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Ramelteon for the treatment of insomnia in menopausal women

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Abstract

Objective—Sleep disturbances have been reported to be one of the most troubling manifestations of menopause. While hormone replacement therapy (HRT) has historically been considered a first-line treatment for menopausal insomnia, many women are now seeking alternatives treatments due to concerns about the risks and side-effects of HRT. The goal of this study was to evaluate the effect of ramelteon, a selective melatonin receptor agonist, for the treatment of menopausal insomnia.

Study Design—A total of 20 healthy peri and postmenopausal women with insomnia participated in this six-week, prospective, open-label trial of ramelteon (8mg) at an academic medical center. Participants completed sleep-wake diaries on a daily basis for 6-weeks. Self-report measures of sleep impairment, daytime functioning, quality of life, and mood were also completed on a bi-weekly basis.

Results—Significant improvements in latency to sleep onset, total sleep time, and sleep efficiency were observed in diary data while gains in sleep quality, sleep impairment, daytime functioning, quality of life, and mood were found on self-report measures. There was no evidence of tolerance or rebound over the course of the trial.

Conclusions—Overall, results suggest that ramelteon is an effective non-hormonal approach for the treatment of insomnia in menopause. Randomized controlled trials are needed to further evaluate the efficacy of this intervention.

Keywords

menopause; insomnia; ramelteon; alternatives to HRT

Sleep disturbances have been reported to be one of the most troubling manifestations of menopause, affecting 45–75 % of women.^{1,2} Menopausal women report a significantly higher rate of sleep difficulties compared to pre-menopausal women, including problems with onset, maintenance, and frequent hypnotic use.³ Although sleep problems may be related to other menopausal complaints such as hot flashes or night sweats, menopausal insomnia can also occur in the absence of these vasomotor symptoms.^{1,2} Because menopausal insomnia is linked with high rates of mental health concerns, functional impairment, and poor quality of life,^{4,5} the effective treatment of sleep disturbances in this population of women is important.

Since many of the physiological changes that occur during menopause result from decreased levels of estrogen, hormone replacement therapy (HRT) has historically been considered a

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first-line treatment for menopausal insomnia.⁶ HRT has been found to decrease latency to sleep onset, nocturnal waking, and total sleep time in menopausal women.³ However, HRT is associated with numerous risks and side effects which often result in a failure to initiate, poor adherence to, or an abrupt discontinuation of treatment regimens.^{7,8,9} Due to these concerns about the HRT side-effect profile, many women are increasingly seeking alternative treatments.¹⁰ For example, 79% (n=395) of the peri and postmenopausal women surveyed at a large community clinic reported using botanical dietary supplements, that they believed to be safe, to address their current health concerns.¹¹

Melatonin is the main hormone secreted by the pineal gland and is involved in the regulation of the sleep-wake cycle. A steep, age-related decline in melatonin has been documented in women up to 15 years postmenopausal with a gradual decline noted thereafter.¹² It has been proposed that individuals with reduced melatonin levels may benefit from melatonin supplementation.¹³ In fact, a recent meta-analysis suggests that exogenous melatonin treatment decreases sleep onset latency and increases both sleep efficiency (e.g., decreased number of awakenings during sleep, shortened periods of wakefulness) and total sleep duration.¹⁴ These improvements in sleep have been linked to improved attention, concentration, fine motor skills, reaction time, daytime alertness, and overall quality of life.^{15,16} Moreover, the administration of exogenous melatonin has specifically been associated with improved sleep quality and good tolerability in perimenopausal women.¹⁷

Thus, ramelteon, a selective melatonin receptor agonist, may be an effective and more readily accepted alternative treatment option for menopausal insomnia. Compared to melatonin, ramelteon is structurally different and is up to 17 times more potent at specific melatonin receptors.¹⁸ In addition, ramelteon has scientific evidence of efficacy and safety at the recommended doses,^{19,20} and is subject to the good manufacture practices enforced by the United States Food and Drug Administration (FDA).ⁱ

This report details the first study to investigate the use of ramelteon (8mg) for the treatment of insomnia in menopausal women. It was hypothesized that ramelteon will result in significant improvement in patient-reported latency to sleep onset (primary hypothesis), as well as significant improvements in patient-rated total sleep time, wake time after sleep onset, number of awakenings, sleep quality, severity of insomnia, quality of life, depressive and anxious symptoms, and daytime functioning (secondary hypotheses) in this 6-week open-label trial.

