Clinical Interventions in Aging

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ORIGINAL RESEARCH

Add-on prolonged-release melatonin for cognitive function and sleep in mild to moderate Alzheimer's disease: a 6-month, randomized, placebo-controlled, multicenter trial

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Purpose: A link between poor sleep quality and Alzheimer's disease (AD) has recently been suggested. Since endogenous melatonin levels are already reduced at preclinical AD stages, it is important to ask whether replenishing the missing hormone would be beneficial in AD and whether any such effects would be related to the presence of sleep disorder in patients.

Patients and methods: The effects of add-on prolonged-release melatonin (PRM) (2 mg) to standard therapy on cognitive functioning and sleep were investigated in 80 patients (men [50.7%], women [49.3%], average age 75.3 years [range, 52–85 years]) diagnosed with mild to moderate AD, with and without insomnia comorbidity, and receiving standard therapy (acetylcholinesterase inhibitors with or without memantine). In this randomized, double-blind, parallel-group study, patients were treated for 2 weeks with placebo and then randomized (1:1) to receive 2 mg of PRM or placebo nightly for 24 weeks, followed by 2 weeks placebo. The AD Assessment Scale–Cognition (ADAS-Cog), Instrumental Activities of Daily Living (IADL), Mini–Mental State Examination (MMSE), sleep, as assessed by the Pittsburgh Sleep Quality Index (PSQI) and a daily sleep diary, and safety parameters were measured.

Results: Patients treated with PRM (24 weeks) had significantly better cognitive performance than those treated with placebo, as measured by the IADL (P=0.004) and MMSE (P=0.044). Mean ADAS-Cog did not differ between the groups. Sleep efficiency, as measured by the PSQI, component 4, was also better with PRM (P=0.017). In the comorbid insomnia (PSQI ≥6) subgroup, PRM treatment resulted in significant and clinically meaningful effects versus the placebo, in mean IADL (P=0.032), MMSE score (+1.5 versus −3 points) (P=0.0177), and sleep efficiency (P=0.04). Median ADAS-Cog values (−3.5 versus +3 points) (P=0.045) were significantly better with PRM. Differences were more significant at longer treatment duration. PRM was well tolerated, with an adverse event profile similar to that of placebo.

Conclusion: Add-on PRM has positive effects on cognitive functioning and sleep maintenance in AD patients compared with placebo, particularly in those with insomnia comorbidity. The results suggest a possible causal link between poor sleep and cognitive decline.

Keywords: acetylcholinesterase inhibitors, memantine, insomnia

Introduction

Alzheimer's disease (AD), a degenerative brain disorder, is the leading cause of dementia in the elderly. The classic hallmarks of AD are cognitive dysfunction and psychiatric and behavioral disturbances, which lead to progressive deterioration of memory, language, and intellect.[1] The degenerative process often produces neurobehavioral symptoms, including sleep disturbances, mainly characterized by nighttime

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awakenings.[2] Sleep has an important role in memory consolidation.[3,4] Emerging evidence links poor sleep to increased AD risk and memory loss.[5–8] However, to prove causality, it is important to show that improvement in sleep can ameliorate the disease.

The loss of cholinergic function is believed to contribute significantly to memory loss and cognitive dysfunction in AD. This deficiency can be partially alleviated by treatment with cholinergic agents, such as acetylcholinesterase inhibitors.[9] Acetylcholinesterase inhibitors, alone or together with memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist aimed at neuroprotection against glutamate neurotoxicity,[10] are the first-line drugs for AD today. However, the sleep problem is not addressed by these medications, and most current hypnotics are not useful because they further impair cognitive functioning[11–14] and may themselves be associated with an increased risk of dementia.[15,16]

Melatonin is the major hormone produced and secreted at night by the pineal gland into the cerebrospinal fluid (CSF) and circulation. It has a major role in regulation of the biological clock, particularly the sleep–wake cycle and the induction of physiological sleep.[17] Early neuropathological changes in AD are accompanied by decreased CSF melatonin levels.[18] The reduced melatonin levels are already found in the preclinical stages and correlate significantly with the severity of mental and sleep impairments in demented patients.[19]

Several studies, mostly open label, have reported on the beneficial effects of melatonin on cognitive decline and sleep in AD and in patients with mild cognitive impairment.[20–25] Of these, six were randomized, double-blind, placebo-controlled trials, with a total of 310 AD patients, mostly with advanced disease. These studies differed considerably in design, patient inclusion/exclusion criteria, melatonin preparations and doses used, end points, and treatment duration. Therefore, the questions, whether melatonin has beneficial effects on cognitive functions in AD, whether its effects are beyond those provided by the standard AD therapy, whether they are sustained over time, and to what extent the effects are driven by improvement in sleep, remain unanswered. These questions were addressed in the current study.

A prolonged-release melatonin (PRM) formulation (Circadin® 2 mg; Neurim Pharmaceuticals Ltd, Tel Aviv, Israel) was developed in order to circumvent the fast clearance of melatonin in the body (half-life [$T_{1/2}$] =0.54–0.67 hours) and has been licensed since 2007 in Europe, Australia, and other countries, for insomnia in patients aged 55 and older.[17] In the target population, PRM provides significant and clinically meaningful improvements in sleep quality, sleep onset latency, and quality of life and importantly, morning alertness and psychomotor performance.[26–28] In particular, it is not associated with negative effects on anterograde memory or cognitive functioning that are impaired in AD.[29] Because good sleep quality is imperative for cognitive functioning, particularly at older age,[5,6,30] the improvement of nighttime sleep and daytime alertness with PRM in AD patients may potentially also alleviate the sleep-related deficits in cognitive functioning. In addition, there is a growing body of evidence suggesting a beneficial effect of melatonin on behavioral deficits associated with cholinergic dysfunction.[31]

The aim of this randomized, placebo-controlled, 6-month study was to evaluate the effects of add-on PRM versus placebo on cognition and sleep, in patients with mild to moderate AD who are treated with standard AD therapy (acetylcholinesterase inhibitors, with and without memantine). For optimal treatment, patients were also instructed to have outdoor light exposure for at least 2 hours per day.[32]

Methods

Study design and participants

The study was performed in five centers, one in the UK (N=35 patients) and four in the USA (N=45 patients). The study protocol, informed consents, and amendments were approved in writing by the appropriate local site Independent Ethics Committee (IEC)/Institutional Review Boards (IRB) (National Health Service [NHS]-Scotland) (IEC, Helsinki Committee/IRB).

All potential candidates for the study were given a current copy of the Informed Consent Form (ICF) to read. Appropriate translations were provided in the native language of the subject. The investigator, study physician, or authorized investigative staff member explained all aspects of the study in lay language and answered all of the candidates' questions regarding the study. The candidates wishing to participate in the study were asked to sign the ICF. No study procedure was performed prior to signing the ICF. Subjects who refused to participate or who withdrew from the study were treated without prejudice. All subjects were given a copy of the signed ICF. Altogether, three ICFs were obtained for each participant outlining: the patient consent to participate, the caregiver consent for patient participation, and the caregiver consent to participate.

