ORIGINAL ARTICLE

Efficacy of prolonged release melatonin in insomnia patients aged 55–80 years: quality of sleep and next-day alertness outcomes

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ABSTRACT

Objective: Melatonin, the hormone produced nocturnally by the pineal gland, serves as a circadian time cue and sleep-anticipating signal in humans. With age, melatonin production declines and the prevalence of sleep disorders, particularly insomnia, increases. The efficacy and safety of a prolonged release melatonin formulation (PR-melatonin; Circadin* 2 mg) were examined in insomnia patients aged 55 years and older.

Design: Randomised, double blind, placebo-controlled.

Setting: Primary care.

Methodology: From 1248 patients pre-screened and 523 attending visit 1, 354 males and females aged 55–80 years were admitted to the study, 177 to active medication and 177 to placebo. The study was conducted by primary care physicians in the West of Scotland and consisted of a 2-week, single blind, placebo run-in period followed by a 3-week double blind treatment period with PR-melatonin or placebo, one tablet per day at 2 hours before bedtime.

Main outcome measures: Responder rate (concomitant improvement in sleep quality and morning alertness on Leeds Sleep Evaluation Questionnaire [LSEQ]), other LSEQ assessments, Pittsburgh Sleep Quality Index (PSQI) global score, other PSQI assessments, Quality of Night and Quality of Day derived from a diary, Clinical Global Improvement scale (CGI) score and quality of life (WHO-5 well being index).

Results: Of the 354 patients entering the active phase of the study, 20 failed to complete visit 3 (eight PR-melatonin; 12 Placebo). The principal reasons for drop-out were patient decision and lost to follow-up. Significant differences in favour of PR-melatonin vs. placebo treatment were found in concomitant and clinically relevant improvements in quality of sleep and morning alertness, demonstrated by responder analysis (26% vs. 15%; $p = 0.014$) as well as on each of these parameters separately. A significant and clinically relevant shortening of sleep latency to the same extent as most frequently used sleep medications was also found (–24.3 vs.–12.9 minutes; $p = 0.028$). Quality of life also improved significantly ($p = 0.034$).

Conclusions: PR-melatonin results in significant and clinically meaningful improvements in sleep quality, morning alertness, sleep onset latency and quality of life in primary insomnia patients aged 55 years and over.

Trial registration: The trial was conducted prior to registration being introduced.

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* Circadin is a registered trade name of Neurim Pharmaceuticals Ltd, Tel Aviv, Israel

Introduction

Insomnia is a subjective complaint of sleep described as delayed, insufficient in duration and/or poor in quality (non-restorative sleep). The sleep disturbance (or associated daytime fatigue) causes clinically significant distress or impairment in social, occupational, or other important areas of functioning (Diagnostic and Statistical Manual for Mental Disorders [DSM-IV]). While inadequate quantity of sleep (sleep duration, sleep latency, number of arousals) are reliably measured in the sleep laboratory, the term 'sleep quality' represents a complex phenomenon that is difficult to define and measure objectively as it contains purely subjective aspects such as 'depth' or 'restful' sleep. Nevertheless 'sleep quality' better reflects the concept of insomnia defined in DSM-IV in the sense that it is more closely related to daytime functioning and wellbeing than the objective, sleep laboratory measurements where there is a significant overlap in the distribution of sleep recordings for subjectively defined insomniacs and good sleepers. The elderly are particularly liable to suffer from insomnia[1]. Even in healthy subjects age is negatively correlated with subjective sleep quality and daytime dysfunction[2]. 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[3–5]. Average sleep quality rather than quantity appears to be better related to health and affects balance and satisfaction with life[6,7]. 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[8]. Although much of the outcome of insomnia derives 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[9,10].

Among the wide variety of available treatments for sleep disturbances, the most commonly prescribed hypnotics are benzodiazepines and non-benzodiazepines ('Z-drugs'), both classes of which are gamma-aminobutyric acid (GABA)-A receptor modulators. Hypnotics primarily address insomnia related to quantitative sleep problems (increased sleep latency, shorter sleep duration) but not necessarily sleep quality, and furthermore fail to improve and even adversely affect daytime vigilance[11,12]. Newer treatments of insomnia with favourable daytime consequences are therefore sought.

