Prolonged-release melatonin for the treatment of insomnia: targeting quality of sleep and morning alertness

Alan Wade[1],
Nava Zisapel[2][†] &
Patrick Lemoine[3]

[†]Author for correspondence
[1]CPS Research, Glasgow, UK
Tel.: +44 141 946 7888;
Fax: +44 141 946 1324;
E-mail:
alangwade@fastmail.fm
[2]Tel Aviv University
and,
Neurim Pharmaceuticals Ltd,
The George S. Wise Faculty of
Life Sciences, Tel-Aviv
69978, Israel
Tel.: +972 3640 9611;
Fax: +972 3640 7643;
E-mail:
navazis@post.tau.ac.il
[3]The Clinique Lyon-Lumière,
33 bis rue du 8 mai 1945,
Meyzieu, France
Tel.: +33 437 443 718;
Fax: +33 437 443 705;
E-mail:
patrick.lemoine99@free.fr

Prolonged-release (PR) melatonin (Circadin®, Neurim Pharmaceuticals, Tel-Aviv, Israel) is a nonbenzodiazepine licensed to treat primary insomnia in patients aged 55 years and older. It exerts its effects by mimicking endogenous melatonin, a hormone which regulates sleep. PR-melatonin has been shown to be effective in improving quality of sleep and morning alertness. An oral dose of 2 mg once-daily for 3 weeks has generally been well tolerated, and does not cause 'hangover' effects or impair memory and psychomotor skills.

Insomnia is a common sleep disorder, the diagnosis of which is based on a patient's complaint of difficulty in initiating or maintaining sleep and/or sleep that is of inadequate quality (nonrestorative sleep). The sleep disturbance should have been present for at least 1 month and be associated with a negative impact on functioning the following day [1,2].

Insomnia occurs in 30–45% of adults [3,4] and is 1.5-times more likely in women than in men [5,6]. The prevalence of insomnia increases with age [7,8]. Insomnia may be secondary – particularly when associated with mental disorders or pain – or primary, that is not attributable to any physical or mental disorder or to any environmental cause. There are widely varying reports of the prevalence of primary insomnia in the general population from 1–10% and ranging up to 25% in the elderly [9,10]. Sleep disorders, including primary insomnia, place a tremendous burden on society due to their association with psychiatric disorders, their negative impact on quality of life, their association with falls and road traffic accidents and the reduced productivity and increased utilization of healthcare services by sufferers [10–16].

There is a poor correlation between the clinical complaints associated with insomnia and the findings at polysomnography that frequently fail to demonstrate any sleep-quality related cause for the problem [17–20]. However, the tenth revision of the International Classification of Diseases (ICD 10) acknowledges that 'there are people who suffer immensely from the poor quality of their sleep, while sleep in quantity is judged subjectively, and/or objectively as within the normal limits' [2]. Sleep quality is thus an important parameter of the clinical complaint of insomnia, with the diagnosis and the evaluation of treatment effects based solely on subjective assessments.

Clinical data shows that poor quality, more than quantity, of sleep corresponds negatively to measures of health, well-being and satisfaction with life [16,21–24]. Compared with good sleepers, subjects with insomnia obtained lower mean sum scores on the cognitive scale of the short form (SF)-36 quality-of-life (QOL) questionnaire and significantly greater impairments in specific QOL domains on the QOL inventory and the Work and Daily Activities Inventory [25]. The National Sleep Foundation and the Gallup Organization survey of 1000 randomly selected Americans revealed dramatic differences in reported waking behaviors and psychosocial measures by insomniacs compared with those who do not report sleep difficulty. These problems include impaired concentration, impaired memory, decreased ability to accomplish daily tasks and decreased enjoyment of interpersonal relationships [10].

Furthermore, in a recent study in healthy older subjects without sleep or wake complaints, diary-based measures of sleep quality correlated positively with physical and mental health-related QOL. No such association was found with any of the polysomnographic sleep quantity measures (time spent asleep, sleep efficiency, sleep latency and rapid-eye movement sleep percent) [26]. The authors concluded that sleep quality and daytime alertness in late life may be more important aspects of successful aging than previously appreciated. Accordingly, the German Society of Sleep Medicine has published a formal consensus defining nonrestorative sleep as the key syndrome in the clinical algorithm to diagnose and treat sleep disorders [27].

To date, treatment of insomnia has primarily concentrated on measuring quantity of sleep, reduced sleep latency and awakening during the night, while tending to ignore the perhaps more important complaint of sleep quality. Hypnotics

such as the benzodiazepines and nonbenzodiazepines, which act on GABA-A receptors in the brain, are the most commonly prescribed treatments for sleep disturbances [28]. These primarily address quantitative sleep problems but can fail to improve or even adversely affect daytime vigilance. However, there is now a growing awareness that, since restorative sleep is essential to daytime functioning, all pharmacological treatments of insomnia must be evaluated with respect to effects on morning alertness and withdrawal symptoms [29,30].

Melatonin

Melatonin (N-acetyl-5-methoxytryptamine) is a hormone produced and secreted by the pineal gland at night (Figure 1). Production is induced by signals from the internal biological clock localized in the suprachiasmatic nuclei (SCN) of the hypothalamus and is inhibited by light perceived by the retina [31]. It is an endogenous sleep regulator and signal of darkness in humans [32]. In preparation for sleep, melatonin induces heat loss, reduces arousal and related brain activation and delays cortisol production [33,34]. Melatonin acts on its own receptors (MT1 and MT2), which are members of the G-protein-linked receptor family [35].

The production of melatonin generally decreases with age [36–40]. Older subjects show an increased lag from sunset to the onset of melatonin pulse and to the melatonin pulse peak, and malsynchronization between melatonin secretion acrophase and the middle of the sleep period [41]. The melatonin pulse starts later, peaks lower and later and ends sooner [36]. The consistently observed age-dependent changes in melatonin production was challenged by one study, which used constant routine conditions and found comparable blood melatonin levels in very healthy males and females to those in younger males. However, the same group has recently found that lack of sleep significantly increases blood melatonin levels in older, even very healthy individuals, and much less so in the young; which may explain the high melatonin levels found in their older subjects [42]. Several studies reported that people over 55 years of age with insomnia have even less 6-sulfatoxymelatonin (6-SMT) excretion than age-matched controls without sleep complaints [39,40,43–46]. However, this has not been found in some studies [47,48].