The patients were recruited outpatients. A total of 80 male and female outpatients (ages 50–85) diagnosed with mild to moderate AD and Mini–Mental State Examination (MMSE) score of ≥15 were recruited to the study. Patients had to have no evidence of focal disease to account for dementia, as

established by computed tomography (CT), positron emission tomography (PET), or magnetic resonance imaging (MRI) scans. Following diagnosis, all patients underwent a 2-week single-blind, placebo run-in period, followed by double-blind randomization to treatment with PRM (Circadin® 2 mg) or placebo for 24 weeks and a 2-week placebo run-out period (Figure 1). To prevent bias, matching placebo tablets, which were identical in appearance, taste, and odor, were used. The treatment was double-blinded, with two parallel treatment groups. Selection for a treatment group was determined by a computer-generated randomization list, in a 1:1 ratio (PRM 2 mg:placebo), using the randomized permuted blocks method. The patients were not synchronized in their living habits, except that study medication was administered orally, one tablet/day, 1–2 hours before bedtime, preferably at 9 pm, after dinner. In addition, patients were instructed to spend 2 hours a day in outdoor daylight. Patients had to have been on stable doses of acetylcholinesterase inhibitor (with or without memantine) for 2 months prior to recruitment. Patients who were using melatonin during the preceding 2 weeks or benzodiazepines or other hypnotics during the preceding 4 weeks and throughout the run-in period, were excluded.

Assessments

The efficacy measures included the change, from baseline to 12 and 24 weeks of the double-blind treatment period, on cognitive parameters assessed by the AD Assessment Scale–Cognition (ADAS-Cog),[33] Instrumental Activities of Daily Living (IADL),[34] and MMSE score[35] (at 24 weeks). Sleep parameters were assessed after 3, 12, and 24 weeks, by the Pittsburgh Sleep Quality Index (PSQI)[36] global score and individual components and by a sleep diary that documented number and duration of midsleep awakenings. The PSQI was completed by the investigator, or investigator designee, with the spouse or caregiver, and patient. In case of contradiction between the caregiver and patient response, the response of the caregiver was chosen. Overall clinical status was assessed by the Clinical Global Impression (CGI) scale,[37] behavioral signs and symptoms by the Neuropsychiatric Inventory (NPI) scale,[38] and patients' well-being by the World Health Organization (WHO)-5 Well-Being Index.[39] Caregiver's sleep was assessed by the Sleep Disorders Inventory (SDI).[40] The safety parameters were assessed at each visit and included spontaneously reported adverse events (AEs) or serious AEs (SAEs), and vital signs (heart rate and blood pressure), physical examination, and laboratory tests.

Statistical analysis

Based on extrapolation of the effect sizes and standard deviations reported by Asayama et al[21] a difference from baseline in the cognitive ADAS-Cog parameter of −3.29 for PRM and 0.5 for placebo after 24 weeks of treatment, a residual standard deviation of 4.5, and the use of a 1:1 randomization ratio, it was assumed that 140 completed patients (70 PRM, 70 placebo) would be sufficient to achieve 95% power at the 5% two-sided significance level for the amended primary objective (ADAS-Cog). The study was thus planned to look at the effects of add-on PRM on cognition and sleep in 140 mild to moderate AD patients, with and without insomnia comorbidity, treated with standard AD therapy.

Due to severe difficulties in recruitment of patients, the study was stopped after about half of the intended patients (80) were recruited. The database was locked, and all data were analyzed on an exploratory basis, according to the preplanned statistical analysis plan.

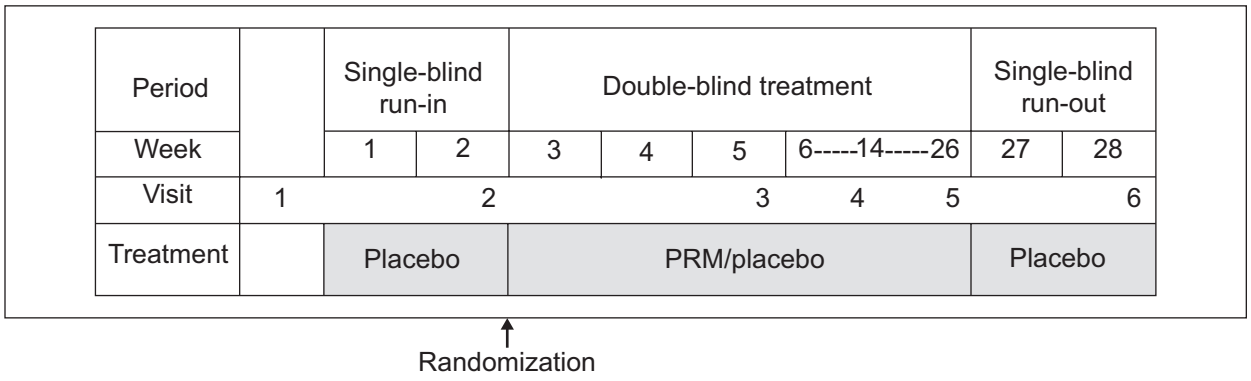

Figure 1 Overall study design.
Notes: The study was comprised of a 2-week, single-blind, placebo run-in period, followed by randomization (1:1) to add-on PRM 2 mg or placebo for 24 weeks. Once the treatment period was over, the patients underwent a 2-week placebo run-out period.
Abbreviation: PRM, prolonged-release melatonin.

Two data sets and a subpopulation were thus analyzed: a) the safety set, which included all patients who were randomized to treatment and who took at least one dose of the study medication; b) the full analysis set (FAS), which included all patients in the safety population who had efficacy data for the ADAS-Cog recorded for baseline and at least one postbaseline-period assessment; and c) the insomnia comorbidity subpopulation, which included all patients in the FAS who had insomnia comorbidity at baseline (PSQI ≥6). Differences between groups were tested at a 5% two-sided significance level to achieve 80% power. The data were analyzed using SAS® version 9.1 (SAS Institute, Cary, NC, USA). We used an observed case approach with regards to missing data.[41] Given the exploratory nature of the study, *P*-values were reported without any adjustment for multiplicity.

Results

A total of 80 patients were enrolled into the study, seven were excluded before randomization, due to noncompliance, and 73 patients were randomized (39 patients into the PRM and 34 into the placebo cohort). A total of 60 patients (82.2%) completed the study (31 [79.5%] in the PRM and 29 [85.3%] in the placebo cohorts). A total of 13 patients were in the insomnia comorbid subpopulation (seven in the PRM and six in the placebo cohorts). Subject disposition is presented in Figure 2.

There were no statistically significant differences in demography or baseline characteristics between the PRM and placebo cohorts (Table S1). In the PRM group, there was a higher percentage of males (59.0% versus 41.2%) (not significant) and a lower proportion of patients who took memantine (29.3% versus 51.6%) (*P*=0.068) compared with the placebo cohort. Treatment compliance remained above 90% in both treatment groups throughout the study.