Melatonin (N-acetyl-5-methoxytryptamine), the major hormone nocturnally produced by the pineal gland, is a sleep regulator and signal of darkness in humans[13]. Thus, the circadian rhythm in synthesis and secretion of melatonin is closely associated with the sleep rhythm in both sighted and blind subjects[14,15]. Daytime administration of exogenous melatonin (when it is not present endogenously) promotes sleep in humans[16,17], presumably by inhibiting circadian wakefulness mechanisms[18,19] and results in modified brain activity compatible with sleep anticipation[20,21]. It is also known that endogenous melatonin levels decrease with age[22]. Decline in melatonin may contribute to the common complaint of poor sleep quality seen among elderly people[23–25]. This raises the possibility of improving sleep in elderly patients by treatment with melatonin substitution. Melatonin itself has a very short half-life and is quickly cleared from the circulation with physiological levels being maintained during the night by continuing output from the pineal gland. PR-melatonin (Circadin* 2 mg) is a prolonged-release formulation of melatonin which when administered orally produces levels of melatonin over the subsequent 8–10 hours thus mimicking the physiological profile. Many previous studies of melatonin in insomnia have been hampered by the wide variety of formulations and doses of melatonin studied, the range of ages of patients studied and the incosistency of outcomes evaluated and insufficient statistical power[26]. A number of studies have demonstrated the objective effectiveness of PR-melatonin in various sleep parameters: sleep latency, efficiency and wake after sleep onset in patients aged 55 years and older. This study was conducted to investigate whether or not treatment with PR-melatonin 2 mg would improve quality of sleep and next-day alertness of older patients suffering from primary insomnia.

We hypothesized that PR-melatonin would significantly improve both quality of sleep and morning alertness compared to placebo in these patients. We selected the Leeds Sleep Evaluation Questionnaire (LSEQ) as the primary tool for these measurements[27]. The LSEQ comprises 10 horizontal 100 mm visual analog scales relating to the following aspects of sleep and daytime behaviour: getting to sleep (GTS; questions 1, 2 and 3); quality of sleep (QOS) (questions 4 and 5); awakening from sleep (AFS; questions 6 and 7); and behaviour following wakening (BFW; questions 8, 9 and 10). The LSEQ is a valid and reliable measure of the effects of drugs on sleep and daytime effects[28] and has been validated in a number of studies, including some involving the PR-melatonin target population (insomnia patients 55 years and older)[29,30]. Furthermore, impaired quality of sleep as assessed by LSEQ was strongly associated with impaired quality of life[31].

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Responder rate analysis for establishing clinical relevance of observed effects in clinical trials is well recognized and is recommended in the European regulatory guidelines for clinical trials[32]. To establish clinical relevance of the observed effects, the minimal clinically significant difference in QOS, which is the difference that is clinically meaningful to the patient, was determined by an anchor-based method using ratings on a five-point severity scale and found to equal 10 mm[33]. As a clinically significant improvement in quality of sleep should lead to improved morning alertness, a responder was defined as a patient who showed improvement in both parameters, that is concomitant improvement from baseline by 10 mm or more on both the QOS and BFW variables of the LSEQ.

Patients and methods

Study design

This was a randomised, double-blind, parallel group clinical trial comprising a 2 week, single-blind, placebo run-in period followed by a 3 weeks double-blind treatment period in which patients were randomised to receive PR-melatonin (Circadin 2 mg, Neurim Pharmaceuticals Ltd, Tel Aviv, Israel), or placebo, given orally as one tablet per day 2 hours before bedtime.

Study subjects

General practitioners in Glasgow and the surrounding areas (West of Scotland) recruited patients into the study. Study visits were conducted by specially selected and trained general practitioners (GPs) along with full-time professional trained research nurses assigned to the practices especially for this purpose.