This apparent relationship between increasing age, declining melatonin production and increasing insomnia prevalence has led to the 'melatonin-replacement' hypothesis that treatment with melatonin therapy may replenish the deficiency in the endogenous sleep-regulating hormone and improve sleep.

Melatonin undergoes first-pass hepatic metabolism [49] and over 80% is excreted exclusively in the urine as 6-SMT [50]. Melatonin has a half-life in human serum of approximately 40 min [49]. It is absorbed rapidly following oral administration, with peak plasma levels occurring between 20 min and 2 h, and the level persisting for up to 1.5 h, depending on the dose, before declining [51,52].

Since melatonin is produced throughout the night period, treatment of disorders that are associated with diminished nocturnal melatonin secretion requires a formulation of the hormone that would reproduce the normal nocturnal pattern of melatonin. Therefore, a prolonged-release formulation of melatonin (PR-melatonin or Circadin®, Neurim Pharmaceuticals, Tel-Aviv, Israel) was developed. This formulation results in peak plasma levels 2.6 h after ingestion, which are maintained for 3.5 h.

A pharmacokinetic study demonstrates that the peak concentration of melatonin in the blood of healthy males following ingestion of 2 mg at 09:00 is approximately six- to eightfold higher than the endogenous peak levels at night. A regular release formulation of melatonin 0.1–0.3 mg provides, at 1 h post-ingestion, peak blood levels of melatonin that are termed 'physiological levels' as they are comparable to those that are present in the blood at night. For example, mean ± SD blood levels following a 0.3 mg oral dose were 182.3 ± 43.5 pg/ml and these decline to the endogenous levels rapidly afterwards [52]. However, brain melatonin concentrations are estimated to be 6–20-times higher than serum levels [53]. Since melatonin readily penetrates the brain, the PR-melatonin 2 mg dose would yield brain melatonin levels comparable to those present normally in the brain at night, and

Figure 1. Melatonin.
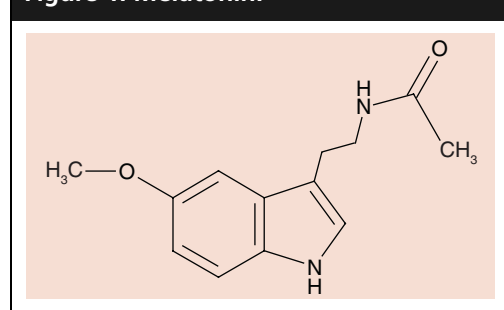
owing to the PR nature of this preparation such levels will be maintained over the entire nocturnal period (**Table 1**) [101].

Background clinical information

Studies on the effects of melatonin on sleep were quite heterogeneous with respect to patient selection (healthy volunteers, primary and secondary insomnia and psychiatric patients), age and gender, dose (0.1–80 mg), formulation (fast or sustained release), treatment duration, end points and methodology, and some were underpowered for the effect size they were attempting to demonstrate [26,54]. A meta-analysis of published studies on the efficacy of exogenous melatonin in the management of primary insomnia indicated that melatonin decreased sleep-onset latency (weighted mean difference) by 7.2 min (95% CI: -12.0, -2.4; n = 12) the respective value for patients older than 65 years was 7.8 min (95% CI: -17.4, -1.7 min) [54].

A separate meta-analysis of 15 studies that enrolled healthy subjects or people with no relevant medical condition other than insomnia indicated that melatonin reduced sleep-onset latency by 3.9 min (95% CI: -2.5, -5.4) and increased sleep efficiency by 3.1% (95% CI 0.7, 5.5) and sleep duration by 13.7 min (95% CI: 3.1, 24.3) [26]. Further studies indicated that melatonin improved the QOL in the elderly, emphasizing the importance of good sleep to quality of well being [55,56].

Clinical studies with PR-melatonin 2 mg

Efficacy: objective findings

The hypnotic effects of PR-melatonin were compared with those of current hypnotic drugs in a randomized, double-blind, cross-over study in 23 healthy subjects (9 men and 14 women, ages 21–53 years). Psychomotor performance before and for 7 h after ingestion of a single dose of placebo, zaleplon 10 mg, zopiclone 7.5 mg, temazepam 15 mg or PR-melatonin 6 mg and total sleep and sleep latency were recorded by polysomnography during 4-min periods with eyes closed immediately before and after each psychomotor test sequence. Findings indicated that the sleep-inducing power of the medications after psychomotor testing was zopiclone > PR-melatonin > zaleplon > temazepam [57]. Further studies comparing the sleep inducing effects of placebo, PR-melatonin 2 mg or zopiclone 5 mg at an early body clock time (17:00) showed that relative to placebo, aircrew on melatonin and zopiclone fell asleep more quickly (PR-melatonin: $p < 0.01$; zopiclone: $p < 0.003$), slept more (PR-melatonin: $p < 0.02$; zopiclone: $p < 0.005$), had fewer awakenings after sleep onset (PR-melatonin: $p < 0.004$; zopiclone: $p < 0.01$) and spent less time awake after sleep onset (PR-melatonin: $p < 0.01$; zopiclone: $p < 0.05$). There were no statistically significant differences between PR-melatonin and zopiclone in any of the sleep parameters [58].

Table 1. Pharmacokinetic properties of prolonged-release melatonin following ingestion at 8 am.				
	AUC 0–24 h (pg/h/ml)	C_{max} (pg/ml)	T_{max} (h)	Plateau time* (h)
Basal state				
Mean ± SD	448 ± 288	58 ± 32	18.5 ± 2.1	6.9 ± 1.7
Median	375	51	18	6.6
Range	150–1017	30–126	16–22	4.7–9.6
Drug fasting				
Mean ± SD	2527 ± 1200	427 ± 211	1.6 ± 0.8	5.1 ± 2.3
Median	2257	393	1.5	4.4
Range	823–4478	180–855	0.5–3	3.1–9.9
Drug with meal				
Mean ± SD	2405 ± 1469	483 ± 253	2.6 ± 1.1	3.5 ± 1.4
Median	2010	390	2.5	3.1
Range	618–5252	205–1020	1–4	1.7–5.5

*Time from T_{max} to 75% C_{max}.

AUC: Area under the curve; C_{max}: Maximum plasma concentration; T_{max}: Time to maximum plasma concentration.

Table obtained from [101].

