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Prolonged-release melatonin improves sleep quality and morning alertness in insomnia patients aged 55 years and older and has no withdrawal effects

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SUMMARY Melatonin, secreted nocturnally by the pineal gland, is an endogenous sleep regulator. Impaired melatonin production and complaints on poor quality of sleep are common among the elderly. Non-restorative sleep (perceived poor quality of sleep) and subsequently poor daytime functioning are increasingly recognized as a leading syndrome in the diagnostic and therapeutic process of insomnia complaints. The effects of 3-weeks prolonged-release melatonin 2 mg (PR-melatonin) versus placebo treatment were assessed in a multi-center randomized placebo-controlled study in 170 primary insomnia outpatients aged ≥55 years. Improvements in quality of sleep (QOS) the night before and morning alertness (BFW) were assessed using the Leeds Sleep Evaluation Questionnaire and changes in sleep quality (QON) reported on five categorical unit scales. Rebound insomnia and withdrawal effects following discontinuation were also evaluated. PR-melatonin significantly improved QOS (−22.5 versus −16.5 mm, $P = 0.047$), QON (0.89 versus 0.46 units; $P = 0.003$) and BFW (−15.7 versus −6.8 mm; $P = 0.002$) compared with placebo. The improvements in QOS and BFW were strongly correlated (Rval = 0.77, $P < 0.001$) suggesting a beneficial treatment effect on the restorative value of sleep. These results were confirmed in a subgroup of patients with a greater symptom severity. There was no evidence of rebound insomnia or withdrawal effects following treatment discontinuation. The incidence of adverse events was low and most side-effects were judged to be of minor severity. PR-melatonin is the first drug shown to significantly improve quality of sleep and morning alertness in primary insomnia patients aged 55 years and older-suggesting more restorative sleep, and without withdrawal symptoms upon discontinuation.

KEYWORDS insomnia, melatonin, morning alertness, sleep quality, treatment, withdrawal

INTRODUCTION

Insomnia is a complaint that sleep is difficult to initiate or maintain, or that it is non-restorative (also termed non-refreshing or poor sleep quality; DSM-IV, 1994; ICD-10, 1992). The prevalence of insomnia and in particular poor subjective sleep quality increases with age (Dement *et al.*, 1982; Hajak, 2001; Nugent *et al.*, 2001; Ohayon, 1996; Ohayon *et al.*, 2001; Roth *et al.*, 1999, 2001; Zeitlhofer *et al.*, 2000) . Approximately 50% of the elderly population report on insomnia and an overall dissatisfaction with quality of sleep (Dement *et al.*, 1982; Ohayon *et al.*, 2001; Roth *et al.*, 2001). Insomnia is associated with significant daytime distress and impaired daytime functioning: it adversely affects psychosocial, physical and occupational functioning, most commonly characterized by fatigue/lethargy, mood disturbances, cognitive inefficiency and motor impairments, social discomfort and non-specific physical ailments (Dement *et al.*, 1982; Ohayon

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et al., 2001; Roth *et al*., 2001; Sateia *et al*., 2000; Zammit *et al*., 1999).