Patients expressing interest in participating in the study were pre-screened for suitability by the nurses using a telephone interview. 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 questionnaire (SHQ) adopted from The Management of Insomnia Guidelines for Clinical Practice[34]. A similar SHQ has recently been recommended by Clinical Practice Guideline-Adult Insomnia[35]. The SHQ characterises the primary sleep complaint according to the different diagnostic criteria (DSM-IV and International Classification of Diseases [ICD]-10). The questionnaire also helps in differentiating primary insomnia from secondary insomnia due to 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, an important element in the evaluation of insomnia patients with medical symptoms[35], was performed at the screening visit by a qualified clinician. In order 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 3 months before the study were excluded. A positive drug screen on visit 2 for benzodiazepines or morphine derivatives led to immediate exclusion. Suitable patients were invited to visit 1 during which they were consented and assessed for inclusion. Major exclusion criteria for the study included use of benzodiazepine or non-benzodiazepine hypnotics within the previous 2 weeks or any psychoactive treatment within the previous 3 months, sleep disorders associated with a psychiatric disorder (e.g., depression, anxiety, dementia), sleep disorders secondary to another medical condition (e.g., sleep apnoea, circadian rhythm sleep disorder), use of prohibited concomitant medication or excessive alcohol consumption, any chronic medical condition that was likely to be the cause of the sleep problem (e.g., chronic pain, benign prostatic hypertrophy) or might interfere with the conduct of the study or a lifestyle likely to interfere with sleep patterns (e.g., shift work, jet-lag). Patients considered for entry into a 2 week placebo run-in phase were males and females aged between 55 and 80 years who were suffering from primary insomnia according to the DSM-IV criteria.

After the 2 week placebo run-in period patients returned for visit 2 and their eligibility was re-evaluated. Patients completed the Leeds Sleep Evaluation Questionnaire (LSEQ) for the three consecutive nights by the end of the baseline period. Patients were eligible to be included in the analysis of the pre-defined study primary and secondary endpoints and were randomised, provided they continued to meet major entry criteria and demonstrated persistent sleep quality complaints (QOS) rating of 40 mm and over on the LSEQ at the end of the single-blind placebo run-in period.

Randomisation was achieved by making a call to an Interactive Voice Response System and receiving

an assigned treatment pack number. The random sequences were in the form of randomly permuted blocks of four nested within study site.

The final study assessments at visit 3 were made 3 weeks after randomisation. Samples were taken at each visit for haematology, biochemistry and urinalysis and adverse events were recorded.

The study protocol and relevant documents were approved by Huntingdon Multi-centre Research Ethics Committee, Cambridge, UK. Participants provided written informed consent.

Endpoints

The primary objective of the study was to compare the relative frequencies of occurrence of patients showing concomitant improvements of 10 mm or more on QOS and BFW in the two treatment groups.

Patients completed the LSEQ for the three consecutive nights at the end of each period. A score on the left of each scale of the LSEQ represents deterioration from usual and the right of each scale represents improvement from usual. A mark in the middle of the scale indicates that no change from usual has been reported. A 3 nights' mean score was calculated for each of the two variables (QOS, BFW) recorded on the last 3 nights of the baseline and treatment periods.

The secondary objectives were to compare the effects of PR-melatonin versus placebo at the end of the 3-week treatment period on the following variables:

(1) The 3 nights' mean of individual parameters derived from the LSEQ (namely GTS, QOS, AFS and BFW); recorded on the last 3 nights of the baseline and treatment periods.

(2) The global score from the Pittsburgh Sleep Quality Index (PSQI)[36,37]. The PSQI comprises nine questions relating to the patient's usual sleep habits during the previous 2 weeks; the second and third weeks of active treatment. It addresses possible reasons for trouble in sleeping as well as daytime behaviour. The patient is asked to give the most accurate reply for the majority of days and nights during this period. An algorithm is used to calculate seven component scores and these are added to give a global PSQI score. The PSQI has been recommended as an essential measure for global sleep and insomnia symptoms in recent expert consensus recommendations for a standard set of research assessments in insomnia[36].