Further studies were carried out in insomnia patients. Garfinkel *et al.* investigated 12 elderly subjects (mean age 76 ± 8 years) with chronic illness and insomnia in a crossover study using wrist actigraphy comparing administration of PR-melatonin for 3 weeks with placebo [59]. PR-melatonin 2 mg produced a statistically significant improvement in sleep efficiency (83 ± 4 vs 75 ± 3%, p < 0.001) and wake time after sleep onset was shorter (49 ± 14 vs 73 ± 13 min, p < 0.001). Sleep latency decreased but this did not reach statistical significance compared with placebo (19 ± 5 vs 33 ± 7 min, p = 0.088). Total sleep time was not affected.

In a crossover, double-blind, placebo-controlled randomized study, Haimov *et al.* investigated the effects of 2 mg fast-release (FR) and PR-melatonin tablets and placebo for 7 consecutive days, 2 h before desired bedtime, on actigraphy-assessed sleep in 26 melatonin-deficient elderly insomniacs (18 institutionalized and 8 independent) [60]. A 2-month period of daily administration of PR-melatonin 1 mg 2 h before desired bedtime concluded the study. Analysis of the first three 1-week periods revealed that PR-melatonin 2 mg significantly improved sleep efficiency (80.4 ± 1.82%, 78.8 ± 1.75% and 77.4 ± 1.96% for the PR-, FR-melatonin and placebo preparations, respectively; ANOVA p < 0.05). In addition, a tendency towards improved sleep-onset latency was found with mean sleep latency values (32 ± 7, 37 ± 11 and 54 ± 13 mins for FR-melatonin, PR-melatonin and placebo, respectively; ANOVA p = 0.06)

Sleep maintenance and initiation were further improved following the 2-month PR-melatonin 1-mg treatment, suggesting that tolerance had not developed. After cessation of treatment, sleep quality gradually deteriorated reverting to prestudy values within 3 months after the study. These findings suggested that melatonin-replacement therapy would be beneficial in the initiation and maintenance of sleep in elderly patients with insomnia.

An objective double-blind, placebo-controlled study was conducted in 24 male and 16 female patients aged 55 years and above with insomnia [101]. Sleep was assessed objectively using polysomnography and all-night sleep electroencephalography (EEG) spectral analysis. Subjective assessment of sleep was made by the Leeds Sleep Evaluation Questionnaire (LSEQ). Vigilance and arousal were assessed by the Leeds psychomotor test battery (critical flicker fusion threshold, recognition, motor and total reaction time) [61]; attention and cognitive skills by the Test of Everyday Attention (TEA) battery [62], and wake-EEG. Withdrawal effects were also assessed 1 day and 3 weeks after treatment. The study consisted of 2 weeks single-blind, placebo treatment, 3 weeks double-blind, placebo-controlled treatment with PR-melatonin 2 mg and a 3-week withdrawal period.

With PR-melatonin treatment, polysomnography-assessed sleep-onset latency decreased by 50% from pretreatment values, 9 min more than with placebo (p = 0.011). The duration of wake prior to sleep onset was reduced by approximately 50% (p = 0.011). No differences were observed between the groups in duration of awakenings after sleep onset, sleep efficiency, sleep duration and the duration of the different sleep stages. The polysomnographic recording indicated return of all sleep variables to baseline values one day after stopping the dosing in both groups. No withdrawal or rebound effects were observed for any of the recorded variables [101].

The mean difference between the effects of PR-melatonin and placebo on objectively-assessed (polysomnography) sleep-onset latency (-9 min) is similar to that obtained with licensed doses of zolpidem (-8.1 min [63,102]), zaleplon (<8.0 min [63,103]) zopiclone [58] and the recently approved melatonin agonist ramelteon (-10 min [104]).

Hence, the ability of PR-melatonin 2 mg to facilitate sleep onset, the primary and only parameter that current hypnotics were licensed on, is similar in efficacy and potency to that of the current hypnotic drugs.

Efficacy: subjective findings

During the clinical assessment of PR-melatonin, subjective assessment of sleep quality was based on three measures: the LSEQ, the Pittsburgh Sleep Quality Index (PSQI) and patients' self-reported diaries.

The LSEQ consists of ten visual analog scales measuring four domains of sleep: getting to sleep (GTS); quality of sleep (QOS); hangover on awakening from sleep (AFS) and behavioral integrity following waking (BFW) the following morning. It has been validated in a number of studies involving the target population of patients aged 55 years and over with insomnia [64]. Clinical response was defined as an improvement of 10 mm or more on the visual analog scales, which is considered to be of clinical importance and relevance [65].
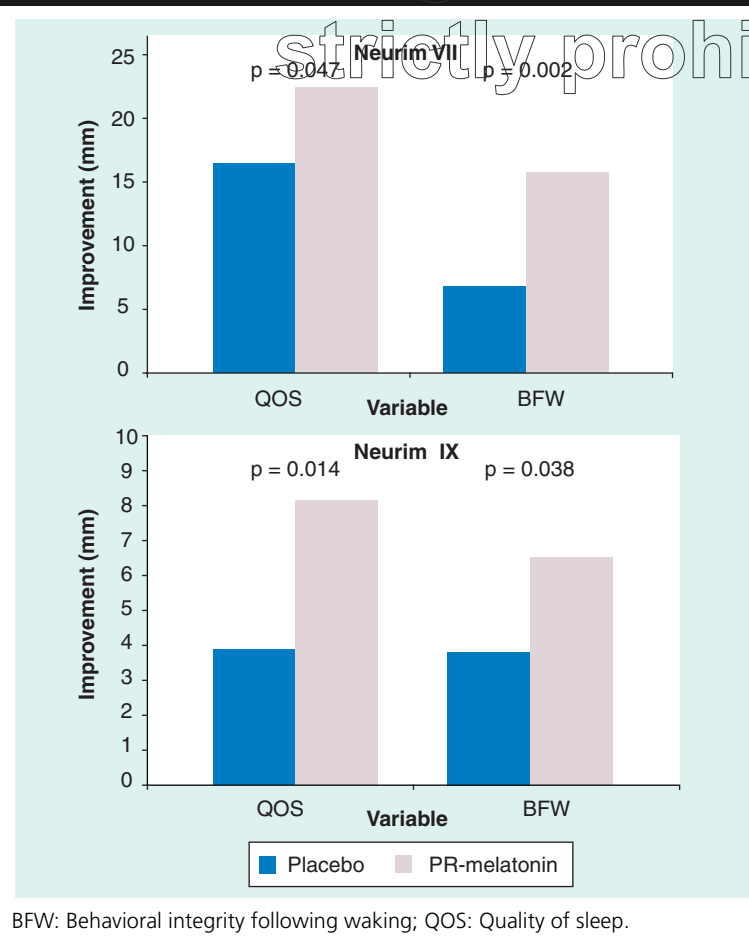
The PSQI comprises nine questions relating to the patients' usual sleep habits during the previous 4 [66] or 2 [67] weeks. An algorithm is used to calculate seven component scores and these are added to give a global PSQI score. The PSQI has been recommended for use by a recent expert consensus panel as part of a standard set of research assessments in insomnia [68].