Method

Participants

Women were recruited through physician referral at UMDNJ/Robert Wood Johnson Medical School as well as from the greater Central New Jersey community via newspaper advertisement. All participants received the study medication free of charge for six weeks, six free study evaluation sessions, and \$25 for each completed study visit (\$150.00 total) to help defray the costs of transportation.

A total of 20 peri or postmenopausal women, aged 40–65, with sleep latency insomnia (at least 3 of 7 nights of sleep latency > 30 minutes) and a total sleep time of < 6.5 hours per night, during the 2 week self assessment (diaries) prior to baseline, participated in the study. Perimenopause was defined as irregular menstrual periods for at least 6 months and postmenopause was defined as a cessation of menstrual periods for at least 12 months. The diagnosis of peri or postmenopausal was also confirmed by the participants' personal physician based on his or her own independent evaluation. The participants' insomnia began, by history,

ⁱ(In the US, supplements such as melatonin are considered food and not controlled by the FDA).

after the onset of perimenopause and did not meet criteria for a primary sleep disorder (e.g., significant sleep disordered breathing [central or obstructive apnea], periodic limb movement disorder [PLMD], or REM sleep behavior disorder [RBD]) based on clinical interview. Participants had no history of HRT in the past 6 months or poor response to a past trial of a sedative hypnotic. Women with surgical or chemically-induced menopause, current Major Depressive Disorder, Generalized Anxiety Disorder, Panic Disorder, Obsessive-Compulsive Disorder, or Post-Traumatic Stress Disorder per DSM-IV criteria (confirmed by the SCID ²¹), a history of alcohol or drug dependence in the past year, any medically unstable condition, as well as those currently taking psychotropic medications, or receiving cognitive-behavioral therapy (CBT) for insomnia were excluded from the study.

Measures

Sleep-Wake Diaries—Subjects were instructed to maintain daily sleep-wake diaries for the 2 weeks prior to baseline, throughout the active treatment phase and for one week after treatment was discontinued. Several sleep parameters were captured in the diaries, including bedtime, arising time, sleep-onset latency, total sleep time (TST), wake after sleep onset (WASO), total number of nighttime awakenings, sleep efficiency, and the number of hot flashes/night sweats per 24-hour period. Participants were instructed to complete the diaries every morning and evening during the monitoring periods, and to bring them to each evaluation session during treatment and at follow up. The sleep-wake diaries used in the current study reflect a modification of the National Sleep Foundation's "Sleep Diary" (©2000, National Sleep Foundation, Washington, DC).

Primary Outcome Measure

Latency to sleep onset was the primary outcome measure derived from the diaries and was averaged over two-week periods.

Secondary Outcome Measures

Additional variables derived from the diaries served as secondary sleep-related outcomes; these included TST, WASO, total number of nighttime awakenings, sleep efficiency, and number of hot flashes/night sweats. TST was calculated by subtracting sleep-onset latency and WASO from the number of hours the patient spent in bed (i.e., arising time minus bedtime). Sleep efficiency was calculated by dividing TST by the number of hours spent in bed.

Self-report measures of sleep impairment (SSI- Sleep Impairment Index²²; 10-point Likert scale to rate Subjective Sleep Quality [Dobkin & Menza, unpublished]), daytime functioning (Ability to Function 0–10 Likert Scale [Dobkin & Menza, unpublished]; Daytime Alertness 0–10 Likert Scale [Dobkin & Menza, unpublished]), quality of life (MENQOL- Menopause Specific Quality of Life Questionnaire²³; Greene Climacteric Scale²⁴) and mood (BDI- Beck Depression Inventory²⁵; BAI-Beck Anxiety Inventory²⁶) also served as secondary outcome measures in this open-label trial. Clinician rated variables of severity of illness and global improvement (i.e., Clinical Global Impression Severity and Improvement Scale²⁷; CGI-S and CGI-I, respectively) were also assessed.