(3) The PSQI component scores, Question 2 (sleep latency) and Question 4 (total sleep time) after 3 weeks' double-blind treatment and the change from baseline levels of these parameters. It has been shown that each of the PSQI individual

component scores measures a particular aspect of the overall construct. Furthermore, control subjects differ from insomnia patients in all individual components[2]. However, the correlation between individual items and global score ranged from 0.83 (subjective sleep quality) to 0.07 (cough or snore during sleep)[2]. In the evaluation of the drug effects it was therefore interesting to look at each component.

(4) The quality of night (QON) and quality of day (QOD) mean daily scores derived from a sleep diary. Patients were instructed to rate each morning the quality of their sleep (QON) over the previous night; and each evening the overall quality of their day (QOD) on a five-point severity rating scale: 1, very bad; 2, bad; 3, fair; 4, good; 5, very good. The results of the 3 last nights of each period were averaged and the changes in each parameter from run-in placebo to treatment were calculated for each patient.

(5) The Clinical Global Improvement (CGI) score[38] was assessed by the clinician at visit 3 following 3 weeks double-blind treatment, the comparison being to baseline, visit 2.

(6) Quality of life derived from the WHO-5 Wellbeing index[39]. This covers positive mood, vitality and general interests.

Statistical issues

Baseline characteristics are summarised as means and standard deviations for continuous variables and ordinal scores, and counts and percentages for categorical variables.

The results presented in this paper are based on patients who met all major entry criteria, had persistent sleep quality complaints at the end of the placebo run-in period and were randomised and provided outcome data at visit 3. This is referred to as the 'full analysis set'. The primary endpoint was analysed using a chi-square test for association, with the odds ratio and 95% confidence interval for PR-melatonin versus placebo calculated from a logistic regression model with randomised treatment group as the only independent variable. For the primary outcome an additional 'intention to treat' analysis was carried out based on all randomised patients, with those without follow-up at visit 3 assumed not to have achieved a primary outcome. It was estimated that 166 patients per treatment group would be required to detect a difference in response rates in the primary efficacy variable between PR-melatonin groups and the placebo group at a 5% significance level with 80% power, assuming the true response rates were 46% for PR-melatonin and 31% for placebo.

For the secondary endpoints (1), (2), (3) (4) and (6) above, the outcomes at visit 3 were compared between the treatment groups, adjusting for the visit 2 measurement using analysis of covariance. Analysis of covariance was also used for the CGI at visit 3 adjusted for the score at visit 2.

Adverse event data were summarised for all subjects randomised to study medication.

Results

Patient disposition and demographics

The passage of the participants through the study is depicted in the CONSORT diagram in Figure 1. A total of 523 patients attended visit 1 and provided informed consent. Of these, 99 failed to demonstrate persistent sleep quality complaints and 70 did not meet other inclusion/exclusion criteria. The remaining 354 patients were eligible for inclusion in the analysis of the primary and secondary outcomes and were randomised: 177 to receive PR-melatonin and 177 to receive placebo. Eight patients (3.5%) in the PR-melatonin group and 12 patients (5.3%) in the placebo group were withdrawn during the double-blind phase and had no outcome data at visit 3. The full analysis set therefore comprised 334 patients – 169 in the PR-melatonin group and 165 in the placebo group. Patients' baseline characteristics were similar in the two treatment groups (Table 1).