Cognition

Table 1 depicts the effects of 24 weeks of PRM and placebo treatment on cognitive skills in the FAS population and the comorbid insomnia subpopulation. By the end of the 24-week treatment period, there was no difference in mean ADAS-Cog score between the treatment groups of the FAS. Median ADAS-Cog score levels improved by 2 points in the PRM-treated group and deteriorated by 0.5 points in the placebo-treated group, but the difference was not statistically

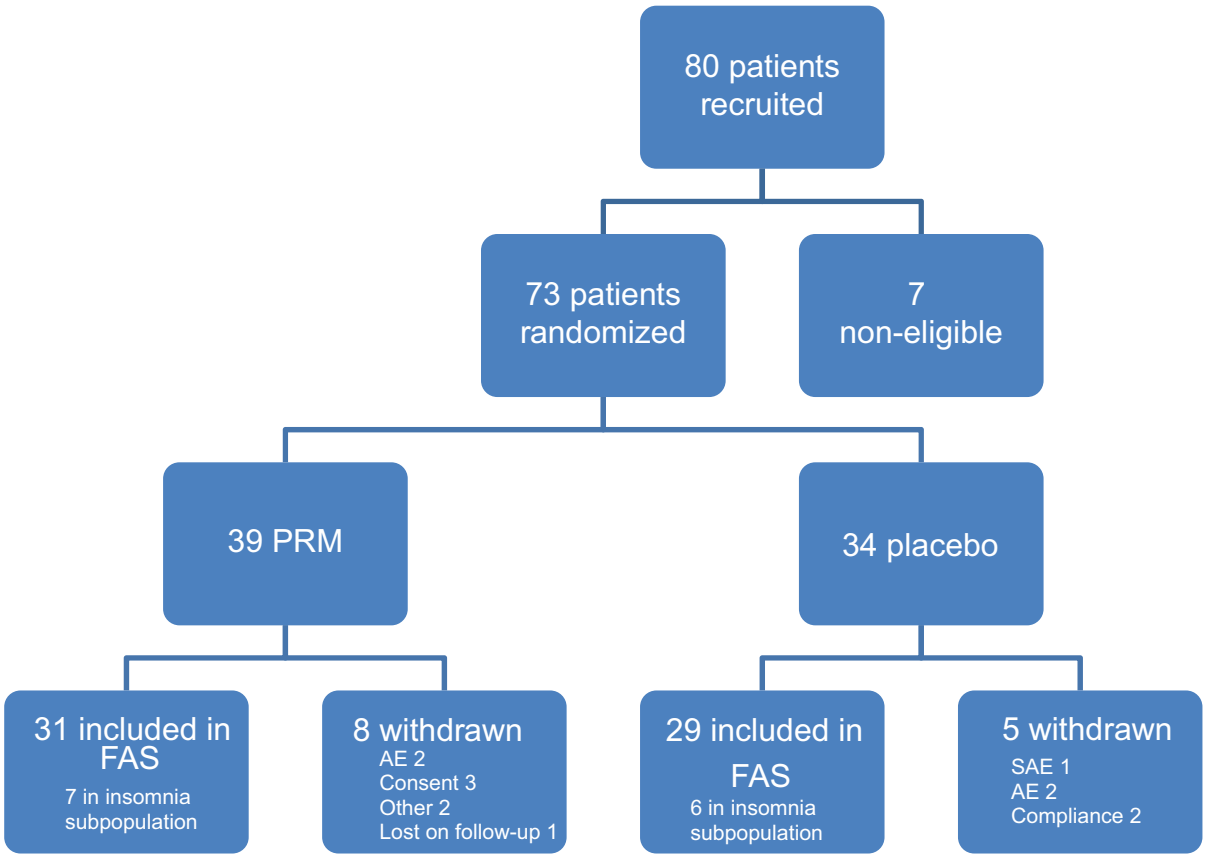

Figure 2 Overall study patient disposition.
Abbreviations: AE, adverse event; FAS, full analysis set; PRM, prolonged-release melatonin; SAE, serious adverse event.

Table 1 Changes from baseline in cognitive outcome, as assessed by ADAS-Cog, IADL, and MMSE after 24 weeks of treatment

	PRM				Placebo				
	N	Mean ± SD	Median	*P**	N	Mean ± SD	Median	*P**	*P***
ADAS-Cog									
FAS									
Baseline	29	24.59±5.57	23.0		26	27.35±8.11	25.5		
24 weeks	29	25.03±8.85	24.0		26	27.54±10.87	26.5		
Changes 24 weeks	29	0.45±5.00	−2.0	0.670	26	0.19±6.28	0.5	0.877	0.448+++
Insomnia subpopulation									
Baseline	6	20.50±3.99	22.0		5	26.6±4.67	26.0		
24 weeks	6	18.00±6.51	19.5		5	27.6±7.73	26.0		
Changes 24 weeks	6	−2.50±3.08	−3.5	0.125	5	1.0±6.04	3.0	0.875+	0.045***
IADL									
FAS									
Baseline	31	3.29±2.64	3.0		29	3.93±2.39	4.0		
24 weeks	31	4.06±2.34	4.0		29	5.55±2.15	6.0		
Changes 24 weeks	31	0.77±1.41	0.0	0.005	29	1.62±1.57	2.0	<0.001	0.004
Insomnia subpopulation									
Baseline	6	0.83±1.33	0.0		5	4.00±3.81	5.0		
24 weeks	6	1.50±1.52	1.5		5	5.80±2.59	7.0		
Changes 24 weeks	6	0.67±1.75	0.0	0.750	5	1.80±1.30	2.0	0.500	0.031
MMSE									
FAS									
Baseline	32	22.1±3.5	22.0		29	21.4±4.7	22.0		
24 weeks	32	21.9±3.8	22.0		29	19.5±6.0	22.0		
Changes 24 weeks	32	−0.3±2.8	0.5	0.622	29	−1.9±3.5	−2.0	0.006	0.044
Insomnia subpopulation									
Baseline	6	24.0±3.7	25.0		5	20.6±3.1	20.0		
24 weeks	6	25.5±3.6	26.0		5	17.8±2.9	17.0		
Changes 24 weeks	6	1.5±2.9	2.5	0.375	5	−2.8±2.9	−3.0	0.250	0.017

Notes: **P*-value indicates significant within the two study groups (paired *t*-test). ***P*-value indicates significant for changes from baseline between the two study groups, with adjustment for baseline assessments (ANCOVA model). ****P*-value indicates significant for changes from baseline between the two study groups (median test). +*P*-value indicates significant within the two study groups (sign-rank test). +++*P*-value indicates significant for changes from baseline between the two study groups, with adjustment for baseline assessment, sex, and age (ANCOVA model).

Abbreviations: AD, Alzheimer's disease; ADAS-Cog, AD Assessment Scale–Cognition; ANCOVA, analysis of covariance; FAS, full analysis set; IADL, Instrumental Activities of Daily Living; MMSE, Mini–Mental State Examination; PRM, prolonged-release melatonin; SD, standard deviation.

significant (Table 1, Figure 3A). In the subpopulation of patients suffering from insomnia comorbidity, there was an improvement (decrease) of −3.5 points in the median ADAS-Cog score in the PRM and a deterioration (increase) of +3 points in the placebo group, and the difference in treatment effect between the groups was significant (*P*=0.045) (Table 1, Figure 3A). After the shorter period (12 treatment weeks), the median ADAS-Cog score improved −2.0 points in the PRM and deteriorated +1 point in the placebo group, and the difference between groups was not statistically significant for this time (data not shown).