Polysomnography provides objective measurements of sleep quantity (e.g. initiation, maintenance, total sleep time) and architecture. No satisfactory correspondence has been established between the common complaint of sleep quality or sleep satisfaction and sleep laboratory parameters (Bastien *et al*., 2003; Riedel and Lichstein, 1998). Current classification (ICD-10) systems acknowledge 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.' (ICD-10, 1999). In line with the lack of such correspondence consensus papers have been issued by several expert groups including a recent report of the American Academy Sleep Medicine Standards of Practice Committee, concluding that polysomnography should not be indicated for the routine evaluation of insomnia (e.g. Costae Silva *et al*., 1996; Littner *et al*., 2003). The diagnosis of poor sleep quality is thus based on subjective assessments and so is the evaluation of treatment effects on sleep quality. In recent years, the focus of clinically oriented sleep medicine has shifted from sleep quantity to sleep quality. Several studies have shown that insomnia related to quality rather than quantity of sleep is associated with impaired daytime functioning (e.g. negative effects on memory, vigilance and psychomotor skills) and quality of life (Roth *et al*., 2001). Inadequate 'subjective sleep quality' and 'daytime dysfunction' are the best predictors of impaired quality of life (Hajak, 2001; Zeitlhofer *et al*., 2000). Impaired quality of sleep as assessed by the Leeds Sleep Evaluation Questionnaire (LSEQ) was strongly associated with impaired quality of life (Rombaut *et al*., 1990). A recent study in Germany has demonstrated that patients with Global Sleep Dissatisfaction (GSD) were two times more likely to report excessive daytime sleepiness compared with insomnia patients without GSD (Ohayon and Zulley, 2001). In concordance with these investigations the German Society of Sleep Medicine has published a formal consensus that defined non-restorative sleep – a reflection of impaired sleep quality according to DSM-IV and ICD-10 criteria – to be the key syndrome in the clinical algorithm to diagnose and treat sleep disorders (Riemann *et al*. 2003). Thus, non-restorative sleep and poor quality of sleep constitute a major component of the problem of insomnia, which in itself is a common complaint and is highly associated with impaired daytime functioning. Although much of the outcomes of insomnia derive from the extent to which it impairs daytime functioning, insomnia drugs have been approved on the basis of improvements in sleep induction and/or maintenance but not in sleep quality and next day performance (Krystal, 2007; Morin, 2003).

Insomnia is mostly treated with benzodiazepine (BZD) and non-benzodiazepine (non-BZD) hypnotic drugs, which potentiate the CNS suppressant activity of brain gamma-aminobutyric acid (GABA–A) receptors (Szabadi, 2006). In addition there is off-label use of the sedative antidepressant trazodone and antipsychotics, which have not been developed to treat insomnia and information on their efficacy and safety in insomnia patients is therefore lacking (Krystal, 2004; Mendelson, 2005). BZDs and non-BZDs are effective sleep promoters and in some cases improve sleep quality (Ancoli-Israel *et al*., 1999; Glass *et al*., 2005; Scharf *et al*., 1991). However, daytime residual disturbances, the development of dependence, as well as withdrawal symptoms associated with most hypnotic drugs is a matter of concern and may present a public health issue. Therefore, all pharmacological treatments of insomnia must be evaluated with respect to effects on morning alertness and withdrawal symptoms, particularly for older patients (Glass *et al*., 2005).

Melatonin (*N*-acetyl-5-methoxy-tryptamine) the hormone produced by the pineal gland at night is the signal of darkness in the organism (Reiter, 1993) and as such has clock-phase resetting and sleep-promoting functions in humans (Zisapel, 2007). Administration of melatonin during daytime, i.e. when it is not present endogenously, promotes fatigue and sleepiness (Anton-Tay *et al*., 1971; Barchas *et al*., 1967; Cramer *et al*., 1974) and modifies brain activation patterns in anticipation of sleep (Gorfine and Zisapel, 2007; Gorfine *et al*., 2006, 2007). Melatonin acts via its own receptors (MT1, MT2), which are members of the G protein-linked receptor family and are involved in the regulation of circadian rhythms and soporific function (Witt-Enderby *et al*., 2003). In addition, lower affinity melatonin binding sites have been described (Laudon *et al*., 1988) and a melatonin binding site termed MT3 has recently been identified as quinone reductase 2 (Witt-Enderby *et al*., 2003) but their physiological roles have not been elucidated. Importantly, melatonin is not sedating: in nocturnally active animals melatonin production is associated with wake, not sleep, periods (Zisapel, 1999) and in humans its sleep-promoting effects become significant about 2 h after intake similar to the physiological sequence at night (Wesensten *et al*., 2005). Melatonin production declines with age and is lower in middle aged and elderly patients with insomnia than in good sleepers (Haimov *et al*., 1994; Leger *et al*., 2004). Several exploratory studies suggested that prolonged release melatonin intended to circumvent the fast clearance of the hormone (i.e. $t½$ 40–50 min; (Waldhauser *et al*., 1984)) may promote sleep in elderly insomnia patients (Garfinkel *et al*., 1995; Haimov *et al*., 1995; Hughes *et al*., 1998; Leger *et al*., 2004; Wurtman and Zhdanova, 1995; Zhdanova *et al*., 2001) although another study did not find significant improvement compared to placebo (Baskett *et al*., 2003).All of these studies focused on quantitative aspects and not on sleep quality and daytime functioning.