Efficacy evaluation

For the full analysis set, 44 (26.0%) patients in the PR-melatonin group showed an improvement of 10 mm or more on both the QOS and BFW scales of the LSEQ, while 25 (15.2%) of the placebo group demonstrated this improvement ($p = 0.014$), odds ratio (95% CI) for
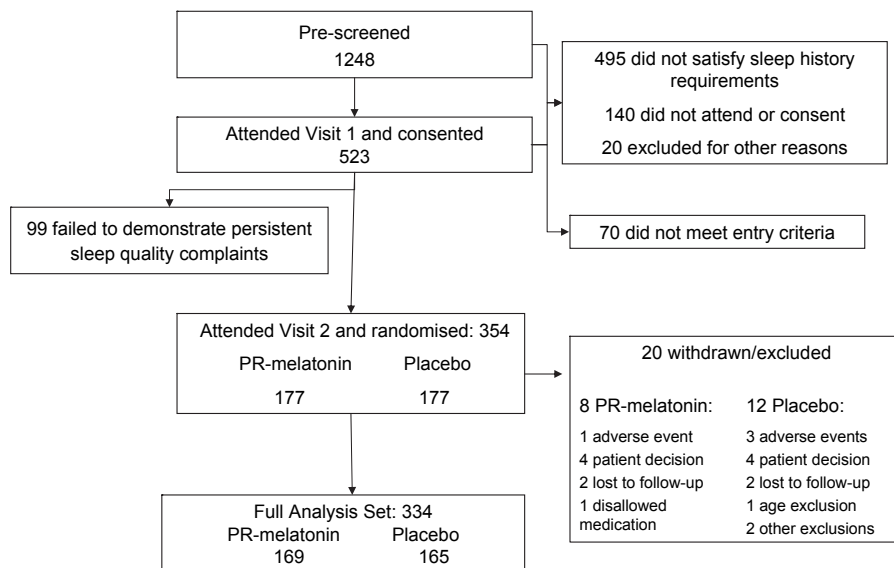

Figure 1. *Consort diagram*

Table 1. *Baseline characteristics of the full analysis set of patients. Numbers are mean (standard deviation) unless stated otherwise indicated*

	PR-melatonin (n = 169)	Placebo (n = 165)	Total (n = 334)
Age, years	66.1 (6.4)	65.3 (6.3)	65.7 (6.4)
BMI, kg/m^2	26.5 (4.0)	26.6 (3.4)	26.6 (3.7)
Seated SBP, mmHg	140 (15)	136 (15)	138 (15)
Seated DBP, mmHg	80 (11)	79 (9)	80 (10)
Heart rate, bpm	71 (9)	71 (8)	71 (9)
Sex, n (%) male	68 (40)	65 (39)	133 (40)
Current smoker, n (%)	20 (12)	21 (13)	41 (12)

BMI = body mass index; bpm = beats per minute; DBP = diastolic blood pressure; SBP = systolic blood pressure

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PR-melatonin versus placebo 1.97 (1.14, 3.41). The corresponding result for the intention to treat analysis yielded a 25% improvement rate for PR-melatonin compared to 14% for placebo ($p = 0.011$), odds ratio (95% CI) 2.01 (1.17, 3.46) (Table 2).

The results for the secondary outcomes are given in Table 3. These demonstrate statistically significant improvement in the PR-melatonin group compared

to placebo for the individual components of the LSEQ (QOS and BFW) of the primary endpoint when assessed on a continuous scale ($p = 0.014$ and $p = 0.038$, respectively) and for GTS ($p = 0.013$), with a trend to improvement for AFS. There was a trend to improvement for the PSQI total score ($p = 0.081$). There was a significant improvement for sleep quality (Component 1 of the PSQI) ($p = 0.036$). PR-melatonin improved mean sleep latency (Q2 of the PSQI) by 24.3 minutes compared to 12.9 minutes for the placebo. With PR-melatonin, baseline adjusted sleep latency was shorter by 8.8 minutes ($p = 0.028$, 95% CI (1.0, 16.7)mins) over that with placebo. Total sleep time (Q3 of the PSQI) was not significantly improved (0.8 hour improvement on PR-melatonin vs. 0.6 on placebo) on PR-melatonin ($p = 0.14$, 95% CI (–0.2, 0.5) hours).

Similarly, there were trends to improvement for QON and QOD, as measured from the patient diary cards, that just failed to reach statistical significance for QON ($p = 0.054$). These findings were supported by a trend to improvement for the CGI.