By the end of the 24-week treatment period, the decline in MMSE in the FAS population was significantly less in the PRM compared with the placebo group (*P*=0.044, baseline adjusted analysis of covariance [ANCOVA]) (Table 1, Figure 3B). The mean decline in MMSE score in the FAS population deteriorated significantly over the 24-week period in the placebo group (*P*=0.006), while it did not change in the PRM group. In the subpopulation of patients suffering from comorbid insomnia, MMSE scores significantly improved with PRM over placebo, showing an increase in MMSE after 24 weeks of 1.5 points, while the placebo group deteriorated by 2.8 points, and the difference in treatment effect between the groups was significant (*P*=0.0177, baseline adjusted ANCOVA) (Table 1, Figure 3B).

A significant effect of PRM compared with placebo was demonstrated in self-care and activities of daily living, assessed by the IADL after 24 weeks of double-blind treatment (*P*=0.004) (Table 1, Figure 3C). These differences remained significant after adjusting for sex and age (*P*=0.005), AD severity, insomnia severity, and memantine intake (*P*=0.019). The effect on IADL was more pronounced at longer treatment duration, and the global treatment effect of PRM over the 24-week period (mixed-effects model

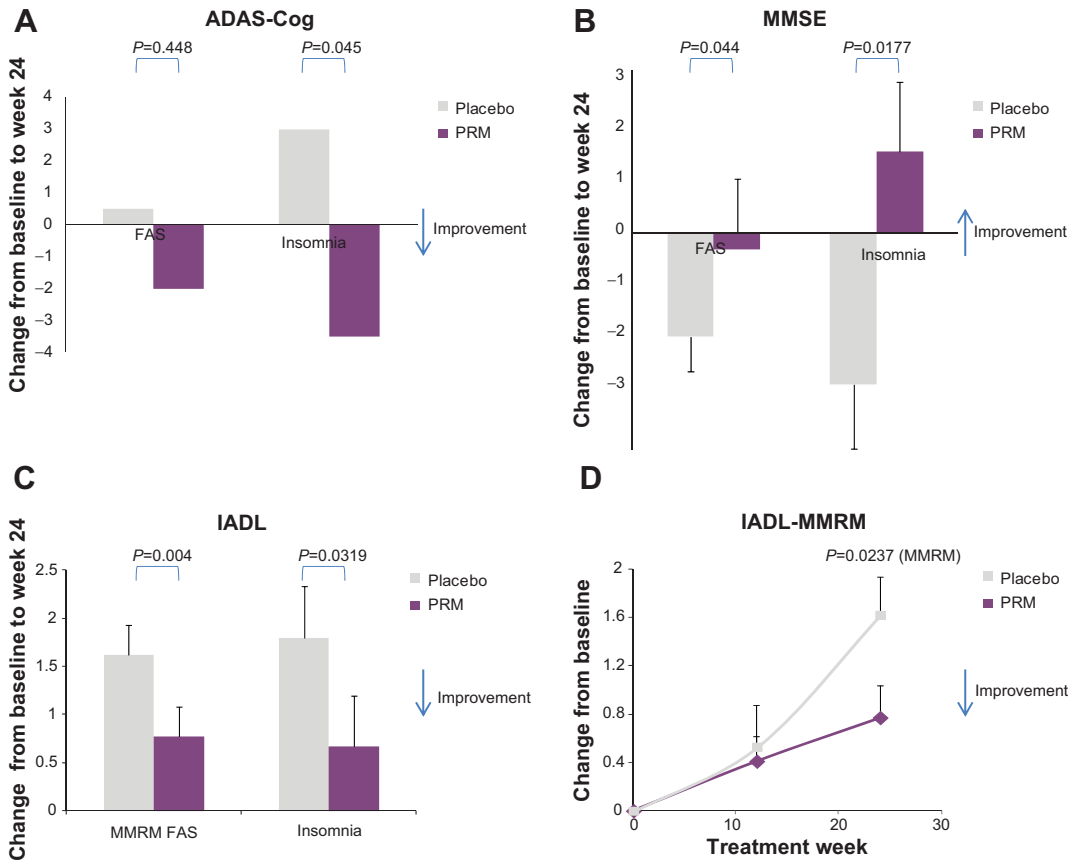

Figure 3 Cognitive assessments.

Notes: (**A**) The change in median ADAS-Cog between baseline and 24 weeks, by treatment FAS and insomnia subpopulation (PSQI ≥6 at baseline). *P*-value indicates significant for changes from baseline between the two study groups (median test). (**B**) The change in mean MMSE (± SEM) between baseline and 24 weeks of treatment in the FAS and in the insomnia subpopulation (PSQI ≥6 at baseline). *P*-value indicates significant for changes from baseline between the two study groups, with adjustment for baseline assessment (ANCOVA model). (**C**) The change in mean IADL (± SEM) between baseline and 24 weeks, by treatment in the FAS and insomnia subpopulation (PSQI ≥6 at baseline). *P*-value indicates significant for changes from baseline between the two study groups, with adjustment for baseline assessment (ANCOVA model). (**D**) Global treatment effect of PRM on mean IADL (± SEM) change from baseline, over the 24-week period (MMRM), in the FAS.

Abbreviations: AD, Alzheimer's disease; ADAS-Cog, AD Assessment Scale–Cognition; ANCOVA, analysis of covariance; FAS, full analysis set; IADL, Instrumental Activities of Daily Living; MMRM, mixed-effects model for repeated measures; MMSE, Mini–Mental State Examination; PRM, prolonged-release melatonin; PSQI, Pittsburgh Sleep Quality Index; SEM, standard error of the mean.

for repeated measures [MMRM]) was also significantly greater with PRM compared with placebo (*P*=0.0237) (Figure 3D).

Likewise, the mean IADL score in the subpopulation of patients suffering from comorbid insomnia was significantly better with 24 weeks of PRM as compared with placebo (*P*=0.0319, baseline adjusted ANCOVA model) (Table 1, Figure 3C).

Sleep

Most patients (>70%) in the study did not have insomnia. Following 24 weeks of treatment, there were no significant differences in treatment effects in the PSQI global score between the groups. The PSQI global score significantly decreased (improved) compared with baseline in the PRM- (−1.62±2.74) (*P*=0.004) but not in the placebo-treated group (−0.74±2.52) (*P*=0.139) (Table 2).

Despite the absence of insomnia comorbidity in the FAS population, PSQI component 4 scores, measuring sleep efficiency, improved significantly in the PRM group over placebo after 24 weeks of treatment (*P*=0.017, baseline adjusted ANCOVA) (Table 2) and over the entire 24-week, double-blind treatment period (MMRM, *P*=0.0312) (Figure 4A). In the comorbid insomnia subpopulation, despite the small sample size, sleep efficiency improved significantly in the PRM group over placebo after 24 weeks of treatment (*P*=0.04) (Table 3, Figure 4B).