A first melatonin analog ramelteon (a specific MT1, MT2 receptor agonist) was recently approved by the USA FDA, for the treatment of insomnia characterized by difficulty with sleep onset. The improvement with ramelteon in sleep onset latency as assessed by polysomnography and patient reports is similar to that reported for melatonin; however, ramelteon does not improve the patient's perceived sleep quality and next day performance compared with placebo (Roth *et al*., 2006).

The purpose of this placebo-controlled study was to assess the efficacy and safety of melatonin in improving quality of

sleep and morning alertness in patients aged 55 years and older who met criteria for primary insomnia. A prolonged-release 2 mg melatonin formulation (PR-melatonin), that essentially mimics the release pattern of the endogenous melatonin at night, was used. In addition, rebound and withdrawal symptoms associated with discontinuing the drug were assessed.

We chose placebo as a comparator for this study for several reasons: first of all, placebo is the primary comparator group in clinical trials. Secondly, there are methodological differences in administration of melatonin and hypnotics: melatonin is to be given 1–2 h before bedtime preferably between 21:00 and 22:00 hours, which is the time of the normal rise in melatonin in healthy young individuals (Lewy, 1999), whereas hypnotics are to be given at bedtime and in bed (for safety reasons such as risk of falls, confusion, etc) and without food. Furthermore, none of these drugs improves the restorative value of sleep. It is, however, important to note that head to head comparison of sleep promoting activities indicated similar potencies of PR-melatonin and zopiclone in sleep induction (Paul *et al*., 2004b). Ramelteon was not used because it was not available at the time of the study. We believe that so far this study is the largest controlled trial on the efficacy and safety of melatonin in insomnia.

METHODS

Study design

This randomized, double blind, placebo-controlled, parallel-group, multi-centre study was carried out in 47 general practitioners' clinics in France and Israel. The study started with a run-in of 2 weeks single blind placebo treatment (run-in) followed by patients' re-evaluation. Those who successfully met eligibility criteria were randomized to receive double-blind placebo or PR-melatonin 2 mg (Circadin®, Neurim Pharmaceuticals Ltd, Tel Aviv, Israel), and entered the 3-week treatment period (treatment) and then a 2-weeks single-blind placebo period (run-out). Patients were instructed to take the study medication daily, after the evening meal, between 1 and 2 h before bedtime and preferably between 21:00 and 22:00 hours.

Patients completed the Leeds Sleep Evaluation Questionnaire (Parrott and Hindmarch, 1978; Zisapel and Laudon, 2002) for the three consecutive nights by the end of each period. In addition, the patients recorded their sleep quality the previous night (QON) and daytime quality each day (QOD) on five-grade severity rating scales. A laboratory screening of concomitant hypnotic drug use was performed each visit to the clinic.

At each visit, investigators completed Tyrer scale assessment of withdrawal symptoms (Tyrer *et al*., 1990), measured patient vital signs, and assessed adverse events. Laboratory tests (haematology, biochemistry and urinalysis) were performed at each visit. This study was conducted in accordance with the World Medical Association Declaration of Helsinki (1989), and the International conference on Harmonization Harmonized Tripartite guideline for good clinical practice. The protocol and the statement of informed consent were approved by an Independent Ethics Committee (IEC; in France, CCPPRB: Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale, and in Israel, the Central EC of the Wolfson Medical Center, Holon) prior to each centre's initiation. All patients provided written informed consent prior to study participation.

Patients

Eligible patients were aged 55 years or older and had a diagnosis of primary insomnia as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, 1994) for at least one month and had consistent complaints on poor sleep quality by the end of the single-blind placebo run-in period. Exclusion criteria were: breathing related sleep disorder, circadian rhythm sleep disorder, dyssomnia not otherwise specified, sleep disorder because of a general medical condition, significant psychiatric or neurological disorders (anxiety, depression, dementia) or use of any medications that affected the central nervous system or sleep/wake function within 2 weeks prior to the first day of the placebo run-in period.

A four-step process was used for screening out patients with secondary insomnia and other sleep disorders. The initial diagnosis of primary insomnia was performed using a sleep history questionnaires (SHQ) recommended by Clinical Practice Guideline-Adult Insomnia (Chesson *et al*., 2000). The SHQ characterizes the primary sleep complaint according to the different diagnostic criteria (DSM-IV and ICD-10). The questionnaire also helps in differentiating primary insomnia from secondary insomnia because of medical and psychiatric disorders (including depression and anxiety) and specific insomnia disorders like circadian rhythm disorders, movement disorders, parasomnias and breathing-related sleep disorders.

