique antidepressant that is a melatonin agonist and selective serotonin antagonist (MASSA) developed by Servier, France. It has an antidepressant action while also improving sleep efficiency and latency (Kasper et al., 2010). The purpose of this review is to analyze and compare the beneficial effects of conventional hypnotic drugs and melatonergic drugs in treating primary and secondary insomnia.

2.1 Benzodiazepines

Benzodiazepines such as estozolam, flurazepam, quazepam or triazolam are commonly used for the short-term management of insomnia (Morin, 2006). Benzodiazepines exert sedative actions through activation of BZ1(ω1) and BZ2(ω2) receptor subtypes of the GABAA receptor complex, of which the activation of BZ1(ω1) accounts for their specific hypnosedative, anxiolytic and anticonvulsant activities (Carlson et al., 2001). The α1 subunit of the GABAA receptor is the receptor complex that mediates the sedative and anxiolytic properties of benzodiazepines (Sanna et al., 2002).

Since their introduction benzodiazepines have been the focus of numerous evaluative investigations for their effect on sleep. In a metaanalysis of 22 studies Nowell and colleagues (1997) concluded that, as compared to placebo, benzodiazepines produced significant decreased latency to sleep onset and augmented total sleep duration and sleep quality. However, because of their adverse effects, benzodiazepines are controversial as a long term therapy (Morin, 2006). Among benzodiazepines' adverse effects, next-day hangover, cognitive and psychomotor impairment, anterograde amnesia, rebound insomnia and potential for abuse are relevant. Next-day hangover, which is often associated with headache, dizziness and decreased mental alertness, is the most frequently reported complaint made by benzodiazepine users (Roth et al., 2007a).

2.2 Non-benzodiazepines

The currently used non-benzodiazepine hypnotics include zolpidem, zaleplon and eszopiclone. Of these, zolpidem, an imidazopyridine derivative, has a rapid onset of action and high affinity for the GABAA- α1-subunit, but less affinity for α2- and α3-subunits than benzodiazepines (Sanna et al., 2002). A number of studies using zolpidem at a standard dose of 10 mg/day have revealed that it improves sleep maintenance only in the initial stages but that the improvement disappears beyond two to four weeks (Morin, 2006; Rosenberg, 2006). Moreover zolpidem is associated with adverse events such as daytime drowsiness, dizziness, headache, and nausea and vomiting. It has also the potential for abuse and dependence (Victorri-Vigneau et al., 2007). These problems are reduced or eliminated when zolpidem is used intermittently rather than every night (Parrino et al., 2008; Walsh et al., 2000a).

Zaleplon, a pyrazolopyrimidine derivative with high affinity and selectivity for the α1-subunit of the GABA-A receptor, which is usually administered at doses of 10 mg in adults and 5 mg in the elderly, decreases sleep latency with no effect on total sleep time or number of awakenings (Elie et al., 1999; Fry et al., 2000; Weitzel et al., 2000). The effects of zaleplon on sleep quality have been shown to be consistent and persisted throughout a 4 week trial period (Morin, 2006). Zaleplon decreases sleep latency in elderly patients at both 5 mg and 10 mg doses. The effect on total sleep time and number of

awakenings is only mild and variable (Ancoli-Israel et al., 1999; Hedner et al., 2000; Walsh et al., 2000b). In one study the efficacy of zaleplon (at 5 mg or 10 mg doses) persisted for up to 12 months (Ancoli-Israel et al., 2005). Like the other non-benzodiazepine agents zaleplon can cause complex sleep-related behavior on rare occasions (Molina and Joshi, 2010). There is a report that zaleplon increases nocturnal melatonin secretion early in sleep (Morera et al., 2009). A number of studies have shown that zaleplon has fewer residual effects than other drugs including lorazepam, zolpidem and zopiclone (Allen et al., 1993; Drover et al., 2000; Paul et al., 2003) .Moreover, zaleplon at 10-20 mg doses does not cause significant driving impairment (Vermeeren, 2004). Zaleplon did not cause any rebound or withdrawal effects at 5-20 mg doses over a period of 2-5 weeks (Ancoli-Israel et al., 1999) and there was no evidence of withdrawal effects during the course of 12 month treatment with 10 mg zaleplon (Ramakrishnan and Scheid, 2007). Because of zaleplon's efficacy and safety in promoting sleep initiation, it has been suggested as useful for treating sleep initiation difficulties (Montplaisir et al., 2003; Morin, 2006). Zaleplon's short duration of action can be beneficial for shift-workers wanting to undergo a second short sleep period before beginning to work (Montplaisir et al., 2003).

Zopiclone and its active stereoisomer eszopiclone are cyclopyrroline derivatives that are agonists at the α1-subunit of the GABAA receptor (Morin and Willett, 2009). Eszopiclone has greater binding activity at the GABAA receptor then the racemic zopiclone (Blaschke et al., 1993) and has fewer anticholinergic side effects. Both zopiclone and eszopiclone have demonstrated efficacy and safety in patients with primary insomnia, as confirmed by patient self reports as well as by polysomnography (PSG) (Hair et al., 2008; Krystal et al., 2003; Morin and Willett, 2009; Zammit et al., 2004). In a 6 month, double blind placebo controlled trial, 3 mg of eszopiclone improved self-reported assessment of sleep initiation, sleep maintenance, sleep quality and sleep duration (Krystal et al., 2003). There was no report on either tolerance or diminished efficacy over the study period. When this study was further extended for another 6-month period eszopiclone was well tolerated, with no reports of withdrawal or discontinuation of treatment.