Three studies were undertaken: Neurim VII, Neurim VIII and Neurim IX. Neurim VIII was abandoned due to quality issues; VII [69] and IX [70] have now been published. These are by far the largest clinical studies of melatonin treatment of primary insomnia. Both reported studies had a similar placebo-controlled, parallel-group design. Patients aged 55 years or more and suffering from primary insomnia as defined by DSM-IV received 2 weeks of placebo assessment and a 3-week treatment period with PR-melatonin or placebo. In Neurim VII, there was a 2-week withdrawal period on placebo.

Lemoine et al. included 189 adult male and female outpatients in France and Israel. PR-melatonin was associated with a statistically significant improvement in both the quality of sleep, measured by the LSEQ, and quality of night (QON), measured by a five-point categorical rating scale, compared with placebo (QOS p = 0.047; QON p = 0.003). A statistically significant improvement in morning alertness measured by the BFW domain of the LSEQ was also observed in the PR-melatonin group compared with the placebo group (p = 0.002). The QOS and BFW results are illustrated in Figure 2. The improvement in QOS with PR-melatonin was significantly correlated with the improvement in BFW (p < 0.01), suggesting a beneficial treatment effect on the restorative value of sleep. This apparent association was further investigated by comparing the clinical response rate of the two groups. This analysis (presented in Table 2) revealed that 47% of patients receiving PR-melatonin had a concomitant improvement in QOS and morning alertness compared with 27% of patients receiving placebo. The difference between the treatment groups was significant (p = 0.009) [69].

Wade et al. included 354 primary care patients in the UK [70]. In this study, the primary end point was predefined as a responder analysis. A responder was defined as a patient who improved by at least 10 mm on both the QOS and BFW scales of the LSEQ. This analysis is contained in Table 2 and demonstrates a significant advantage of PR-melatonin over placebo (26 vs 15%; p = 0.014). Statistical superiority of PR-melatonin was also demonstrated in the QOS component as assessed by both the LSEQ and PSQI (p = 0.014 and 0.036, respectively), sleep latency as assessed by the patients LSEQ score (GTS; p = 0.013) and performance the following morning as assessed by BFW of the LSEQ (p = 0.038). Figure 2 presents the QOS and BFW results. Sleep latency was shortened to the same extent as with most frequently used sleep medications (-24.3 vs -12.9 min; p = 0.028). QOL measured by the WHO-5 questionnaire [71] also improved significantly (p = 0.034). The results of this study provided evidence that PR-melatonin 2 mg can produce clinically relevant improvements in QOS and morning alertness in older patients suffering from nonrestorative sleep (Figure 2 & Table 2) [70].

Safety & tolerability

Preclinical data on melatonin have not revealed any effects to cause concern regarding the long-term use of PR-melatonin 2 mg in humans.

Figure 2. Effect of prolonged-release melatonin versus placebo on the Leeds Sleep Evaluation Questionnaire quality-of-sleep & behavioral integrity following waking variables.

BFW: Behavioral integrity following waking; QOS: Quality of sleep.

Table 2. Responder rate analysis in Leeds quality-of-sleep and behavioral integrity following waking components.

Treatment	Number (%)	Responders	
		Difference from placebo (%)	p-value
Neurim VII			
Placebo (n = 88)	24 (27)	–	0.0095
PR-melatonin (n = 77)	36 (47)	20	–
Neurim IX			
Placebo (n = 164)	25 (15)	–	0.014
PR-melatonin (n = 168)	44 (26)	11	–

Studies for Neurim VII and Neurim IX taken from [69] and [70], respectively.

The whole safety dataset comprises 1361 patients in short-term studies, 373 patients who received PR-melatonin for 6 months and 146 patients who received PR-melatonin for more than 1 year. Headache, pharyngitis, back pain and asthenias were the most common adverse events (AEs), which were experienced by more than 2% of the population in this dataset, and were not necessarily related to treatment [101]. As shown in Table 3, when normalized for exposure period (per 100 patient-weeks), the rate of these AEs with PR-melatonin was less than with placebo.

Data (pooled AEs) from earlier studies and pivotal studies in patients taking or not taking concomitant medications (hormone replacements, calcium-channel blockers, β-blockers, angiotensin-converting enzyme inhibitors, NSAIDs, antidiabetics, cholesterol-lowering agents, anticoagulants, benzodiazepine and zolpidem) have not raised any concerns and show no differences in frequencies and kind of AEs between patients on PR-melatonin or placebo and those taking concomitant medications [69,70,101].

Table 3. Summary of adverse events.

Adverse event	Rate per 100 patient weeks	
	Prolonged-release melatonin	*Placebo*
Headache	0.45	1.62
Pharyngitis	0.41	0.58
Back pain	0.28	0.34
Asthenia	0.28	0.51
Rhinitis	0.20	0.55
Bronchitis	0.19	0.30
All adverse events	3.17	8.21

In reproductive studies, melatonin induced some toxicological effects on the embryo–fetal development in rabbits and on the post-natal development in rats. Therefore, the use of PR-melatonin is not recommended during pregnancy and lactation. No other endocrine or reproductive effects were observed.

Rebound insomnia, characterized by a return of insomnia worse than that prior to treatment, has been associated with the abrupt withdrawal of some benzodiazepine hypnotics. There is no evidence of rebound insomnia with use of PR-melatonin at recommended doses [69,101]. In the double-blind, placebo-controlled trial conducted by Lemoine *et al.*, a decline in the improvement experienced by patients receiving PR-melatonin was apparent during the placebo run-out once treatment had been stopped [69]. Notably, by the end of the 2-week run-out period, QOS, BFW and QON values were still better than baseline levels. Furthermore, no significant withdrawal effects, as assessed with the Tyrer scale, were associated with stopping the active drug after 3 weeks of treatment.