Then, a physical examination, which is an important element in the evaluation of insomnia patients with medical symptoms (Chesson *et al*., 2000) was performed at the screening visit by a qualified clinician. To rule out psychiatric disorders, including depression anxiety and dementia, the patients went through a detailed psychological assessment that included the Raskin Depression scale, Covi anxiety scale and the Mini Mental State (MMS) on the first visit. Patients who scored 6 or more on the Raskin depression scale and Covi anxiety scale and patients with a score ≤24 or ≤26 on the MMS (depending on the socio-educational level of the patient) were non-eligible for inclusion in the study. History of severe psychiatric disorders, especially psychosis, anxiety and depression were major exclusion criteria. Finally, patients that were using psychotropic treatments (neuroleptics, antiepileptics, barbiturates, antidepressants, anxiolytics, or lithium) in the last 3 months before the study were excluded. A positive drug screen on visit two for benzodiazepines, barbiturates, sedating anti-histamines, hydroxyzine, doxylamine, zaleplon, zopiclone, or zolpidem led to immediate exclusion.

The intent-to-treat (ITT) population comprised of 170 patients aged 55–93 years. 82 patients were randomized to PR-melatonin 2 mg [29 males, 53 females, mean age 68.5 SD 7.62 years; Mean Body Mass Index (BMI) 25.1 SD 2.84] and 88 to placebo (29 males 59 females, mean age 68.5 SD 8.95 years Mean BMI 24.8 SD 3.23). Of these, 78 of the PR-melatonin and 86 of the placebo groups completed the study.

Measures

Leeds sleep evaluation questionnaire

The LSEQ is currently the main outcome measure of sleep and daytime effects in clinical trials studying insomnia and has been validated in a number of studies involving the target population of insomnia patients aged 55 years and older (Tarrasch *et al*., 2003). This questionnaire includes 10 visual analogue scales (VAS) that measure four domains of sleep and morning behaviour: ease of getting to sleep (GTS – mean of questions 1, 2 and 3); quality of sleep (QOS – mean of questions 4 and 5); hangover on awakening from sleep (AFS – mean of questions 6 and 7) and alertness and behavioural integrity the following morning (BFW – mean of questions 8, 9, and 10). On the three last days of each period (placebo run-in, double-blind treatment and placebo run-out), subjects were asked to evaluate aspects of their current sleep and morning behaviour compared to the respective values before starting run-in, by a single vertical mark through each of the 10 questions of the 100 mm VAS scales. Patients were not allowed to review their measurements in previous treatment periods. The results of the three last nights of each period were averaged for each of the four parameters and the changes in each parameter from run-in placebo (baseline) to treatment and to placebo run-out were calculated for each patient.

Sleep diaries

Patients were instructed to rate each morning the quality of their sleep (QON) the last night each evening the overall quality of day (QOD) on five-grade severity rating scales: 1, very bad; 2, bad; 3, fair; 4, good; 5, very good. The sleep quality data collected during the last 3 days of run-in was used to evaluate the baseline disease severity and data collected during the last 3 days of treatment and first three days of run-out period was used to assess rebound insomnia. The results of the three last nights of each period were averaged and the changes in each parameter from run-in placebo to treatment and from treatment to placebo run-out were calculated for each patient.

Tyrer benzodiazepine withdrawal symptom questionnaire (BWSQ)

Withdrawal effects were assessed by change in BWSQ (Tyrer *et al*., 1990) total score from the end of treatment and end of the run-out visits. Patients were asked to recall 20 symptoms experienced in the last 24 h. They were also asked to recall any additional symptoms. Each symptom was evaluated on a three-point scale: 0, no; 1, yes, sometimes; 2, yes, often.

Statistical analyses

Efficacy analyses were performed on the ITT population, which comprised all eligible patients who had received at least one dose of study medication and had at least one post-baseline evaluation for the LSEQ during the 3-week treatment period. A subgroup analysis was also carried out, post-hoc, in a group of patients with severe disease characterized by bad/very bad quality of sleep at baseline. This subpopulation was defined by mean QON on the last 3 nights of run-in of 2.33 or less.