Non-benzodiazepine sedative-hypnotics have been effective in reducing sleep latency but only moderately effective in increasing total sleep time and sleep efficiency. Both benzodiazepine and non-benzodiazepine drugs are associated with adverse side effects such as impairment of memory and cognition, psychomotor retardation and next day hangover effects and both share the potential for producing tolerance and dependency (Bellon, 2006; Zammit, 2009).

Ideally, a hypnotic agent should not only decrease sleep latency but should also increase total sleep time and sleep efficiency (Turek and Gillette, 2004). Moreover usage of such a hypnotic drug should not produce undesired effects such as residual sedation, cognitive or psychomotor impairment or potential of abuse (Roth et al., 2006). Walking, eating, driving or engaging in other activities while asleep without remembering it the next day have been reported for many of benzodiazepine and non-benzodiazepine drugs (Ayadi et al., 1998; Molina and Joshi, 2010; Simmer, 1999). Because all available options of insomnia treatment have some serious flaws (Egger et al., 2006) efforts have been undertaken to develop sleep promoting agents that are better tolerated and have a more acceptable side effect profile after long-term administration (Srinivasan et al., 2009).

2.3 Melatonin and insomnia

The first clinical evidence for the involvement of melatonin in sleep was obtained by Aaron Lerner, the discoverer of melatonin (Lerner 1958, 1959). Lerner and Case (1960) administered 200 mg of melatonin intravenously to two volunteers who became sleepy. Subsequently Lerner and his collaborators treated 5 patients with hyperpigmentation using prolonged ingestion of 1 g melatonin daily (Nordlund and Lerner 1977). They noted that all patients became drowsy. Further suggestions of melatonin's importance for sleep derived from speculations that the decrease in melatonin production with age could be responsible for the increase in sleep disruptions seen in the elderly (Brown et al., 1979; Haimov et al., 1994; Iguchi et al., 1982).

Melatonin replacement therapy has been shown to be beneficial in treating elderly insomniacs (Bellipanni et al., 2005; Dollins et al., 1994; Garfinkel et al., 1995; Leger et al., 2004; MacFarlane et al., 1991; Monti et al., 1999; Zhdanova et al., 1995; Zhdanova et al., 1996). Reduced endogenous melatonin production seems to be a prerequisite for effective exogenous melatonin treatment of sleep disorders. In Alzheimer's disease in which melatonin is also reduced, melatonin has not been shown to be effective(Gehrman et al. 2009). However in Alzheimer's disease there is a functional disruption of the suprachiasmatic nuslei (SCN) clock genes(Wu et al. 2006) together with greatly diminished expression of the MT1 receptors in the SCN(Wu et al. 2007). Moreover there are decreases in MT1 and MT2 receptor immunoreactivity in both pineal and cortex(Brunner et al. 2006) as well as increased MT1 (Savaskan et al. 2002) and decreased MT2 (Savaskan et al. 2005) reactivity in the hippocampus so that effects of melatonin are likely to be altered, especially in the later stages of the disease(Wu and Swaab 2007).

A survey on the effects of melatonin in sleep disturbances, including all age groups (and presumably individuals with normal melatonin levels), failed to document significant and clinically meaningful effects of exogenous melatonin on sleep quality, efficiency and latency (Buscemi et al., 2004). In contrast, a metaanalysis undertaken including 17 different studies with 284 subjects, most of whom were older, concluded that melatonin is statistically effective in increasing sleep efficiency and reducing sleep onset time (Brzezinski et al., 2005). Based on this, the use of melatonin in the treatment of insomnia, particularly in aged individuals with nocturnal melatonin deficiency, was proposed. However, the metaanalysis included various different preparations of melatonin, most of which were very short acting and hence would not be expected to have major effects on sleep efficiency. Circadin, the slow release preparation of melatonin recently approved by the EMEA, has proven to be effective in increasing sleep quality, morning alertness and quality of life in middle aged and elderly insomniac patients (Garfinkel et al., 1995; Leger et al., 2004; Wade et al., 2007; Lemoine et al. 2007).

2.3.1 Basic physiology of melatonin

Melatonin is secreted by the pineal gland mainly at night with maximum plasma levels occurring between 02.00 to 03.00 AM (Arendt and Skene, 2005). The half life of melatonin is 20 - 30 min (Claustrat et al., 2005). The low bioavailability of orally administered melatonin has been attributed to its first pass metabolism in the liver due to the activity of cytochrome P450 monooxygenases (CYPA2 and CYP1A) which metabolize substantial amounts of the methoxyindole (Fourtillan et al., 2001).

Melatonin has both sedating and entraining effects.