An improvement (decrease) of −5.5 (*P*=0.031) points in the PRM compared with −3.8 in the placebo group was observed after 24 weeks (Table 3) in PSQI global scores, but the difference between groups did not reach the predefined statistical significance level (*P*=0.303).

The quality of sleep at week 12 (sleep diary) was significantly increased in the PRM group (*P*=0.007) and did

Table 2 Effects of PRM and placebo on PSQI global score and items, by treatment and period – FAS population

PSQI item	Period	PRM				Placebo				
		N	Mean	SD	*P*-value[a]	N	Mean	SD	*P*-value[a]	*P*-value[b]
PSQI global	Baseline	31	4.61	3.25		29	4.03	3.55		
	Changes 12 wks	31	−1.52	3.38	0.018*	29	−0.21	2.69	0.682	0.131
	Changes 24 wks	29	−1.62	2.74	0.004*	27	−0.74	2.52	0.139	0.351
Component 1	Baseline	31	0.77	0.76		29	0.55	0.63		
	Change 12 wks	31	−0.26	0.73	0.058	29	0.03	0.50	0.712	0.193
	Change 24 wks	29	−0.14	0.79	0.355	25	0.04	0.54	0.714	0.841
Component 2	Baseline	31	1.16	1.16		29	0.97	1.12		
	Change 12 wks	31	−0.48	1.06	0.016*	29	−0.14	0.83	0.380	0.229
	Change 24 wks	29	−0.34	1.37	0.186	27	−0.30	0.91	0.103	0.656
Component 3	Baseline	29	0.38	0.68		29	0.45	0.83		
	Change 12 wks	29	−0.31	0.71	0.026*	26	−0.04	0.87	0.824	0.072
	Change 24 wks	27	−0.30	0.72	0.043*	25	−0.28	0.61	0.032*	0.443
Component 4	Baseline	29	0.86	1.06		29	0.59	1.12		
	Change 12 wks	28	−0.46	1.45	0.102	26	0.00	1.17	1.000	0.373
	Change 24 wks	27	−0.67	1.11	0.004*	24	0.00	0.72	1.000	0.017*
Component 5	Baseline	31	0.94	0.44		29	0.97	0.42		
	Change 12 wks	31	−0.10	0.47	0.264	29	0.00	0.53	1.000	0.357
	Change 24 wks	29	−0.21	0.56	0.056	27	−0.15	0.46	0.103	0.546
Component 6	Baseline	31	0.00	0.00		29	0.07	0.37		
	Change 12 wks	31	0.00	0.00	NA	29	−0.07	0.37	0.326	NA
	Change 24 wks	29	0.00	0.00	NA	27	−0.04	0.44	0.663	0.295
Component 7	Baseline	31	0.58	0.92		29	0.45	0.74		
	Change 12 wks	31	−0.16	0.78	0.258	29	0.10	0.90	0.541	0.300
	Change 24 wks	29	−0.10	0.67	0.415	27	0.04	0.76	0.802	0.753
Question 2	Baseline	31	27.39	24.6		29	19.66	17.1		
(SL, minutes)	Change 12 wks	31	−8.32	21.8	0.042*	28	−1.32	9.90	0.486	0.348
	Change 24 wks	29	−9.28	25.3	0.059	26	0.69	45.7	0.939	0.619
Question 4	Baseline	29	7.91	1.80		29	8.69	2.40		
(TST, hours)	Change 12 wks	29	0.58	1.38	0.032*	26	−0.28	1.87	0.454	0.221
	Change 24 wks	27	0.73	1.21	0.004*	25	0.06	1.28	0.811	0.109

Notes: [a]*P*-value comparison within the two study groups (paired *t*-test); [b]*P*-value comparison of changes from baseline between the two study groups (baseline adjusted ANCOVA model). *$P \leq 0.05$.

Abbreviations: ANCOVA, analysis of covariance; FAS, full analysis set; PRM, prolonged-release melatonin; PSQI, Pittsburgh Sleep Quality Index; SD, standard deviation; wks, weeks; SL, sleep latency; TST, total sleep time; NA, not applicable.

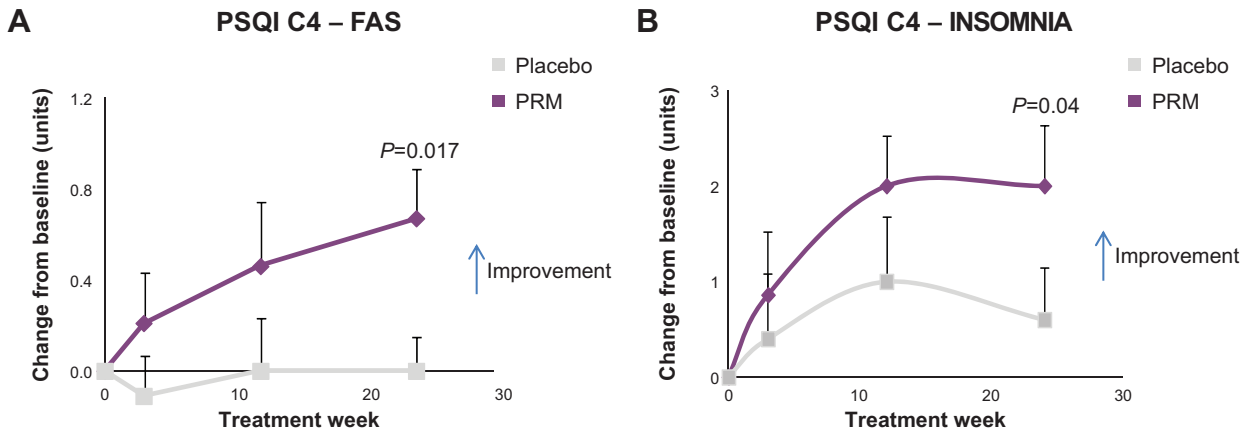

Figure 4 Sleep assessments.

Notes: (**A**) The improvement from baseline (absolute value) in mean sleep efficiency over time (sleep efficiency PSQI component 4) – FAS. (**B**) The improvement from baseline (absolute value) in mean sleep efficiency (sleep efficiency PSQI component 4) in the insomnia subpopulation (PSQI ≥6 at baseline). *P*-value indicates significant changes from baseline between the two study groups, with adjustment for baseline assessment (ANCOVA model).

Abbreviations: ANCOVA, analysis of covariance; C4, component 4; FAS, full analysis set; PRM, prolonged-release melatonin; PSQI, Pittsburgh Sleep Quality Index.