The significance of difference in efficacy between PR-melatonin and placebo-treated groups was analyzed using a two-sided Student's t test for independent samples. The number of patients who reported on improvement, or no change, or worsening in QON and the number of patients showing a clinically relevant response (concomitant improvements in QOS and BFW) were compared between the active and placebo groups using Chi-Square tests (2×3 and 2×2 comparisons respectively).

Safety and tolerability

The population for safety analysis (safety set) included all patients known to have taken at least one dose of study medication. Clinical safety measures included a physical examination, forbidden hypnotic drug screening in urine and routine laboratory tests (assessed centrally). These were completed before treatment administration, at end of treatment and 2 weeks following cessation of treatment. Adverse events were recorded at each visit, and reasons for withdrawal were documented.

RESULTS

Patients' disposition and characteristics

A total of 170 patients (mean age 68.5; SD 8.31 years, 66% women) were randomized to treatment. No significant differences were observed among the treatment groups with respect to demographic characteristics baseline sleep history, age, height, weight, body mass index and history of tobacco, alcohol, or caffeine use. The percentage of patients with a common medical condition and percentage of patients with a history of prior medication were similar among the treatment groups. A total of six patients discontinued treatment during the randomized treatment phase of the study; four patients (4.9%) in the PR-melatonin group (one for lack of efficacy, one for failing screening criteria, one on request and one for taking forbidden medication), and two patients (2.3%) in the placebo group (one for adverse event (somnolence) and one

for poor compliance). Overall, 78 patients in the PR-melatonin group and 86 patients in the placebo group completed this 7-week trial, resulting in an overall completion rate of 96% in the ITT population. The majority of patients (77%) in both treatment groups were receiving prior medication and the nature and prevalence of prior medication was similar in both groups. Medications for cardiovascular conditions (mostly fenofibrate) were the most common in both treatment groups (100 patients; 48 in the PR-melatonin and 52 in the placebo randomized groups). Of these patients, seven (three randomized to PR-melatonin and four to placebo) were concomitantly treated with atenolol, a beta adrenoreceptors blocking drug, known to suppress melatonin production (Arendt *et al.*, 1985). Twenty-six of the patients (11 in the PR-melatonin and 15 in the placebo groups) used benzodiazepines and non-benzodiazepines hypnotics before entering the trial.

Efficacy

The effects of PR-melatonin (2 mg 3 weeks) on quality of sleep (LSEQ-QOS) are presented in Fig. 1a. Patients treated with PR-melatonin reported a statistically significant improvement in sleep quality compared with that at run-in (42.8 versus 65.54 mm, $P < 0.0001$; each patient own control). The mean improvement from baseline in sleep quality was significantly higher in the PR-melatonin group compared with that in the parallel placebo treated group (−22.5 versus −16.5 mm, $P = 0.047$).

The effects of PR-melatonin (2 mg 3 weeks) on morning alertness (BFW) are presented in Fig. 1b. Patients treated with PR-melatonin reported a statistically significant improvement in morning alertness compared with those at run-in (44.56 versus 60.10 mm, $P < 0.0001$; each patient own control). The mean improvement from baseline in morning alertness was significantly higher in the PR-melatonin group compared with that in the parallel placebo treated group (−15.67 versus −6.79 mm, $P = 0.002$).

Subgroup analyses revealed a greater treatment effect for PR-melatonin compared with the respective placebo treated group among patients with severe sleep quality problem (baseline QON ≤ 2.3) on QOS and BFW variables ($P = 0.027$ and $P = 0.003$ respectively; Table 1).

The improvement in QOS with PR-melatonin was significantly correlated with the improvement in BFW (Rval = 0.77, $P < 0.001$; Fig. 2a). The apparent association between these effects was further investigated by comparing responder rates in the two groups. A change of 10 mm or more on the 100 mm VAS indicates a clinically relevant effect (Zisapel and Nir, 2003). A responder was thus defined as a patient demonstrating concomitant improvements by 10 mm or more in QOS and BFW. This analysis revealed that 47% in the PR-melatonin group compared with 27% in the placebo group improved concomitantly in quality of sleep and morning alertness; the difference between treatment groups was significant ($P < 0.01$; Fig. 2b).