As initially shown by Norlund and Lerner (1977) and confirmed by several others melatonin has a sleep inducing effect when given in large doses. There have been numerous other reports of sedation following doses of melatonin ranging from 50 to 1000 mg, and with little or no side effects (Carman et al. 1976; Dollins et al. 1993; Lieberman et al. 1984; Vollrath et al. 1981; Waldhauser et al. 1987). In 1984 Arendt and coworkers reported that a lower dose of 2 mg given daily to volunteers for 4 weeks at 5 pm significantly increased self-rated fatigue(Arendt et al. 1984), however even this smaller dose resulted in blood levels 10 to 100 times physiologic peaks. Another study reported that not only did evening melatonin treatment in doses of 3 or 6 mg shorten sleep latency and improve sleep efficiency but that subjects reported that sleep was “deeper” (Nave et al. 1995). Moreover, doses as low as 0.3 mg of melatonin that produce blood levels in the physiologic range are now known to induce sleepiness when given in the early evening (Zhdanova et al. 1995; Zhdanova et al. 1996). Several studies have shown a sleep promoting effect of melatonin administered during the day in doses ranging from 0.1 to 10 mg (Dollins et al. 1993; Dollins et al. 1994; Hughes and Badia 1997; Nave et al. 1996; Pires et al. 2001; Reid et al. 1996; Tzischinsky and Lavie 1994; Wyatt et al. 2006). The soporific effect of melatonin has been shown to be dependent on the circadian phase(Tzischinsky and Lavie 1994; Wyatt et al. 2006) and a study by Smith and coworkers showed a minimal action of morning melatonin administration on daytime sleep following night shift work(Smith et al. 2005). It has been theorized by several authors that melatonin antagonizes an SCN-dependent alerting mechanism (Dijk and Cajochen 1997; Sack et al. 1997; Scheer and Czeisler 2005; Shochat et al. 1997). This concept arises from the belief that the sleep-wake cycle is governed by two processes, a drive for sleep that increases during wakefulness (and decreases during sleep) that is opposed by a circadian process controlled the SCN (Daan et al. 1984). Together these processes control the timing and propensity for sleep and wakefulness.

Redman and colleagues were first to establish that daily injections of melatonin entrained the rest-activity cycle in the rat when given at the appropriate time in the cycle (Redman et al. 1983). Subsequently Arendt and coworkers documented phase advancing effects of melatonin in humans(Arendt et al. 1985) and since then both phase response curves with nearly symmetrical advances and delays (Lewy et al. 1992) have been documented by several groups (Zaidan et al. 1994;Middleton et al. 1997;Lewy et al. 1998). However, Wirz-Justice and coworkers (2002) found no evidence for phase delay after a single morning melatonin injection suggesting that morning melatonin may be a weak cue that requires repeated administration and Crowley and coworkers (2003) reported that morning melatonin treatment did not significantly increase circadian adaptation to shift work.

Melatonin exerts its physiological actions through G-protein coupled membrane MT1 and MT2 melatonin receptors (Dubocovich et al., 2000). These receptors are expressed in the hypothalamic SCN of humans, the biological clock that regulates circadian rhythms, including the secretion of pineal melatonin itself (Weaver and Reppert, 1996). Melatonin inhibits SCN firing via MT1 receptors (von Gall et al., 2002), and activation of MT2 receptors in the SCN mediate melatonin's phase shifting effects (Dubocovich et al., 2000; Hunt et al., 2001). These effects which are presumably linked to the activation of GABAergic mechanisms in the SCN (Golombek et al., 1996; Wan et al., 1999) are the putative mechanisms by which melatonin contributes to the circadian timing of the sleep-wake cycle by activating the "sleep switch". The sleep switch model, originally proposed by Saper and colleagues (Saper et al., 2005), states that there are "flip-flop" reciprocal inhibitions among various brain nuclei associated with sleep and wakefulness. Because MT1 and MT2 receptors are now known to be widespread in brain (Brunner et al., 2006; Mazzucchelli et al., 1996; Savaskan et al., 2005; Uz et al., 2005; Wu et al., 2006), the soporific effect of melatonin at higher pharmacologic doses may be related to actions at sites other than the SCN. This may explain the strong sleep promoting action of high doses of melatonin and ramelteon (Fisher et al. 2008) and of the potent MT2 agonist (IIK7) in the rat (Fisher and Sugden, 2009). The test situation was one in which the agents were administered half way through the dark cycle at a time when these nocturnal animals were usually awake.

It has been shown that sleep quality and quantity are maximal if sleep occurs at the optimal circadian phase (Czeisler et al. 1980;Dijk and Czeisler 1994). Because melatonin has both phase shifting and soporific effects its actions should be maximized when it is administered daily at bedtime time in order to stabilize the circadian phase while simultaneously promoting sleep thus taking full advantage of both actions.

As above mentioned, since melatonin has a short half-life, a number of long acting melatonin agonists have been developed that could also have twin sleep promoting and rhythm regulating actions.