Table 3 Effects of PRM and placebo on PSQI global score and items, by treatment and period – insomnia comorbidity subpopulation

PSQI item	Period	PRM				Placebo				*P*-value[b]
		N	Mean	SD	*P*-value[a]	N	Mean	SD	*P*-value[a]	
PSQI global	Baseline	7	9.86	1.68		6	10.00	1.79		
	Changes 12 wks	7	−5.29	3.45	0.063	6	−2.83	2.56	0.063	0.194
	Changes 24 wks	6	−5.50	2.88	0.031*	5	−3.80	1.30	0.063	0.303
Component 1	Baseline	7	1.57	0.79		6	1.33	0.52		
	Change 12 wks	7	−0.57	0.79	0.250	6	−0.33	0.52	0.500	0.775
	Change 24 wks	6	−0.83	0.41	0.063	5	−0.40	0.55	0.500	0.211
Component 2	Baseline	7	2.71	0.49		6	2.67	0.82		
	Change 12 wks	7	−1.43	1.13	0.063	6	−0.67	0.82	0.250	0.223
	Change 24 wks	6	−1.50	1.22	0.125	5	−1.40	0.55	0.063	0.906
Component 3	Baseline	7	1.43	0.53		6	1.67	0.82		
	Change 12 wks	7	−1.29	0.76	0.031*	6	−0.67	1.21	0.375	0.162
	Change 24 wks	6	−1.33	0.82	0.063	5	−1.20	0.84	0.125	0.693
Component 4	Baseline	7	2.43	0.53		6	2.67	0.52		
	Change 12 wks	7	−2.00	1.41	0.031*	6	−1.00	1.67	0.375	0.099
	Change 24 wks	6	−2.00	1.55	0.063	5	−0.60	1.34	0.500	0.040*
Component 5	Baseline	7	1.14	0.38		6	1.17	0.41		
	Change 12 wks	7	0.14	0.38	1.00	6	−0.17	0.41	1.00	0.145
	Change 24 wks	6	0.00	0.63	1.00	5	−0.20	0.45	1.00	0.596
Component 6	Baseline	7	0.00	0.00		6	0.00	0.00		
	Change 12 wks	7	0.00	0.00	NA	6	0.00	0.00	NA	NA
	Change 24 wks	6	0.00	0.00	NA	5	0.00	0.00	NA	NA
Component 7	Baseline	7	0.57	1.13		6	0.50	0.84		
	Change 12 wks	7	−0.14	1.35	1.00	6	0.00	1.10	1.00	0.865
	Change 24 wks	6	0.17	0.41	1.00	5	0.00	0.71	1.00	0.650
Question 2	Baseline	7	55.71	32.9		6	47.50	11.7		
(SL, minutes)	Change 12 wks	7	−29.3	31.5	0.031*	6	−10.3	9.52	0.125	0.186
	Change 24 wks	6	−35.0	37.4	0.063	5	−35.6	8.76	0.063	0.404
Question 4	Baseline	7	5.64	0.63		6	5.42	1.32		
(TST, hours)	Change 12 wks	7	2.14	1.18	0.031*	6	0.75	1.57	0.500	0.108
	Change 24 wks	6	1.63	1.28	0.063	5	1.20	0.67	0.063	0.462

Notes: [a]*P*-value comparison within the two study groups (paired *t*-test); [b]*P*-value comparison of changes from baseline between the two study groups (baseline adjusted ANCOVA model). *$P \leq 0.05$.

Abbreviations: ANCOVA, analysis of covariance; PRM, prolonged-release melatonin; PSQI, Pittsburgh Sleep Quality Index; SD, standard deviation; SL, sleep latency; TST, total sleep time; wks, weeks; NA, not applicable.

not change significantly in the placebo group (Table S2). A trend for a statistically significant difference was observed between the treatment groups at week 12 (P=0.065), and a statistically significant difference between groups was measured over the 12-week period (MMRM, P=0.0295). In the subpopulation of patients suffering from comorbid insomnia, a trend for a statistically significant difference in quality of sleep was observed at week 12 (P=0.091, by median test). The difference in mean change in quality of sleep assessed in the diary after 12 weeks of treatment was 0.48 units (Table S2).

Other parameters

No difference in NPI severity score was observed for the change from baseline to either week 12 or week 24 between groups. A statistically significant difference in NPI distress score was observed between the groups at week 24 (P=0.026). NPI distress scores increased significantly in the PRM group between baseline and week 24 (3.1±7.59) (P=0.033) and decreased nonsignificantly in the placebo group (−0.24±4.17) (P=0.758). However, the increase in the NPI distress score of the PRM group was not considered to be clinically relevant.[42] No differences in NPI severity score or in NPI distress score were observed for the comorbid insomnia subpopulation (data not shown).

Sleep, measured by the SDI, improved in the PRM group as compared with the placebo after 24 weeks of treatment, demonstrating trends of significance (P=0.09) (data not shown). Caregiver distress, measured by the SDI, decreased in both treatment groups, in the FAS and in the insomnia subpopulation. No other significant differences between groups were demonstrated. No significant interactions between treatment effects and concomitant memantine intake or disease severity were found.

Safety

The incidence of AEs occurring in two or more patients (>5% of patients) is displayed in Table S3 and of drug-related AEs in Table S4. Most AEs reported during the study were transient, mild or moderate in severity, and not considered to be related to the study drug. The most common AEs were urinary tract infection (17.6% of patients in the placebo compared with 2.6% in the PRM cohort), diarrhea (10.3% of patients in the PRM compared with 5.9% in the placebo cohort), and upper respiratory tract infection (8.8% of patients in the placebo compared with 5.1% in the PRM cohort). Drug-related AEs were reported by eight patients (20.5%) in the PRM and by two (5.9%) in the placebo cohort, with no statistical difference between the two groups (post hoc analysis) (chi-squared Fisher's exact test, P=0.0933). Three patients from each cohort discontinued due to AEs.

No deaths occurred during the study. Three SAEs were reported by two patients (5.1%) in the PRM and nine by five patients (14.7%) in the placebo cohort, with no statistical difference between the two groups (post hoc analysis) (chi-squared Fisher's exact test, P=0.2396); none were related to the study drug. Two patients (5.9%) in the placebo cohort withdrew from the study due to SAEs – one patient due to severe myocardial infarction and one due to esophageal stenosis.

No clinically significant changes in physical examination, vital signs, or lab parameters were observed during the study in either of the study groups.

Discussion

The current study assessed the efficacy and safety of once daily add-on PRM compared with placebo over a 24-week period, in patients diagnosed with mild to moderate AD who were on stable doses of acetylcholinesterase inhibitors, with or without memantine. Assessments were made of changes in cognitive functioning and sleep since insomnia itself might negatively impact cognitive functioning. All end points were analyzed, both for the total FAS population (N=65) and for the subpopulation of patients suffering from comorbid insomnia (PSQI ≥6 at baseline [N=13]). The results show evidence of efficacy and safety of long-term add-on PRM in mild and moderate AD and particularly, in patients with comorbid insomnia.