A statistically significant better outcome for the PR-melatonin group on the WHO-5 well being index ($p = 0.034$) was demonstrated and 70% of patients who responded to PR-melatonin (i.e. demonstrated concomitant improvements in QOS and BFW)

Table 2. *Primary endpoint: responder rate analysis of PR-melatonin versus placebo in two components of the Leeds Sleep Evaluation Questionnaire: quality of sleep (QOS) and behaviour following wakefulness (BFW)*

	PR-melatonin		Placebo	
	n	%	*n*	%
Improvement of ≥ 10 mm on the Leeds QOS and BFW scales				
Yes	44	(26)	25	(15)
No	124	(73)	139	(84)
Missing	1		1	

Odds-ratio for PR-melatonin versus placebo = 1.97 (95% CI 1.14, 3.41)
Chi-square test = 6.04, $p = 0.014$

Table 3. *Secondary endpoint data: Results presented are mean (standard deviation) of results at visit 2 (V2) and visit 3 (V3) and of the change (V3 – V2) for each outcome and for each treatment group*

	PR-melatonin			Placebo				
	V2	V3	(V3 – V2)	V2	V3	(V3 – V2)	ETE	*p*-value
LSEQ, mm								
QOS	54.5 (9.3)	45.9 (16.0)	–8.6 (16.3)	53.7 (9.7)	49.5 (14.8)	–4.2 (14.7)	–4.0 (–7.2, –0.8)	0.014
BFW	51.6 (10.6)	44.7 (15.3)	–7.0 (14.1)	52.2 (12.1)	48.0 (14.4)	–4.1 (13.9)	–3.0 (–5.9, –0.2)	0.038
GTS	53.0 (7.6)	45.7 (13.8)	–7.3 (13.3)	52.0 (7.5)	48.4 (11.4)	–3.6 (11.3)	–3.3 (–5.8, –0.7)	0.013
AFS	52.0 (8.4)	47.5 (14.2)	–4.5 (13.4)	52.7 (9.6)	49.8 (13.0)	–2.9 (14.3)	–2.0 (–4.8, 0.8)	0.16
PSQI								
Total	10.6 (2.6)	8.1(3.7)	–2.5 (3.3)	10.4 (2.7)	8.6 (3.7)	–1.8 (3.3)	–0.6 (–1.3, 0.1)	0.081
C1 (sleep quality)	2.0 (0.7)	1.4 (0.8)	–0.6 (0.9)	2.0 (0.7)	1.6 (0.8)	–0.4 (0.8)	–0.2 (–0.3, –0.0)	0.036
Q2 (sleep latency, minutes)	65.1 (70.7)	40.8 (54.5)	–24.3 (47.6)	57.9 (65.4)	45.0 (59.0)	–12.9 (39.7)	–8.8 (–16.7, –1.0)	0.028
Diary								
QON	2.6 (0.7)	3.0 (0.8)	0.4 (0.8)	2.6 (0.7)	2.9 (0.9)	0.3 (0.8)	0.2 (–0.0, 0.3)	0.054
QOD	3.1 (0.7)	3.4 (0.6)	0.2 (0.7)	3.3 (0.6)	3.4 (0.7)	0.1 (0.7)	0.1 (–0.0.0.2)	0.21
CGI	N/A	3.0 (1.1)	N/A	N/A	3.2 (1.1)	N/A	–0.2 (–0.4, 0.1)	0.14
WHO-5 index	16.0 (3.4)	17.7 (3.9)	1.7 (3.3)	15.5 (4.5)	16.6 (4.5)	1.1 (4.0)	0.8 (0.1, 1.5)	0.034

The estimated treatment effect (ETE) [PR-melatonin – placebo] (95% confidence interval) and associated *p*-value is also given as estimated from the ANCOVA. The exception is for the Clinical Global Improvement scale (CGI) where there was no equivalent baseline score and adjustment is for the Global Clinical Impression at baseline

AFS = awakening from sleep; BFW = behaviour following wakening; C1 = component 1; CGI = Clinical Global Improvement scale; GTS = getting to sleep; LSEQ = Leeds Sleep Evaluation Questionnaire; PSQI = Pittsburgh Sleep Quality Index; Q2 = question 2; QOD = quality of day; QON = quality of night; QOS = quality of sleep

experienced a clinically relevant improvement in quality of life (equivalent to 3 units or more on the WHO-5 scale) compared to only 24% in non-responders.