2.4 LY 156735

The chlorinated derivative of melatonin, LY 156735 (Beta-methyl-6–chloromelatonin), is a MT1/MT2 agonist whose chronobiotic effects have been documented after a nine hour simulated phase shift(Nickelsen et al. 2002). The pharmacokinetics, pharmacodynamics and safety of LY 156735 was examined in a placebo controlled study using escalating doses of 20, 35, 50 and 100 mg in eight healthy volunteers(Mulchahey et al. 2004). LY 156735 produced sleepiness at all doses and unlike melatonin treatment (Gilbert et al. 1999; Kitajima et al. 2001; Sletten et al. 2001; Sletten et al. 2001) did not cause effects such as such as hypothermia, hypotension or bradycardia. In a double blind study 40 patients with chronic insomnia randomly received each of 20 mg, 40 mg, 100 mg and placebo on two consecutive nights with a 5 day washout between treatments. LY 156735 showed significantly improved subjective and objective measures of sleep onset latency at the higher doses and a trend to improvement at the 20 mg doses(Zemlan et al. 2005). Recent studies in a rat model of spinal cord injury have suggested that LY 156735 is a potential treatment for this disorder (Fee et al. 2010) .

2.5 Ramelteon

Ramelteon (RozeremTM) 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-8yl)ethyl propionamide), developed by Takeda Pharmaceutical Company, Japan, and approved as a novel hypnotic agent by the American Food and Drug Administration in 2005. Like melatonin, ramelteon acts on both MT1 and MT2 receptors (Miyamoto, 2009; Pandi-Perumal et al., 2007), although unlike melatonin its action persists for a longer time..

Ramelteon is usually administered orally in the evening at a dose of 8 mg. After oral administration, ramelteon is rapidly absorbed with a Tmax of less than 1 h (Stevenson et al., 2004a,b). It is metabolized mainly in the liver by oxidation to hydroxyl and carbonyl derivatives which are then conjugated with glucuronide. CYP1A2 is the major isozyme involved in the hepatic metabolism of ramelteon; the CYP2C subfamily and CYP3A4 isozymes are involved to a lesser degree (Karim et al. 2006). Four principal metabolites of ramelteon, named M-I, M-II, M-III, and M-IV, have been identified. Of these M-II occurs at a much higher concentration with a systemic level 20-100-fold greater than ramelteon itself. The ramelteon metabolite M-II also acts as a MT1/MT2 agonist. The potency of M-II is only 10% of its parent compound, however its levels are about 30 fold higher and its half life (2-5 h) is longer than that of ramelteon, thus it may account for ramelteon's considerably extended therapeutic half life (Karim et al., 2006).

2.4.1 Clinical trials with ramelteon

Ramelteon has been found effective in treating patients with chronic insomnia. In a double blind randomized crossover investigation by Erman et al. (2006) involving 117 patients aged 16 to 64 years drawn from 13 centers in Europe, efficacy, safety and dose response of ramelteon were evaluated. Each patient in the study was randomized to a dose sequence of 4, 8, 16 and 32 mg of ramelteon. In subjects who completed the study (103 patients) all doses of ramelteon produced a statistically significant reduction in time to reach persistent sleep (LPS) and increased total sleep time (TST) as measured by (PSG). In a subgroup analysis those with screening LPS that was >66.5 min experienced dramatic reductions in LPS. Mean LPS was 26.2 to 29.8 across the various treatment groups as compared to 48.8 min for placebo. In contrast those with screening LPS < 66.5 showed a more modest effect. LPS was 15.7 to 21.8 across doses while the placebo group had an LPS of 26.2. Only the 32 mg dose showed a significant effect ($p < 0.05$). TST changes though significant in all groups were modest (placebo 400.2 min and various dose groups 422.0 to 418.3). An important observation from this study was that ramelteon did not produce residual sedation, psychomotor retardation or memory impairment.

The efficacy of ramelteon has been evaluated in 829 outpatients (> 65 years) suffering from chronic insomnia of which 128 discontinued their treatment (Roth et al., 2006). In this double blind study ramelteon was given in doses of 4 to 8 mg/day for a total period of 5 weeks. Both doses of ramelteon caused significant reductions in sleep onset latency (16% to 35%) at the end of one, three and five weeks. Moreover the superiority of ramelteon over placebo in reducing latency was consistently demonstrated at both doses. At 5 weeks sleep latency for placebo was 70.6 min, for 4 mg. was 63.4 min and for 8 mg was 57.7 min. Total sleep time was also increased by both doses of ramelteon. However, ramelteon did not improve the patient's perceived sleep quality and next day performance compared with placebo. Sleep promotion was independent of dose as was also reported in the study by Erman and coworkers (2006).

In another study a decrease of LPS, TST and improved sleep efficiency was reported in a two night three period crossover design with doses of 4 and 8 mg of ramelteon in 100 elderly patients recruited from 17 sleep centers (Roth et al., 2007b). LPS for 4 mg (28.7 min) and 8 mg (30.8 min) differed from placebo (38.4 min, $p < 0.001$ for 4 mg and $p = 0.005$ for 8 mg). TST for 4 mg and 8 mg differed significantly from placebo (359.4 min., 362.0 min and 350.4 min.) although the effect size was small. Sleep efficiency for 4 mg and 8 mg also differed significantly from placebo (74.9%, 75.5% and 73.1%) although the effect size was very small.