Effects on cognition

In agreement with published data on the change in the ADAS-Cog parameter in AD patients treated with acetylcholinesterase inhibitors, with and without memantine,[9] there was no significant deterioration in mean group cognitive state, as measured by the ADAS-Cog, for both treatment groups, after 24 weeks of the double-blind period. The median ADAS-Cog deteriorated somewhat in the placebo and improved in the PRM group, but the difference between groups was not statistically significant. Compatible with this notion, longer treatment periods and a larger sample size than those used in our study are needed to demonstrate significant decline in the ADAS-Cog score in the placebo group and demonstrate PRM treatment effects with this instrument. The other two instruments (MMSE and IADL) were evidently more sensitive to change within a 24-week period. Thus, cognition, as measured by the MMSE, deteriorated significantly in the placebo group over the 24-week period but did not change in the PRM group. The difference between the PRM and placebo effects was significant (P=0.044). Furthermore, after the 24-week, double-blind treatment period, PRM demonstrated clinically meaningful and statistically significant amelioration over placebo for self-care and activities of daily living, as measured by the IADL (P=0.004).

The benefit was even more pronounced in the subpopulation suffering from insomnia comorbidity. There was an improvement (decrease) of −3.5 points in median ADAS-Cog scores in the PRM and deterioration of +3 points in the placebo group after 24 weeks of double-blind treatment, and the difference in treatment effect between groups was significant (P=0.045). The difference in treatment effect between the groups (6.5 points on the median ADAS-Cog) was considered clinically meaningful.[43,44]

Moreover, PRM improved MMSE scores over placebo, showing an increase in MMSE scores after 24 weeks of 1.5 points, while the placebo group scores deteriorated by 2.8 points. The difference in treatment effects in MMSE (4.5 points) with PRM over placebo in the insomnia subpopulation was statistically significant (P=0.0177) and was considered clinically meaningful.[45] Furthermore, there was a significantly lesser deterioration in mean IADL score with PRM compared with placebo (P=0.0319).

The effect on IADL was more pronounced after 24 weeks than after 12 weeks of treatment. This might suggest amelioration of disease progression with PRM compared with placebo. However, it is quite clear that the decline in IADL in the placebo arm at 12 weeks was low, if a linear decline was to be expected. This can be possibly attributed to time-dependent changes in the placebo effect previously shown to mostly affect the first assessments of cognitive functioning in AD trials.[46,47] Further long-term trials will be needed to examine whether the greater effect of PRM with longer treatment duration represents attenuation of cognitive decline.

Effects on sleep

Most patients in the FAS population did not have insomnia, and thus, as expected, the treatment effect of PRM compared with that of placebo on the global PSQI score did not reach statistical significance.

Despite the absence of insomnia comorbidity in the FAS population, PSQI component 4, measuring sleep efficiency, improved significantly in the PRM group over placebo after 24 weeks of treatment (P=0.017) and over the entire 24-week, double-blind treatment period (MMRM, P=0.0312). In the comorbid insomnia subpopulation, despite the small sample size, sleep efficiency improved significantly in the PRM group over placebo after 24 weeks of treatment (P=0.04).

Altogether, the results obtained for the sleep variables are suggestive of beneficial effects of add-on PRM therapy on sleep maintenance in the AD patients. Notably, the sleep parameter mostly affected by PRM in AD patients is sleep efficiency, which is also the main parameter affected by the disease.[2,48] Such effects, according to studies in children with neurodevelopmental disorders, may be more pronounced with PRM formulations because they are able to sustain active melatonin levels throughout the night.[49–51] Beside sleep, the ability of melatonin to affect hippocampal networks and subsequently cognition may rely on presence of the hormone at high levels during the night, when this area is sensitive to the hormone.[52,53]

Several studies, including six randomized, double-blind, placebo-controlled trials, with a total of 310 AD patients, have previously reported on the effects of melatonin on sleep in AD patients, mostly with advanced disease. In three of these studies (N=83), there were no significant effects of melatonin (1.5–6 mg sustained-release formulations, 3–8.5 mg immediate-release formulations, 10 days −7 weeks) compared with placebo on sleep or behavioral aspects.[54–56] In one study (N=50), light treatment plus melatonin (5 mg, 10 weeks) increased daytime wake, activity levels, and strengthened the rest–activity cycle,[57] and in another study (N=20 unmedicated patients), there were significant improvements in ADAS-Cog and ADAS-non-Cog scores with melatonin (3 mg, 4 weeks) compared with placebo but no significant differences in MMSE scores and sleep, although it is unknown whether such effects were sustained at longer treatment duration.[21] It is interesting to note that most studies reporting negative effects of melatonin on sleep in AD used actigraphy to assess sleep. In another study of 2.5 mg sustained-release melatonin for 2 months in AD patients (N=157), both actigraphy and caregiver ratings of sleep were used. Whereas caregiver ratings of sleep quality showed improvement with melatonin compared with placebo treatment, the actigraphy data failed to show significant differences between treatment groups, and no other benefit was reported.[58] The use of actigraphy as a substitute for sleep polysomnography in AD patients was recently debated.[59,60] On the other hand, sleep quality can be negatively affected by emotional distress and caregiver burden. It is thus possible that actigraphy and subjective assessments of sleep will differ in reported sleep parameters and treatment effects. These methodological differences, in addition to differences in study design, duration, melatonin formulation, and dose, may account for the inconsistencies between results obtained in the previous studies.

A pertinent question is whether the effects of add-on PRM treatment on sleep were similar in AD patients with insomnia comorbidity to those previously seen in nondemented patients with insomnia aged 55 years and older. The results of this study show that as for AD patients, the improvement in sleep develops progressively, reaching stable plateau levels at 12 weeks (Figure 4A and B). A similar evolution of response with time of treatment was reported previously in nondemented patients with insomnia aged 55 and older[61] and was considered to represent consolidation of the circadian system.

The greater effects of PRM on cognition in the insomnia subpopulation support the notion that sleep is critical for memory performance. Recent studies indicate that sleep duration and sleep quality may play a role in cognitive performance in healthy older adults.[5] A recent study on sleep quality and preclinical AD concluded that beta-amyloid deposition in the preclinical stage of AD is associated with worse sleep quality but not with changes in sleep quantity.[62] PRM restores the body's normal sleep–wake cycle, improves sleep quality and daytime functioning, maintains the physiological sleep structure in insomnia patients, and as found in the present study, improves sleep maintenance in AD patients.[26,63] This may explain the improvement in ADAS-Cog, IADL, and MMSE observed in AD patients with insomnia comorbidity after PRM treatment. Importantly, treatment of the sleep complaints with traditional hypnotics may not be beneficial and may even be deleterious in AD patients because of the impairments in cognitive and memory functioning associated with these drugs.[11–13] Furthermore, long-term use of benzodiazepine hypnotics is associated with an increased risk for dementia.[15,16] Because PRM improves sleep without the risk of memory or cognitive impairment, the improvement of sleep can further contribute to the overall efficacy of PRM in

AD, as found in the present study.[13,29,64] The efficacy results obtained in AD patients with insomnia comorbidity are most interesting, in particular with respect to the interaction between insomnia and AD, and larger studies of PRM in this population are warranted.

An important question is whether the add-on PRM treatment was attenuating disease progression. Evaluation of the change in the cognitive parameters over time indicates that while the placebo group deteriorated progressively during the 24 weeks (as measured by the IADL and MMSE), a significantly lesser decline in cognitive functioning was seen in the PRM-treated cohort after 12 and 24 weeks of treatment, suggesting that PRM attenuated the cognitive decline. Further studies will have to be undertaken to understand whether this trend could represent disease modification.