A randomized, double-blind, four-way cross-over study was performed in 16 volunteers aged 55 years or older to determine the effects of therapeutic doses of PR-melatonin, zolpidem, their combinations and placebo on cognitive functions [101]. Unlike zolpidem, PR-melatonin 2 mg alone did not impair psychomotor functions, driving skills or memory recall at any time after dosing.

There was no increase in somatic symptoms compared with those at baseline as assessed by specially designed instruments (CHESS-84 and the Tyrer scale). Finally, among sleep or safety parameters, no evidence was found for withdrawal dependence or rebound insomnia with PR-melatonin during early and late withdrawal, except for the re-emergence of insomnia. Nevertheless, because melatonin is classified as a hypnotic (ATC code N05CH melatonin-receptor agonists), the risks of withdrawal, dependence and abuse will be subject to further post-marketing monitoring [101].

Drug interactions

There is evidence from a randomized, double-blind, crossover study in elderly subjects that PR-melatonin potentiates the effects of benzodiazepine hypnotics [72]. A total of 21 elderly subjects who had been taking benzodiazepines on a daily basis were given PR-melatonin 2 mg for 3 weeks and placebo for 3 weeks. PR-melatonin

significantly improved sleep efficiency (85.44 ± 2.4 vs 75.23 ± 2.2; p < 0.001) and total sleep time (384 + 14.6 vs 351 + 14.9; p = 0.027) and decreased wake after sleep onset (39.58 + 7.6 vs 76.8 + 12.5; p < 0.001), sleep latency (11.75 + 20 vs 29.24 + 6.2; p = 0.007) and number of awakenings (11.41 + 1.45 vs 16.7 + 1.45; p = 0.004) compared with placebo. These results are suggestive of a pharmacodynamic interaction between PR-melatonin and benzodiazepines as some of the measures were not demonstrated with PR-melatonin alone.

An interaction between PR-melatonin and zolpidem has also been demonstrated in a randomized, double-blind, crossover study in middle-aged and elderly volunteers [101]. While PR-melatonin alone had no effect on psycho-motor functions, memory recall and driving skills, it exacerbated the effects of zolpidem on these variables.

These results suggest a pharmacodynamic interaction between PR-melatonin and GABA-A modulators. Pharmacodynamic interactions (increased sleepiness) have also been observed with thioridazine, imipramine and desipramine [101]. While no pharmacokinetic interactions were found with these drugs, cimetidine 800 mg increased the plasma concentration of melatonin.

A blunted nocturnal surge in melatonin excretion has been described in patients who maintain elevated blood pressure during the night despite antihypertensive therapy [73]. The potency of PR-melatonin to reduce night-time blood pressure in treated hypertensive patients with nocturnal hypertension was studied [74]. A total of 38 treated hypertensive patients (22 males, mean age 64 ± 11 years) with confirmed nocturnal hypertension (mean night-time systolic blood pressure > 125 mm Hg), according to repeated 24-h ambulatory blood pressure monitoring (ABPM), were randomized in a double-blind fashion to receive either controlled release (CR)-melatonin 2 mg or placebo 2 h before bedtime for 4 weeks. A 24-h ABPM was then performed. CR-melatonin treatment reduced nocturnal systolic BP significantly from 136 ± 9 to 130 ± 10 mm Hg (p = 0.011) and diastolic BP from 72 ± 11 to 69 ± 9 mm Hg (p = 0.002), whereas placebo had no effect on nocturnal BP. The reduction in nocturnal systolic BP was significantly greater with PR-melatonin than with placebo (p = 0.01), and was most prominent between 02:00 and 05:00 (p = 0.002). Thus, an addition of PR-melatonin 2 mg at night to stable antihypertensive treatment may improve nocturnal BP control in treated patients with nocturnal hypertension.

Conclusion

Insomnia is a common disturbance of sleep quantity and quality affecting daytime functioning and health. There are substantial clinical data showing that poor sleep quality rather than quantity corresponds to measures of health, daytime functioning, physical and cognitive well-being and satisfaction with life. The main benefit of PR-melatonin 2 mg is a concomitant improvement in both QOS and morning alertness (evidence of restorative sleep) in patients aged 55 years and over with insomnia. Improvements were not only statistically significant but are also considered clinically significant and relevant, having been demonstrated by a responder analysis. There are no particular safety concerns.

In conclusion, according to the available clinical results, PR-melatonin appears to be safe and well tolerated at the recommended dose and indication [54].

Future perspective

Marketing authorization for PR-melatonin (Circadin®, Neurim Pharmaceuticals, Tel-Aviv, Israel) as monotherapy for short-term treatment of primary insomnia, characterized by poor QOS, in patients aged 55 years and over was granted by the European Commission on 26 July 2007. This is the first melatonin-receptor agonist approved for clinical use in the EU and the only melatonin product approved for clinical use.

The regulatory approval of PR-melatonin for this indication represents a new therapeutic principle in insomnia therapy, particularly for elderly patients. Its efficacy in improving QOS and morning alertness in patients aged 55 years and above is derived from the physiological function of the endogenous hormone as a sleep regulator and circadian clock synchronizer. It is the only insomnia drug demonstrated to improve daytime performance. Importantly, and unlike the benzodiazepine and nonbenzodiazepine hypnotics, PR-melatonin treatment is not associated with memory impairments, residual daytime or hangover effects, and there is no rebound insomnia or withdrawal symptoms upon discontinuation. This is likely to generate interest among practitioners and patients.

The long-term efficacy of PR-melatonin remains to be investigated. Proof of efficacy is based on 21 days of treatment. Although insomnia tends to be chronic, the minimal treatment period needed to attain full benefit would be of interest for future research.

PR-melatonin has not been granted marketing authorization for indications other than for short-term treatment of primary insomnia in patients aged 55 years and over. However, future developments may lead to its approval for other indications. For example, the apparent potentiation of benzodiazepine hypnotics by PR-melatonin indicates that PR-melatonin may effectively facilitate discontinuation of benzodiazepine therapy while maintaining good quality sleep [75]. Trials of PR-melatonin for other indications, including nocturnal hypertension and benign prostate hyperplasia, are ongoing.