The efficacy of ramelteon in different doses was evaluated in yet another multicenter double blind placebo controlled study 5 week that included 29 sleep laboratories (Zammit et al., 2007). Ramelteon was administered in both 8 mg/day and 16 mg /day doses to 405 patients aged 18 to 64 years suffering from chronic insomnia. Of these, 371 patients completed the double blind study, while 367 completed the single blind follow up. PSG was used for sleep evaluation. Primary outcome measure was LPS that was significantly reduced with both doses of ramelteon as compared to placebo at the end of week one (placebo, 47.9 min; 8 mg. 32.2 min; 16 mg 28.9 min). This difference persisted through to week 5 (placebo 42.5 min; 8 mg 31.5 min; 16 mg 29.5 min). Total duration of sleep also was prolonged with both doses of ramelteon but only at week one (placebo 375.2 min; 8 mg 394.2 min; 16 mg 397.6 min). In a later study including 289 adult subjects, ramelteon at both 8 mg and 16 mg doses significantly reduced latency to persistent sleep. Total sleep time was also significantly increased by both doses of ramelteon (Zammit, 2009).

In yet another study ramelteon given at a 8 mg dose, caused reductions in LPS at week 1 (63% for ramelteon vs. 39.7 % for placebo, $P < 0.001$) (Mini et al., 2008). At the end of week 3 the reduction in the same parameter was 63% with ramelteon and 41.2% with placebo ($P < 0.01$) while at the end of week 5, it was 65.9% with ramelteon and 48.9% with placebo ($P < 0.05$). Therefore improvement in LPS was sustained throughout the study.

Ramelteon (8 mg) was also evaluated in a six month PSG study including 451 adults (> 18) with chronic insomnia (Mayer et al., 2009). This multicenter trial involved 46 centers in USA, Europe, Russia and Australia. Over the study period ramelteon consistently reduced LPS sleep as compared to placebo. The baseline LPS decreased from 70.75 min to 32.02 min at week one with ramelteon and then remained around the same level at subsequent visits (months 1, 3, 5 and 6). The difference in LPS from placebo

was about 15 min at week one and then about 9 minutes at each of the subsequent visits. No adverse events such as next morning residual effects, withdrawal symptoms, or rebound insomnia were found.

In another 6-week long study conducted on 20 healthy menopausal women, 8 mg ramelteon significantly decreased LPS and augmented TST and sleep efficiency (Dobkin et al., 2009). There was no evidence of either tolerance or rebound insomnia.

Taken together the above studies suggest that ramelteon has a clinically useful effect in improving sleep latency while effects on total sleep time and sleep efficiency, though significant may not be clinically meaningful.

Because of its greater potency over melatonin in influencing melatonin MT1 and MT2 receptors it has been suggested that prolonged use of ramelteon could cause desensitization of melatonin receptors in the SCN. However no evidence for such an effect has been reported even though unlike melatonin which has a very short half-life the active ramelteon metabolite M-II has an extended half-life.

In the 2006 study by Erman and coworkers the incidence of side effects was similar to the placebo group. The most common were headaches 4.9%, 5.8%, 4.8%, 4.7%, and 5.8%; somnolence 1.0%, 0.0%, 1.9%, 3.7%, and 1.9%; and sore throat 1.0%, 3.9%, 0.0%, 0.0% and 3.9% for placebo and ramelteon 4 mg, 8mg, 16 mg and 32 mg respectively. One patient receiving 4 mg. ramelteon had a severe sinus headache considered to be possibly related to the treatment. In the Roth and coworker study (2006) the incidence of adverse effects was also in general similar to the placebo group with the most common being dizziness 6.6%, 6.8% and 8.4% and headache 4.4%, 4.3% and 5.8% for placebo and ramelteon 4 mg and 8 mg respectively. One patient who received 8 mg of ramelteon had a transient ischemic attack that was determined to be possible related to the study medication. The Roth et al. (2007) study reported headache in 1.0%, 4.0% and 3.0% and nausea in 0.0%, 5.0% and 2.0% in the placebo, 4mg and 8mg ramelteon groups respectively. One subject in the placebo group had a sinus headache considered severe but no subjects withdrew from the study. In the Zammit et al. study (2007) the most common adverse event was headache and the incidence was similar in all groups, 18.3% for the placebo group, 19.4 % for 8 mg ramelteon and 17.8 % for 16 mg ramelteon. The other common events were somnolence 1.5%, 7.9% and 7.4%; fatigue 2.3%, 9.4% and 4.4% and nausea 2.3%, 4.3% and 4.4% for the placebo, ramelteon 8 mg and ramelteon 16 mg respectively. Thus in general the drug was well tolerated.

In addition ramelteon did not produce any memory, cognitive (Erman et al. 2006; Roth et al. 2007) or psychomotor impairment (Erman et al. 2006; Roth et al. 2005; Roth et al. 2007; Zammit 2007) and in general did not differ from placebo. Furthermore, it did not produce any next day hangover effects or discontinuation related rebound insomnia or withdrawal symptoms (Johnson et al. 2006; Roth et al. 2006; Mayer et al. 2009).

In a study of endocrine effects of 6 month treatment with 16 mg of ramelteon in adult insomnia patients (18 to 45 years) no effects were seen on thyroid, adrenal and most reproductive functions (Richardson and Wang-Weigand 2009). However, transient elevated prolactin levels were found in women, although there were no effects on average menstrual cycle length, duration of menses, and ovulation probability.