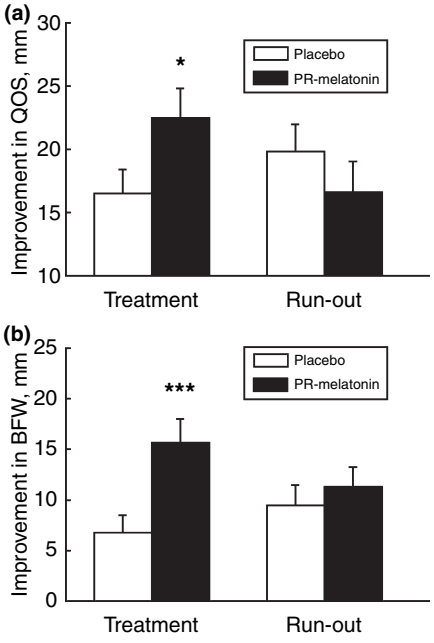

Figure 1. Effect of PR-melatonin versus placebo on (a) LSEQ-QOS variable and (b) LSEQ-BFW. Mean and SEM values of the changes from baseline in QOS and BFW variables following the 3 weeks treatment and 2 weeks placebo run-out periods are depicted. *P*-values are for comparisons between the effects of placebo and PR-melatonin. $*P \leq 0.050$; $***P \leq 0.005$.

Table 1 Efficacy of PR-melatonin versus placebo in subpopulation with severe sleep disturbance (baseline QON ≤ 2.3)

	Placebo (n = 43)	*PR-melatonin* (n = 44)	P-*value*
Baseline QOS (SD), mm	68.5 (12.0)	69.4 (11.5)	NS
Treatment effect QOS (SD), mm	−17.5 (16.6)	−26.7 (21.5)	0.027
Baseline BFW (SD), mm	59.7 (14.0)	63.6 (14.2)	NS
Treatment effect BFW (SD), mm	−6.3 (16.4)	−18.2 (20.2)	0.003

There was no significant difference in response rate between patients who were using hypnotics before the trial and those who had no previous experience with hypnotics. Of patients who used hypnotics before the trial 72% responded to PR-melatonin as compared to 20% who responded to placebo ($P < 0.01$).

The effects of PR-melatonin (2 mg 3 weeks) on quality of sleep ratings (QON) are presented in Fig. 3a. Patients treated with PR-melatonin reported a statistically significant improvement in QON compared with those at placebo run-in (3.2 versus 2.3 units, $P < 0.0001$). Compared with the parallel placebo arm, the mean improvement in QON reported in the PR-melatonin group was significantly higher than that in the placebo treated group (0.89 versus 0.46 U, $P = 0.003$). In the PR-melatonin treated group 54.8% of the patients reported on improvement in QON by 1 categorical

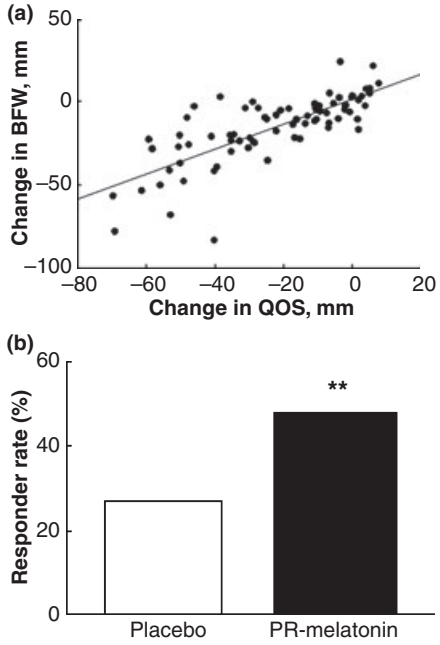

Figure 2. (a) Correlation between the change from baseline (end of run-in) in end of PR-melatonin treatment LSEQ-QOS and BFW values. Rval = 0.77; ****$P < 0.001$. (b) Clinical response rate (% patients showing concomitant improvements of ≥10 mm in both QOS and BFW of total patients in group) with PR-melatonin treatment **$P \leq 0.01$.