Executive summary

Mechanisms of action

- The hormone melatonin is an endogenous sleep regulator and its production tends to decline with age.
- Prolonged-release (PR) melatonin was recently approved in the EU for treatment of insomnia, characterized by poor quality of sleep, in patients aged 55 years and older. It exerts its action by mimicking the release profile of the endogenous hormone.
- Melatonin acts via its own receptors (MT1 and MT2), which are members of the G-protein-linked family.

Pharmacokinetic properties

- Melatonin undergoes first-pass hepatic metabolism and over 80% is excreted exclusively in the urine as 6-sulfatoxymelatonin.
- It is short-lived in humans with a half-life in plasma of only 40–50 min.
- Following oral administration, melatonin is rapidly absorbed with peak plasma levels occurring between 20–240 min and it persists for up to 1.5 h, depending on dose, before declining.
- A PR formulation was developed with the intention of circumventing the rapid clearance and mimicking the physiological release profile of the hormone.
- Peak plasma levels occur at 2.6 h and persist over 3.5 h after ingestion before declining, thus covering the nocturnal period.

Clinical efficacy

- Objective evidence of efficacy of PR-melatonin 2 mg was demonstrated in a double-blind, placebo-controlled sleep laboratory study in 40 insomnia patients aged 55 years and older. PR-melatonin reduced sleep-onset latency by approximately 50% (9 min more than that with placebo; p = 0.011) and significantly improved daytime psychomotor performance.
- Two randomized controlled trials have demonstrated efficacy of PR-melatonin 2 mg using subjective assessments of sleep quality in 170 and 354 insomnia patients aged 55 years and older, respectively. PR-melatonin significantly improved quality of sleep and morning alertness compared with placebo (47 vs 27%; p < 0.01 and 26 vs 15%; p = 0.014, respectively) and quality of life (p = 0.038).

Safety & tolerability

- The incidence of adverse events with PR-melatonin was low and less than with placebo.
- Some of the adverse effects include headache, pharyngitis, back pain and asthenia.
- PR-melatonin does not impair memory or psychomotor and driving skills and has no discernible withdrawal symptoms.

Drug interaction

- PR-melatonin potentiated the effects of benzodiazepines and nonbenzodiazepines.
- No safety concerns were raised with concomitant use of other commonly used medications (e.g., antihypertensive, antidiabetic and lipid-lowering drugs).

Dosage & administration

- Melatonin is available as PR tablets for oral use. The recommended dose is 2 mg 1–2 h before bedtime after food. This dose should be continued for 3 weeks.

Bibliography

1. DSM-IV APA: In: *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (4th Edition)*. American Psychiatric Association. Washington DC, USA (1994).

2. ICD-10 WHO: Tenth Revision of the International Classification of Diseases, Chapter V (F). In: *Mental and Behavioural Disorders. Clinical Descriptions and Diagnostic Guidelines*. WHO 1992. Geneva, Switzerland, 182–184 (1992).

3. American Psychiatric Association TFoD-I: Task force on DSM-IV. In: *Diagnostic and Statistical Manual of Mental Disorders (4th Edition), Text Revision (DSM-IV-TR)*. American Psychiatric Association. Washington, DC, USA (2000).

4. NIH NIoH. Consensus Development Program: *NIH State-of-the-Science Conference Statement on Manifestations and Management of Chronic Insomnia in Adults*. Bethescla, MD, 13–15 June 2005.

5. Vitiello MV, Larsen LH, Moe KE: Age-related sleep change: Gender and estrogen effects on the subjective-objective sleep quality relationships of healthy, noncomplaining older men and women. *J. Psychosom. Res.* 56(5), 503–510 (2004).

6. Prinz PN, Vitiello MV, Raskind MA, Thorpy MJ: Geriatrics: sleep disorders and aging. *N. Engl. J. Med.* 323(8), 520–526 (1990).

7. Dement WC, Miles LE, Carskadon MA: 'White paper' on sleep and aging. *J. Am. Geriatr. Soc.* 30(1), 25–50 (1982).

8. Monane M: Insomnia in the elderly: *J. Clin. Psychiatry* 53(Suppl.) 23–28 (1992).

9. Roth T, Roehrs T: Insomnia: epidemiology, characteristics, and consequences. *Clin. Cornerstone* 5(3), 5–15 (2003).

10. Roth T, Ancoli-Israel S: Daytime consequences and correlates of insomnia in the United States: results of the 1991 National Sleep Foundation Survey. II. *Sleep* 22(Suppl. 2), S354–S358 (1999).

11. Leger D, Guilleminault C, Deframce R, Domont A, Paillard M: Prevalence of sleep/wake disorders in persons with blindness. *Clinical Science* 97, 193–199 (1999).

12. Brassington GS, King AC, Bliwise DL: Sleep problems as a risk factor for falls in a sample of community-dwelling adults aged 64–99 years. *J. Am. Geriatr. Soc.* 48(10), 1234–1240 (2000).

13. Metlaine A, Leger D, Choudat D: Socioeconomic impact of insomnia in working populations. *Ind. Health* 43(1), 11–19 (2005).

14. Avidan AY, Fries BE, James ML, Szafara KL, Wright GT, Chervin RD: Insomnia and hypnotic use, recorded in the minimum data set, as predictors of falls and hip fractures in Michigan nursing homes. *J. Am. Geriatr. Soc.* 53(6), 955–962 (2005).

15. Ozminkowski RJ, Wang S, Walsh JK: The direct and indirect costs of untreated insomnia in adults in the United States. *Sleep* 30(3), 263–273 (2007).

16. Hajak G: Epidemiology of severe insomnia and its consequences in Germany. *Eur. Arch. Psychiatry Clin. Neurosci.* 251(2), 49–56 (2001).

17. Bastien CH, LeBlanc M, Carrier J, Morin CM: Sleep eEG power spectra, insomnia, and chronic use of benzodiazepines. *Sleep* 26(3), 313–317 (2003).

18. Riedel BW, Lichstein KL: Objective sleep measures and subjective sleep satisfaction: how do older adults with insomnia define a good night's sleep? *Psychol. Aging* 13(1), 159–163 (1998).