Caution is advised with respect to potential drug-drug interactions. Co-administration with the cytochrome P450 enzyme (CYP3A4) inhibitors ketoconazole and fluconazole have been shown to increase the area under the plasma or serum concentration-time curve and increase the maximum concentration and half-life of ramelteon (Thomson PDR 2010; Thomson PDR 2010; Karim et al. 2004). In contrast the CYP3A4 inducer will result in reduced exposure to ramelteon (Thomson PDR 2010). Fluvoxamine, which is a strong CYP1A2 inhibitor will cause increased exposure to ramelteon (Thomson PDR 2010).

Together, data gathered from clinical studies indicate that ramelteon is a benign agent that has major advantages over conventional sedative-hypnotics in treating chronic insomnia as well as insomnia associated with other medical and psychiatric illnesses. It should be noted however, as pointed out by Wurtman (2008), that there is a paucity of long term studies with ramelteon. Hence its safety with extended administration should be further investigated before it is considered for that use. MT1 and MT2 receptors are now known to be widespread in the brain and the body. What will be the effect of continuing exposure to ramelteon? Moreover certain rare adverse events have been reported with hypnotics only in post marketing surveillance. These include not only allergic reactions but also complex sleep behaviors which have been reported in individual case reports (Zammit 2009). These have not been reported with ramelteon but possibly might appear with long term treatment.

2.6 Tasimelteon

Tasimelteon (VEC-162 previously BMS-214778) {(1R-trans)-N-[[2-(2,3-dihydro-4-benzofuranyl)cyclopropyl] methyl] propanamide} is a MT1/MT2 agonist. In animal studies it has been shown to have phase shifting properties that are similar to melatonin but with less vasoconstriction(Vachharajani et al. 2003). In a phase II study of transient insomnia after a 5 hour phase advance, 39 healthy individuals from two US sites randomly assigned to tasimelteon (10, 20, 50, or 100 mg or placebo (n=8) showed a shift in the melatonin rhythm, reduced sleep latency and increased sleep efficiency after tasimelteon compared with placebo(Rajaratnam et al. 2009). Moreover in a phase III study of a five hour phase advance including 411 healthy individuals from 19 US sites comparing the same doses, tasimelteon improved sleep latency, sleep efficiency, and wake after sleep onset (i.e., sleep maintenance) (Rajaratnam et al. 2009). In both studies side effects did not differ from placebo.

3. Sleep disturbances in depression and the use of sedative-hypnotics

Depression is ranked as one of the top 10 causes of morbidity and mortality (Rosenzweig-Lipson et al., 2006) sleep disturbance being one of the most prominent features of the illness (Armitage, 2007), as well as being one of the DSM-IV diagnostic criteria for depression (American Psychiatric Association, 2000). Patients suffering from major depressive disorder (MDD) or bipolar depressive disorder exhibit

marked difficulties in initiation and maintenance of sleep, poor quality of sleep and frequent nocturnal and early morning awakenings (Lam, 2006; Riemann et al., 2001).

Chronic insomnia is the most commonly reported complaint in depression. The NIMH Epidemiologic Catchment Area (ECA) study of sleep disturbances and psychiatric disorders has identified sleep disturbances as a highly significant risk factor for subsequent development of depression (Ford and Kamerow, 1989). PSG studies in depressives reveal reductions in EEG delta waves during the first non-rapid eye movement (NREM) sleep period (Buysse, 2005). The temporal distribution of delta waves is also altered in depression.

Altered intra night temporal distribution of REM sleep with increased amounts of early REM sleep and reductions in REM latency are the specific EEG sleep pattern that has been associated with depression. Decreased REM sleep latency is commonly seen in depressive disorders and patients with decreased REM sleep latency prior to treatment have increased risk for depression (Giles et al., 1987). Increased incidence of depressive symptoms correlates with poor sleep quality, and chronic insomnia disturbances appear to be a major risk factor for depression. Prevention of persistent sleep disturbance may help to reduce the risk of relapse or recurrence of depression (Lustberg and Reynolds, 2000).

3.1 Use of antidepressants and insomnia

Not only depressive disorder per se but also antidepressant drug therapy can worsen the symptoms of insomnia. There is now considerable evidence that a number of commonly prescribed antidepressants including the tricyclics, monoamine oxidase inhibitors (MAOIs), serotonin-norepinephrine (NE) reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRIs) may aggravate sleep complaints (Pandi-Perumal et al., 2008).

Currently SSRIs are the drugs of choice for the treatment of depressive disorders. SSRIs constitute 80% of the prescriptions of all antidepressants (Celada et al., 2004). Despite their widespread use SSRIs have numerous side effects, the most prominent being their disturbing effects on sleep and sexual function (Moltzen and Bang-Andersen, 2006). It is reported that nearly 25% of depressed patients treated with SSRIs complain of symptoms of insomnia (Armitage, 2007). For example, the SSRI sertraline has been found to prolong sleep onset latency and reduce total sleep time within 14 days after treatment of depressive patients (Winokur et al., 2001). Similarly, the use of fluoxetine resulted in reductions of sleep efficiency (Winokur et al., 2001).