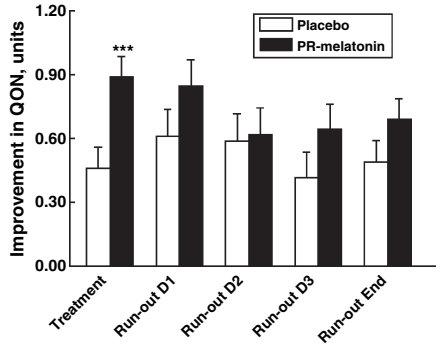

Figure 3. Effect of PR-melatonin versus placebo on QON (mean + -SEM change from baseline) following the 3 weeks randomized treatment period, withdrawal days 1, 2, 3 and end (2 weeks) of placebo run-out. *P*-values are for comparisons between the effects of placebo and PR-melatonin. ***$P \leq 0.005$.

unit or more by the end of the 3 weeks treatment period, 45.2% reported on no change (between 1 and −1) and none(0%) reported on worsening by 1 U or more. Respective results in the placebo treated arm were 39.1% reporting on improvement, 55.2% on no change and 5.7% reporting on worsening in QON. This difference in treatment effects between PR-melatonin and placebo was significant ($\chi^2_{(2)} = 7.09$; $P = 0.029$).

For the other two secondary efficacy parameters, GTS and AFS derived from the LSEQ and the QOD derived from the diary cards improvement from baseline did not significantly differ between treatments.

No interaction was found between treatment effects and any concomitant medications (including atenolol) taken in the study.

Withdrawal symptoms

A decline in the improvement experienced by PR-melatonin patients for the primary as well as secondary efficacy parameters was apparent once treatment had been stopped. However by the end of the 2 weeks run-out period, QOS, BFW and QON values were still better than the respective baseline values. No such decline was seen in the placebo group (Figs 1, 3). Rebound insomnia in patients was evaluated for the first three nights of the placebo run-out period. During each of the three nights, as well as the last three nights by the end of the 2-week run-out period, patients in the PR-melatonin treatment group maintained a similar or greater improvement in QON from baseline when compared with those receiving placebo (Fig. 3).

Results from the Tyrer Questionnaire, which assesses withdrawal symptoms, showed no apparent relationship to either treatment group for new symptoms experienced during the run-out period compared with the double-blind period with 29% of patients in each group experiencing new symptoms. In the PR-melatonin group, the most prevalent symptoms at run-out were muscle pain, widespread tingling and prickling and an unusual taste in the mouth. In the placebo group, the most prevalent symptoms at run-out were muscle spasms, muscle pains, tremors, feeling of unreality, depression, memory lapses and nausea. None of these symptoms were new.

Tolerability and safety

There were no clinically significant changes or remarkable differences between the treatment groups in vital signs or physical examination results following 3 weeks of double-blind study treatment. During the treatment period, 18 patients reported treatment emergent adverse events (AEs) with nine patients in each treatment group. Most reported AEs were mild in severity. The most commonly reported AEs during the double-blind period of the study were diarrhoea (1 patient in each group), haematuria and urinary tract infection each occurring in two patients randomized to placebo. One severe adverse event (anxiety) occurred during the double-blind period of the study in a patient randomized to receive placebo.

DISCUSSION

The results of this randomized placebo controlled study indicate that PR-melatonin significantly improves quality of sleep in patients with primary insomnia aged 55 years and older compared with placebo treatment. The improvement in QOS was even more pronounced in patients with more severe sleep difficulties. Because insomnia is associated with significant daytime distress, improvement in sleep is only of value if it

produces benefits to the patient in well-being or performance the following day. The efficacy of PR-melatonin is thus further demonstrated in significantly improving self-reported morning alertness compared with placebo treatment.