19. Costa e Silva JA, Chase M, Sartorius N, Roth T: Special report from a symposium held by the World Health Organization and the World Federation of Sleep Research Societies: an overview of insomnias and related disorders – recognition, epidemiology, and rational management. *Sleep* 19(5), 412–416 (1996).

20. Littner M, Hirshkowitz M, Kramer M *et al.*: Practice parameters for using polysomnography to evaluate insomnia: an update. *Sleep* 26(6), 754–760 (2003).

21. Pilcher JJ, Ginter DR, Sadowsky B: Sleep quality versus sleep quantity: relationships between sleep and measures of health, well-being and sleepiness in college students. *J. Psychosom. Res.* 42(6), 583–596 (1997).

22. Pilcher JJ, Ott ES: The relationships between sleep and measures of health and well-being in college students: a repeated measures approach. *Behav. Med.* 23(4), 170–178 (1998).

23. Zeitlhofer J, Schmeiser-Rieder A, Tribl G *et al.*: Sleep and quality of life in the Austrian population. *Acta Neurol. Scand.* 102(4), 249–257 (2000).

24. Rombaut N, Maillard F, Kelly F, Hindmarch I: The quality of life of insomniacs questionnaire (QOLI). *Med. Sci. Res.* 18, 845–847 (1990).

25. Zammit GK, Weiner J, Damato N, Sillup GP, McMillan CA: Quality of life in people with insomnia. *Sleep* 22(Suppl. 2), S379–S385 (1999).

26. Driscoll HC, Serody L, Patrick S *et al.*: Sleeping well, aging well: a descriptive and cross-sectional study of sleep in 'successful agers' 75 and older. *Am. J. Geriatr. Psychiatry* 16(1), 74–82 (2008).

27. Riemann D FJ, Mayer G, Peter JH: The guidelines for 'non-restorative sleep': relevance for the diagnosis and therapy of insomnia. *Somnologie* 7(2), 66–76 (2003).

28. Szabadi E: Drugs for sleep disorders: mechanisms and therapeutic prospects. *Br. J. Clin. Pharmacol.* 61(6), 761–766 (2006).

29. Glass J, Lanctot KL, Herrmann N, Sproule BA, Busto UE: Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. *BMJ* 331(7526), 1169–1176 (2005).

30. Krystal AD: Treating the health, quality of life, and functional impairments in insomnia. *J. Clin. Sleep Med.* 3(1), 63–72 (2007).

31. Reiter RJ: Melatonin: the chemical expression of darkness. *Mol. Cell Endocrinol.* 79(1–3), C153–C158 (1991).

32. Brzezinski A, Vangel MG, Wurtman RJ *et al.*: Effects of exogenous melatonin on sleep: a meta-analysis. *Sleep Med. Rev.* 9(1), 41–50 (2005).

33. Zisapel N, Tarrasch R, Laudon M: The relationship between melatonin and cortisol rhythms: clinical implications of melatonin therapy. *Drug Dev. Res.* 65(3), 119–125 (2005).

34. Zisapel N: Sleep and sleep disturbances: biological basis and clinical implications. *Cell. Mol. Life Sci.* 64(10), 1174–1186 (2007).

35. Witt-Enderby PA, Bennett J, Jarzynka MJ, Firestine S, Melan MA: Melatonin receptors and their regulation: biochemical and structural mechanisms. *Life Sci.* 72(20), 2183–2198 (2003).

36. Nair NPV, Hariharasubramanian N, Pilapil C, Issac I, Thavundayil JX: Plasma melatonin - an index of brain aging in humans ? *Biol. Psychiatry* 21, 141–150 (1986).

37. Waldhauser F, Weiszenbacher G, Tatzer E *et al.*: Alterations in nocturnal serum melatonin levels in humans with growth and aging. *J. Clin. Endocrinol. Metab.* 66(3), 648–652 (1998).

38. Kennaway DJ, Lushington K, Dawson D, Lack L, van den Heuvel C, Rogers N: Urinary 6-sulfatoxymelatonin excretion and aging: new results and a critical review of the literature. *J. Pineal Res.* 27(4), 210–220 (1999).

39. Haimov I, Laudon M, Zisapel N *et al.*: Sleep disorders and melatonin rhythms in elderly people. *BMJ* 309(6948), 167 (1994).

40. Leger D, Laudon M, Zisapel N: Nocturnal 6-sulfatoxymelatonin excretion in insomnia and its relation to the response to melatonin replacement therapy. *Am. J. Med.* 116(2), 91–95 (2004).

41. Youngstedt SD, Kripke DF, Elliott JA, Klauber MR: Circadian abnormalities in older adults. *J. Pineal Res.* 31, 264–272 (2001).

42. Zeitzer JM, Daniels JE, Duffy JF, Klerman EB, Shanahan TL, Dijk DJ, Czeisler CA: Do plasma melatonin concentrations decline with age? *Am. J. Med.*. 107(5), 432–436 (1999).

43. Zeitzer JM, Duffy JF, Lockley SW, Dijk DJ, Czeisler CA: Plasma melatonin rhythms in young and older humans during sleep, sleep deprivation, and wake. *Sleep* 30(11), 1437–1443 (2007)

44. Hajak G, Rodenbeck A, Staedt J, Bandelow B, Huether G, Ruther E: Nocturnal plasma melatonin levels in patients suffering from chronic primary insomnia. *J. Pineal Res.* 19, 116–122 (1996).

45. Mishima K, Okawa M, Shimizu T, Hishikawa Y: Diminished melatonin secretion in the elderly caused by insufficient environmental illumination. *J. Clin. Endocrinol. Metab.* 86(1), 129–134 (2001).

46. Riemann D, Klein T, Rodenbeck A *et al.*: Nocturnal cortisol and melatonin secretion in primary insomnia. *Psychiatry Res.* 113(1–2), 17–27 (2002).

47. Lushington K, Dawson D, Kennaway DJ, Lack L: The relationship between 6-sulphatoxymelatonin and polysomnographic sleep in good sleeping controls and wake maintenance insomniacs, aged 55–80 years. *J. Sleep Res.* 8, 57–64 (1999).

48. Baskett JJ, Wood PC, Broad JB, Duncan JR, English J, Arendt J: Melatonin in older people with age-related sleep maintenance problems: a comparison with age matched normal sleepers. *Sleep* 24, 418–424 (2001).