Due to the increasing awareness of these effects, co-prescription of sedative hypnotic agents has become a common practice for managing insomnia associated with depression. Among the most frequently represented sedative-hypnotics which are prescribed along with antidepressants are the benzodiazepines. However, despite their use for this purpose for nearly 20 years, there continues to be

a lack of controlled PSG studies that assess the effectiveness of benzodiazepines as an add-on therapy with either SSRIs or SNRIs in MDD (Thase, 2007).

Although the sedative-hypnotics counteract the sleep onset latency changes after antidepressants, they have several side effects and their prolonged use may result in dependence. Hence, there is a clear necessity to develop an effective treatment strategy for sleep problems associated with depression. An ideal antidepressant should decrease sleep onset latency and waking after sleep onset as well as maintain alertness and well-being throughout the day (Kupfer, 2006).

3.3 Agomelatine

Agomelatine is a melatonin agonist and selective serotonin antagonist. It is a unique antidepressant with MT1 and MT2 receptor agonist activity that also has 5-HT2c antagonist properties. Agomelatine is a naphthalenic compound with an overall selectivity for MT1 and MT2 receptors but no significant affinity to muscarinic, histaminergic, adrenergic or dopaminergic receptor subtypes (Rouillon, 2006). Agomelatine has a short plasma half-life (1–2 h). It is metabolized primarily by the cytochrome CYP 450 1A2 (90%) and 2C9 (10%) isoenzymes, with initial hydroxylation (1A2) and demethylation (2C9), followed by glucuronide conjugation and sulphonation.

In multicenter trials undertaken in Europe (Kennedy and Emsley, 2006; Kupfer, 2006; Loo et al., 2002) agomelatine at a dose of 25 mg/day was found to be effective in reducing the depressive symptoms in patients with MDD. The effectiveness of agomelatine in severely depressed patients is particularly significant inasmuch as this patient group is resistant to SSRIs or SNRIs.(Loo et al., 2002) Agomelatine represents an innovation in the treatment of depression because it has few adverse effects and is associated with early resolution of depressive symptoms (den Boer et al., 2006).

In addition agomelatine is effective in reducing sleep complaints in depressed patients. Treatment of depressed patients with agomelatine for six weeks increased the duration of NREM sleep without affecting REM sleep thus causing improvements in both sleep quality and continuity (Quera Salva et al., 2007). In a study which compared agomelatine with venlafaxine, agomelatine at 25 mg/day promoted earlier and greater improvements on the “criteria of getting into sleep” in a Leeds sleep evaluation questionnaire (Guilleminault, 2005). The improvement in sleep quality was evident at the first week of agomelatine, but not of venlafaxine, use. In another study it was reported that agomelatine normalizes NREM sleep changes found in depressed patients. The changes in NREM preceded the improvement seen in Hamilton depression score (Lopes et al., 2005; Lopes et al., 2007). Agomelatine is thus a dual action drug that can produce rapid antidepressant effects while also improving sleep quality. This is very important clinically inasmuch as improvements in sleep among depressed patients are associated with a reduced rate of recurrence of depressive symptoms and, conversely, complaints of poor sleep in depressed patients are associated with a poor response to subsequent antidepressant treatment (Kupfer, 2006; Zupancic and Guilleminault, 2006). A recent study provides strong support for the

superior chronobiological effects of agomelatine in patients with MDD(Kasper et al., 2010). As compared to sertraline, agomelatine increased the relative amplitude of the circadian rest-activity cycle by the end of week one and in parallel there were improvements in sleep efficiency and in sleep latency from week one to week six. Over a six week treatment period depressive and anxiety symptoms improved more with agomelatine than with sertraline.

A possible superior efficacy of agomelatine over other antidepressants has been suggested by several investigators (Norman and Burrows, 2007). Agomelatine is unique because it has a chronobiological basis for its action. Since agomelatine effects are mediated through both MT1 and MT2 melatonergic receptors and 5-HT2c serotonergic receptors it acts differently in different circadian phases of the day-night cycle (Millan, 2006). While it promotes and maintains sleep at night, it also maintains alertness during the day. At night the sleep promoting melatonergic effects prevail over its potentially antihypnotic 5-HT2c antagonism, whereas during the day the antidepressant actions through antagonism of 5-HT2c receptors is uncoupled from melatonin's nocturnal hypnotic effects. These effects are in contrast to traditional antidepressants which elevate the mood of depressed patients of the patients during daytime, an effect that is sustained in the night causing impairment in sleep quality (Ruhe et al., 2007).

Agomelatine has an excellent safety and tolerability record, showing no difference from placebo except for dizziness (5.9% vs 3.5%; $p<0.05$) (Kennedy and Rizvi 2010). Emergent adverse events including gastrointestinal, cardiovascular, and body weight effects were generally lower than sertraline or venlafaxine in active comparative trials(Kennedy and Rizvi 2010). Moreover, antidepressant-induced sexual dysfunction was significantly lower than the SSRIs (paroxetine, sertraline and fluoxetine) and venlafaxine in both spontaneous reports and using structured instruments (Kennedy and Rizvi 2010). There were transient increases in transaminases mainly with a higher dose of 50 mg per day, with an incidence similar to that of venlafaxine. These were isolated, occurred mainly in the first month and without clinical signs and were reversible. In a study with the active comparator paroxetine, there was no evidence of discontinuation symptoms and these symptoms did not differ from those following placebo (Montgomery et al. 2004).