There is now compelling evidence for the association between shorter sleep duration and poor sleep quality to greater beta amyloid burden and higher risk for AD.[7,8,62,65,66] Based on the aforementioned evidence and the results obtained from our study, a plausible mechanism for PRM effects in AD could be that the improved sleep efficiency leads to lower risk of accumulation of beta amyloid deposition[62] and/or increase in beta amyloid clearance from the brain,[65] which can ultimately result in the attenuation of AD progression. If so, patients with good sleep quality can potentially also benefit from the neuroprotective effects of the hormone.[67,68]

Overall, PRM was well tolerated as most AEs were of mild or moderate severity and resolved without sequelae. No deaths occurred during the study, and none of the SAEs reported were considered related to the study drug.

Conclusion

We conclude that the add on of PRM to acetylcholinesterase inhibitor, with or without memantine therapy, might be an effective and safe means for improvement in cognitive functioning and sleep maintenance in mild to moderate AD patients. The benefit may be greater for those with insomnia comorbidity, probably because good sleep is critical for proper cognition and memory processing. Keeping in mind that larger sample size and longer study duration are required in order to validate these results, the results are compatible with the accumulating evidence on a causal relationship between poor sleep and cognitive decline in AD.

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Disclosure

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Supplementary materials

Table S1 Baseline characteristics of the study population

Parameter	PRM	Placebo
	N=39	N=34
Mean age (years) ± SD (N)	73.5±8.6	77.3±6.6
Age range (years)	52.0–85.0	57.0–85.0
Sex males, N (%)	23 (59.0)	14 (41.2)
Sex females, N (%)	16 (41.0)	20 (58.8)
Height (cm) ± SD	163.2±18.9	163.7±10.3
Weight (kg) ± SD	75.7±14.3	70.3±14.7
Body mass index (kg/m^2) ± SD	27.5±4.5	25.7±4.1
Medical history		
CNS (including psychiatric) N (%)	38 (97.4)	33 (97.1)
Cardiovascular N (%)	31 (79.5)	28 (82.4)
Hypertension N (%)	20 (51.2)	17 (50)
Ischemic heart disease N (%)	4 (10.2)	3 (8.8)
Endocrine/metabolic N (%)	20 (51.3)	18 (52.9)
Type 2 diabetes N (%)	5 (12.8)	6 (17.6)
Musculoskeletal N (%)	28 (71.8)	22 (64.7)
AD severity and medications		
Mild (MMSE >20) N (%)	23 (67.6)	17 (54.8)
Moderate (MMSE 15–20) N (%)	11 (32.4)	14 (45.2)
Patients taking memantine, N (%)	10 (29.4)	16 (51.6)
Lifestyle habits		
Patients consuming alcohol, N (%)	21 (53.8)	11 (32.4)
Patients consuming caffeine, N (%)	35 (89.7)	26 (76.5)
Patients consuming cigarettes, N (%)	5 (12.8)	2 (5.9)
Sleep habits		
Number of awakenings/night ± SD (%)	1.8±1.5 (39)	1.7±1.4 (31)
Total sleep hours/night ± SD (%)	7.7±2.0 (39)	7.8±2.2 (34)
PSQI ≥6 N (%)	7 (22.6)	6 (20.7)
PSQI <6 N (%)	24 (77.4)	23 (79.3)

Abbreviations: AD, Alzheimer's disease; CNS, central nervous system; MMSE, Mini–Mental State Examination; PRM, prolonged-release melatonin; PSQI, Pittsburgh Sleep Quality Index; SD, standard deviation.

Table S2 The change in sleep quality measured from sleep diary parameters, between baseline and 12 weeks of treatment (FAS)

	PRM				Placebo				
	N	Mean ± SD	Median	*P**	N	Mean ± SD	Median	*P**	*P***
Baseline	34	2.94±0.75	3		30	2.99±0.87	3		
12 weeks	29	3.25±0.66	3		27	2.88±1.06	3		
Changes 12 weeks	30	0.34±0.63	0	0.007	26	–0.14±1.12	0	0.535	0.065

Notes: **P*-value indicates significant within the two study groups (paired *t*-test). ***P*-value indicates significant for changes from baseline between the two study groups, with adjustment for baseline assessments (ANCOVA model).
Abbreviations: ANCOVA, analysis of covariance; FAS, full analysis set; PRM, prolonged-release melatonin; SD, standard deviation.

Table S3 Number (%) of patients who had an adverse event (AE), in the safety population

	PRM		Placebo	
	N	(%)	N	(%)
Subjects treated	39	(100.0)	34	(100.0)
Subjects reporting AEs	32	(82.1)	23	(67.6)
Number of AEs	86		70	
Subjects reporting drug-related AEs	8	(20.5)	2	(5.9)
Number of drug-related AEs	12		2	
Subjects reporting SAEs	2	(5.1)	5	(14.7)
Number of SAEs	3		9	
Subjects reporting drug-related SAEs	0	(0)	0	(0)

Notes: Percentage based on number of patients in the safety population for each treatment group.
Abbreviations: AE, adverse event; PRM, prolonged-release melatonin; SAE, serious adverse event.

Table S4 Overall adverse events and most frequent events, by system organ class and preferred term, in >5% of patients (two patients) in any cohort, and drug-related AEs

System organ class/ preferred term	PRM N=39		Control N=34	
	N	(%)	N	(%)
All AEs	32	(82.1)	23	(67.6)
Angina pectoris	2	(5.1)	–	–
Abdominal discomfort	2	(5.1)	1	(2.9)
Diarrhea	4	(10.3)	2	(5.9)
Nausea	–	–	2	(5.9)
Vomiting	2	(5.1)	1	(2.9)
Fatigue	3	(7.7)	1	(2.9)
Blood creatinine increased	–	–	2	(5.9)
Blood glucose increased	2	(5.1)	1	(2.9)
Decreased appetite	2	(5.1)	–	–
Back pain	2	(5.1)	1	(2.9)
Abnormal dreams	2	(5.1)	–	–
Agitation	2	(5.1)	2	(5.9)
Cognitive disorder	1	(2.6)	2	(5.9)
Insomnia	2	(5.1)	1	(2.9)
Urinary tract infection	1	(2.6)	6	(17.6)
Cough	2	(5.1)	–	–
Nasopharyngitis	2	(5.1)	1	(2.9)
Upper respiratory tract infection	2	(5.1)	3	(8.8)
Drug-related AEs	8	(20.5)	2	(5.9)
Fatigue	2	(5.1)	1	(2.9)
Fall	1	(2.6)	–	–
Thyroid neoplasm	1	(2.6)	–	–
Abnormal dreams	2	(5.1)	–	–
Burning feet syndrome	1	(2.6)	–	–
Headache	–	–	1	(2.9)
Somnolence	1	(2.6)	–	–
Delusion	1	(2.6)	–	–
Restlessness	1	(2.6)	–	–

Note: Percentage based on number of patients in the safety population for each treatment group.
Abbreviations: AE, adverse event; PRM, prolonged-release melatonin; SAE, serious adverse event.