49. Waldhauser F, Waldhauser M, Lieberman HR, Deng MH, Lynch HJ, Wurtman RJ: Bioavailability of oral melatonin in humans. *Neuroendocrinology* 39(4), 307–313 (1984).

50. Arendt J, Skene DJ: Melatonin as a chronobiotic. *Sleep Med. Rev.* 9(1), 25–39 (2005).

51. Arendt J: *Melatonin and the Mammalian Pineal Gland.* Chapman & Hall, London, UK, 207–211 (1995).

52. Zhdanova IV, Raz DJ: Effects of melatonin ingestion on cAMP and cGMP levels in human plasma. *J. Endocrinol.* 163(3), 457–462 (1999).

53. Rousseau A, Petren S, Plannthin J, Eklundh T, Nordin C: Serum and cerebrospinal fluid concentrations of melatonin: a pilot study in healthy male volunteers. *J. Neural Transm.* 106, 883–888 (1999).

54. Buscemi N, Vandermeer B, Hooton N, Pandya R, Tjosvold L, Hartling L *et al.*: The efficacy and safety of exogenous melatonin for primary sleep disorders. A meta-analysis. *J. Gen. Intern. Med.* 20(12), 1151–1158 (2005).

55. Karasek M: Melatonin, human aging, and age-related diseases. *Exp. Gerontol.* 39(11–12), 1723–1729 (2004).

56. Jean-Louis G, Kripke DF, Ancoli-Israel S: Sleep and quality of well-being. *Sleep* 23(8), 1115–1121 (2000).

57. Paul MA, Gray G, MacLellan M, Pigeau RA: Sleep-inducing pharmaceuticals: a comparison of melatonin, zaleplon, zopiclone, and temazepam. *Aviat. Space Environ. Med.* 75(6), 512–519 (2004).

58. Paul MA, Gray G, Sardana TM, Pigeau RA: Melatonin and zopiclone as facilitators of early circadian sleep in operational air transport crews. *Aviat. Space Environ. Med.* 75(5), 439–443 (2004).

59. Garfinkel D, Laudon M, Nof D, Zisapel N: Improvement of sleep quality in elderly people by controlled-release melatonin. *Lancet* 346(8974), 541–544 (1995).

60. Haimov I, Lavie P, Laudon M, Herer P, Vigder C, Zisapel N: Melatonin replacement therapy of elderly insomniacs. *Sleep* 18(7), 598–603 (1995).

61. Hindmarch I: Instrumental assessment of psychomotor functionsand the effects of psychotropic drugs. *Acta Psychiatr. Scand.* 89(Suppl. 380), 49–52 (1994).

62. Robertson IH, Ward A, Ridgeway V, Nimmo-Smith I: The structure of normal human attention: the test of everyday attention. *J. Clin. Exp. Neuropsychol.* 2, 523–534 (1996).

63. Ancoli-Israel S, Walsh JK, Mangano RM, Fujimori M: Zaleplon, a novel nonbenzodiazepine hypnotic, effectively treats insomnia in elderly patients without causing rebound effects. Primary Care Companion *J. Clin. Psychiatry* 1(4), 114–120 (1999).

64. Tarrasch R, Laudon M, Zisapel N: Cross-cultural validation of the Leeds sleep evaluation questionnaire (LSEQ) in insomnia patients. *Hum. Psychopharmacol.* 18(8), 603–610 (2003).

65. Zisapel N, Nir T: Determination of the minimal clinically significant difference on a patient visual analog sleep quality scale. *J. Sleep Res.* 12(4), 291–298 (2003).

66. Buysse D, Reynolds III C, Monk T, Berman S, Kupfer D: The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. *Psychiatry Res.* 28, 193–213 (1989).

67. Backhaus J, Junghanns K, Broocks A, Riemann D, Hohagen F: Test-retest reliability and validity of the Pittsburgh Sleep Quality Index in primary insomnia. *J. Psychosom. Res.* 53, 737–740 (2002).

68. Buysse DJ, Ancoli-Israel S, Edinger JD, Lichstein KL, Morin CM: Recommendations for a standard research assessment of insomnia. *Sleep* 29(9), 1155–1173 (2006).

69. Lemoine P, Nir T, Laudon M, Zisapel N: Prolonged-release melatonin improves sleep quality and morning alertness in insomnia patients aged 55 years and older and has no withdrawal effects. *J. Sleep Res.* 16(4), 372–380 (2007).

70. Wade A, Ford I, Crawford G *et al.*: Efficacy of prolonged release melatonin in insomnia patients aged 55–80 years. *Curr. Med. Res. Opin.* 23(10), 2597–2605 (2007).

71. Bech P, Olsen LR, Kjoller M, Rasmussen NK: Measuring well-being rather than the absence of distress symptoms: a comparison of the SF-36 Mental Health subscale and the WHO-Five Well-Being Scale. *Int. J. Methods Psychiatr. Res.* 12(2), 85–91 (2003).

72. Garfinkel D, Laudon M, Zisapel N: Improvement of sleep quality by controlled-release melatonin in benzodiazepine-treated elderly insomniacs. *Arch. Gerontol. Geriatr.* 24(2), 223–231 (1997).

73. Jonas M, Garfinkel D, Zisapel N, Laudon M, Grossman E: Impaired nocturnal melatonin secretion in non-dipper hypertensive patients. *Blood Press* 12(1), 19–24 (2003).

74. Grossman E, Laudon M, Yalcin R *et al.*: Melatonin reduces night blood pressure in patients with nocturnal hypertension. *Am. J. Med.* 119(10), 898–902 (2006).

75. Garfinkel D, Zisapel N, Wainstein J, Laudon M: Facilitation of benzodiazepine discontinuation by melatonin: a new clinical approach. *Arch. Intern. Med.* 159(20), 2456–2460 (1999).

Websites

101. EMEA: Circadin® EPA Report (2007). www.emea.europa.eu/humandocs/PDFs/EPAR/circadin/H-695-en6.pdf

102. Zolpidem: clinical review: FDA (1992). www.fda.gov/cder/foi/nda/pre96/019908_S000_AmbienTOC.htm.)

103. Zaleplon: scientific discussion: EMEA (2004). www.emea.eu.int/humandocs/Humans/EPAR/sonata/sonata.htm

104. Ramelteon: clinical review: FDA (2005). www.fda.gov/cder/foi/nda/2005/021782s000_RozeremTOC.htm