It is important to note that in principle on the 100 mm LSEQ scales a value of 50 mm (centre of the VAS) means no change and a movement of 50 mm to the low end of the VAS represents maximal improvement possible. In reality mean QOS, at baseline was approximately 65 mm and the mean movement of 22 mm to the low end of the VAS thus represents 34% of the maximal improvement the patient may experience. Mean BFW improved by 15.7 mm from the baseline values; this improvement represents 26% of the maximal benefit the patient may experience. Moreover, the improvement in BFW was highly correlated with the improvement in QOS (Rval 0.77; $P < 0.001$) suggesting an increase in the restorative value of sleep. This has proven difficult to demonstrate for most hypnotics and also for the melatonin receptor agonist ramelteon recently approved by the US-FDA for sleep-onset insomnia, none of which has beneficial effects on morning alertness (Glass *et al*., 2005; Roth *et al*., 2006). While not measured here, it is important to note that the shrotening of sleep latency with PR-melatonin has been shon to be similar to that of zopiclone (Paul *et al*., 2004b) and zaleplon (Paul *et al*., 2004a), and its effect over placebo is of a magnitude comparable with that published for other hypnotics such zaleplon and ramelteon (Ancoli-Israel *et al*., 1999; Roth *et al*., 2006).

Responder rate analysis is a well-recognized mean for establishing clinical relevance of observed effects in clinical trials (Kieser *et al*., 2004). The difference of 20% in rate of patients who demonstrated concomitant and clinically relvant imporvements in QOS and BFW, corresponds to an NNT (Number Needed to Treat, number of patients who must receive a particular therapy to reach a benefit) of five. This is further supported by the improvement in QON wherein the difference between the PR-melatonin and placebo responder rates is 15.7%, which corresponds to an NNT of six. According to a recent meta-analysis the efficacy of the major hypnotic drugs in improving sleep quality in the elderly population is much lower, with an NNT value of 13 (Glass *et al*., 2005).

Bellon (2006) proposed that patients who have never received benzodiazepines or non-benzodiazepines hypnotics would respond better to melatonin. We find no support for such hypothesis in this trial as the same and even a tendency for a somewhat greater response rate was found among patients who had previously been treated with hypnotics. This supports the notion that PR-melatonin has a different efficacy profile than these drugs.

The mechanism of action behind this effect of PR-melatonin on morning alertness remains to be elucidated. Recent studies in healthy volunteers indicated that the effects of zopiclone, zaleplon and temazepam on sleep induction were accoompanied with detrimental effects on psychomotor performance whereas, PR-melatonin, in spite of a prolonged period of perceived sleepiness, caused no impact on performance (Paul *et al*., 2003, 2004a). Thus, it is possible that with sedative hypnotics improvement in morning alertness is masked by their CNS depressant effects whereas no such suppression occurs with PR-melatonin. Another explanation relates to the effects of PR-melatonin on the cortisol rhythm. Elevation of plasma cortisol impairs sleep in middle-aged but not younger adults (Vgontzas *et al*., 2001). Elevated nocturnal plasma and urinary cortisol levels correlated with impaired sleep in patients with severe primary insomnia (Rodenbeck *et al*., 1998). Exploratory studies in patients with insomnia aged 55 years and older, suggested that administration of PR-melatonin in the evening was able to rectify the early onset cortisol production (Zisapel *et al*., 2005). This delay in nocturnal cortisol onset may explain in part the improvement in sleep quality and morning alertness in elderly patients with insomnia.

The pharmacological activity of PR-melatonin is also evident from the decline seen in all efficacy parameters after stopping the active treatment, while no such decline was seen after placebo. The discontinuation of PR-melatonin was not associated with any rebound effects in quality of sleep and morning alertness. Moreover, during the first nights after discontinuation, the benefit to patients was still evident, suggesting a sustained effect, not simply symptom management. In addition, with PR-melatonin, as with the melatonin agonist ramelteon (Roth *et al*., 2006) patients did not show any emerging symptoms during the run-out period, suggesting a lack of treatment-withdrawal effects. Noticeably, because it has shown no evidence of abuse and dependence ramelteon is not designated as a controlled substance thus allowing it to be prescribed for the long-term period. An extremely good safety profile of PR-melatonin was demonstrated with no obvious differences in safety parameters between the active treatment and the placebo group.

In conclusion, while impairments in health, function and quality of life are a central feature of insomnia, insomnia treatment has been targeted solely to improving problems falling and staying asleep. This study shows that 3-week nightly PR-melatonin administration improves patient-reported quality of sleep and increases morning alertness in a 55 years and older insomnia patient population suggesting enhancement in the restorative value of sleep. There was no evidence of significant rebound insomnia or withdrawal effects after the discontinuation of treatment. With the safety and unique efficacy profiles, PR-melatonin represents a new and valuable treatment for insomnia in patients aged 55 years and older.

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