Because it is chiefly metabolized in the liver it should not be administered to patients with liver disease(McAllister-Williams et al. 2010). Agomelatine is contraindicated in patients receiving concomitant potent CYP1A2 inhibitors such as fluvoxamine or ciprofloxacin. However, paroxetine which is a moderate 1A2 inhibitor and fluconazole (a potent 2C9 inhibitor) have little effect on agomelatine levels (McAllister-Williams et al. 2010).

Despite the foregoing, the relationship of sleep symptoms to depression and agomelatine treatment deserves to be further examined. In particular, are those patients with a specific sleep pattern such as early morning waking or with difficulty with sleep initiation more likely to respond to agomelatine than those without that pattern? If so, would it be possible to use the sleep pattern of depressed patients to predict the likelihood of response? The answer to that question does not appear to have been addressed in any of the reports to date. A second issue that has not been considered is that existing depression rating scales include sleep symptoms as part of the scale. For instance the 17 item Hamilton

Rating Scale for depression includes three items related to insomnia and later expanded versions added diurnal variation(Hamilton 1960). Analysis of depression ratings separate from sleep symptoms is warranted to determine what part of the change is simply an improvement in sleep.

All available evidence indicates that agomelatine is very well tolerated, is as effective as other second generation antidepressants, unlike other antidepressants has little or no withdrawal effects, and also unlike them addresses the sleep disturbances and abnormalities seen in depression. Thus agomelatine is an attractive new alternative in treatment of depression.

4. Conclusions

Over the last 20 years, treatment of insomnia has relied on benzodiazepines and non-benzodiazepine drugs. The useful anxiolytic and sleep promoting properties of these agents have made them the most widely prescribed of all classes of pharmaceuticals. The drawbacks of benzodiazepines and their derivatives however are well known. They can produce cognitive and memory impairment, psychomotor retardation, next day hangover effects, and dependence. Available evidence indicates that although non-benzodiazepines are useful in reducing sleep latency, they are only moderately effective in increasing total sleep time and sleep efficiency. A need has thus been recognized for alternative sleep promoting agents.

As sleep disturbances are associated with reduced nocturnal secretion of melatonin, melatonin replacement therapy has been used to treat chronic insomnia, and also has been found effective in treating other sleep disturbances such as sleep phase delays. Melatonin's short half-life has represented one of the challenges hampering its application in therapy. The melatonin agonists ramelteon (as well as the long acting form of melatonin, Circadin) have been developed to address this concern, and in clinical trials have been effective for treating adult and elderly insomniacs in short term trials. In treating patients with ramelteon they should be advised that ramelteon has a different type of effect from the other sleeping pills. The sleep produced is more natural and that they can wake up if needed without being excessively sedated.

Unlike traditional sedative-hypnotics which induce sedation through GABAergic mechanisms (which can produce CNS depression), ramelteon has a unique chrono-hypnotic action that does not cause next day hangover effects, dependence or memory impairment. In studies done to date it has been effective in reducing LPS and also in causing a modest increase in TST. Ramelteon has been shown to have phase shifting actions in normal subjects (Richardson et al. 2008) but such studies have not yet been done in insomnia patients. No studies done to date have examined the melatonin phase of the patients. Thus effects in patients could be due either to the sleep-promoting action, the phase shifting action or by a combined action. The argument that long term use of ramelteon will result in desensitization of melatonin receptors has not been substantiated, furthermore no withdrawal reported have been seen. Hence ramelteon is considered to be a good hypnotic drug for the treatment of primary insomnia and as

well as insomnia due to other causes. On the other hand, because few long term studies have been reported such use should be employed with caution.

Since insomnia is one of the hallmark symptoms of depressive disorders, a major difficulty with conventional antidepressant therapy, especially the SSRIs, is that they often disturb sleep and may therefore increase sleep problems. Recently a novel melatonergic antidepressant with both melatonin agonist properties and 5-HT2c antagonist properties (agomelatine) has been introduced. It is effective not only for ameliorating symptoms of depressive illness and reducing depression scores, but unlike other antidepressants it improves sleep quality and reduces sleep complaints. Moreover side effects are similar to placebo, but unlike the SSRIs it shows no evidence of withdrawal symptoms and there is also no evidence of sexual dysfunction. Agomelatine is a novel dual action antidepressant, which is efficacious in treatment of both depressive illness and the associated sleep complaints. The improvement of depressive symptoms coupled with the lack of sexual side effects and absence of withdrawal symptoms following abrupt discontinuation make it a very attractive alternative in treatment of depressive disorders. One outstanding question that should be addressed is whether it is those depressed patients with sleep problems who respond best to treatment, and if so what type of sleep disorder. Furthermore, because most rating scales for depression include insomnia items it is difficult to disentangle depression responses from insomnia responses in studies conducted to date. That issue should also be addressed to determine the extent to which the “depression improvement” is an “improvement in sleep”.

More clinical trials are needed to confirm the efficacy and side effects of these melatonergic drugs and others under development in the long term treatment of chronic primary insomnia as well as of insomnia associated with depression and other psychiatric conditions.

Competing interest statement and disclosure statement

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. 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 a potential conflict of interest that might have influenced the views expressed in this manuscript.

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