Safety evaluation

Adverse events were ascertained for all patients during the study and up to 30 days following completion of the double-blind therapy. In the PR-melatonin group 43 (24%) patients reported 50 events. In the placebo group 37 patients (21%) reported 49 events. The most commonly reported adverse events were 'Nasopharyngitis' and 'Headache or migraine'. 'Nasopharyngitis' was reported by five patients in the PR-melatonin group and by four patients in the placebo group. 'Headache or migraine' accounted for four events in the PR-melatonin patients and 11 in placebo patients. Only one adverse event was reported as severe. This was a case of 'emotional distress due to a bereavement' in a patient in the PR-melatonin group.

Pulse and temperature measurements were similar for the two treatment groups at each visit (data not shown) and there were no differences between the two groups in laboratory measurements.

Discussion

The primary endpoint for the study was the rate of patients responding to the dual outcome of improvement in quality of sleep and morning alertness. The results show that PR-melatonin was superior to placebo and this is supported by improvement in the individual components of the LSEQ. Further, all variables studied were either significantly improved in the PR-melatonin group or tended to benefit. In particular, there were significant improvements in sleep latency as measured by the PSQI and the LSEQ and in quality of life as measured by the WHO-5 index. The difference in the percentage of responders between the PR-melatonin and placebo groups is 11% in the full analysis set, corresponding to a number needed to treat (NNT) value of 9. For comparison, the results of a recent meta-analysis which evaluated the efficacy of hypnotic drugs in the elderly population show that these drugs, which are acknowledged effective hypnotics, have a NNT value of 13[11] in improving sleep quality. No improvement of morning alertness or daytime vigilance has ever been claimed or demonstrated for any of these drugs. The chance of being a responder showing a concomitant improvement in quality of sleep and morning alertness in the PR-melatonin group was almost twice that of the placebo group (odds ratio 1.97). The odds ratio for response in the single outcome of sleep quality with zaleplon 10 mg was reported to be 1.12 after 1 week and 0.86 after 2 weeks of treatment[40]. Indeed, zaleplon is not claimed or demonstrated to have a beneficial effect on quality of sleep. An odds ratio of 2 provides clear evidence that PR-melatonin's effect on the subjective quality of sleep and morning alertness is clinically relevant.

Sleep performs a restorative function for the brain and body, improving the sense of energy and 'wellbeing'[41]. Improvement in sleep should thus improve the patient's wellbeing the following day. This has proven difficult to demonstrate for most hypnotics. We have demonstrated significant improvements in morning alertness as measured by LSEQ and quality of life as measured by WHO-5. This effect on quality of life further demonstrates the clinical relevance of the positive effect on morning alertness. Thus, not only is the percentage of subjects likely to respond to PR-melatonin twice that of placebo, but also that the improvement with PR-melatonin is more likely to result in improved quality of life. In contrast, according to a recent meta-analysis[11] of sedative hypnotics adverse cognitive events were 4.78 times more common ($p < 0.01$) and reports of daytime fatigue were 3.82 times more common ($p < 0.001$) in individuals using a hypnotic compared with placebo.

Significant differences in favour of PR-melatonin were also found in sleep latency as measured by the PSQI. The improvement in sleep latency (8.8 minutes over placebo) is of a magnitude similar to that of zaleplon and ramelteon (8 minutes over placebo)[12,40,42].

PR-melatonin demonstrated a good safety profile with no obvious differences in safety parameters between the active treatment and placebo groups. It is also important to note that unlike benzodiazepine and non-benzodiazepine ('z-drugs') hypnotics, PR-melatonin use is not associated with impairment of psychomotor functions, memory recall and driving skills in this population[43].

Future studies should assess the implications of the improvement in morning alertness on social and occupational functioning and maintenance of these effects.

Conclusions

The results of this study demonstrate that in older patients suffering from non-restorative sleep

the use of PR-melatonin can produce clinically relevant improvements in sleep quality and morning alertness resulting in an improvement in a sense of wellbeing. Improvements in sleep latency were also observed.

The safety and efficacy profile of PR-melatonin, as used in this study, and lack of detrimental effects on memory and vehicle driving shown in other studies, supports its use in the treatment of primary insomnia in patients over the age of 55 years.

Acknowledgements

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