Rebound and tolerance were also calculated from sleep diaries after completion of the trial. Rebound was defined as a sleep latency time in the week following discontinuation of the study medication that was significantly greater than the patient's baseline sleep latency time. Tolerance was defined as a loss of efficacy regarding sleep latency over the 6 weeks of the trial. Adverse events were also monitored at every visit by directly querying the participant.

Procedure

This was a six-week, prospective, open-label study of ramelteon (8mg) with patient-rated latency to sleep onset (diaries) as the primary outcome. The study had the full approval of UMDNJ-Robert Wood Johnson Medical School IRB. A statement of informed consent was signed prior to the initiation of any study procedures.

Preliminary screening was conducted by telephone. Appropriate individuals were scheduled for an in-person evaluation. At the screening visit, a detailed sleep, medical and psychiatric history was obtained via clinical and semi-structured interview (SCID21). Individuals who qualified for the study based on these initial screening procedures were given instructions regarding the completion of sleep diaries.

Eligible women completed daily diaries for 14 days between the screening and baseline appointments. The sleep diary was then reviewed at the baseline appointment. If the inclusion criteria regarding sleep impairment were met, women completed additional questionnaires assessing sleep impairment, daytime functioning, quality of life, and mood disturbance as described above.

Following the baseline visit, participants were instructed to take ramelteon (8mg) nightly for six weeks. All women completed daily sleep diaries for the remainder of the study. Women returned for follow-up evaluations and diary review, as well as to complete questionnaire packets (as described above) at the end of weeks 2, 4, & 6. They also returned for a visit at week 7, one week after discontinuing ramelteon, in order to assess rebound and tolerance effects.

Statistical Analysis

Data analysis included all patients who started the trial and took at least one dose of ramelteon. Data was analyzed using mixed models repeated measures analysis of variance using the MIXED procedure of SAS Version 9.1 with restricted maximum likelihood estimation.²⁸ Variance components were used to model the covariance structure for all analyses. Planned contrasts were conducted to examine differences between specific evaluation points if the omnibus test was significant. The results of planned contrasts were adjusted for multiple comparisons (i.e., bonferroni correction). Data was collected between May 2006 and November 2007.

Results

Characteristics of the Sample

Two premenopausal and eighteen postmenopausal women (15 Caucasian, 4 African-American, 1 Hispanic) were enrolled in the treatment trial. Participants ranged in age from 41 to 61 years (with a mean of 52 years, SD=4.89). For perimenopausal women, the mean length of time of irregular periods was 11 months (SD=7 months). For postmenopausal women, the average time since the cessation of menstrual periods was 5.33 years (SD= 3.72 years). The mean latency to sleep onset at baseline was 46 minutes and the average total sleep time prior to treatment was 5 hours 36 minutes. On the baseline CGI-S, 35% of participants were rated as having mild (n=1) or moderate (n=7) insomnia, while the insomnia of 65% of women was rated as marked (n=12) or severe (n=1).

Fourteen women (70%) completed the trial. Three women dropped out of treatment due to lack of efficacy (i.e., two women experienced no change after taking the study drug for one and two weeks respectively; one woman reported her insomnia worsened after taking the study drug for three days), one because of side effects (i.e., fatigue), and two for reasons unrelated to the study medication (i.e., transportation, scheduling).

Primary Outcome

Latency to sleep onset (diaries) improved over the course of the study, $F(3,46)=6.62$, $p<.001$. The average improvement in latency to sleep onset was 22 minutes across all participants. Means and standard deviations for variables captured by the sleep diary, as well as the results of planned contrasts, can be found in Table 1.

Secondary Outcomes

Diaries—Total sleep time $F(3,46)=8.25$, $p<.001$ (with an average increase of one hour and twenty-four minutes), sleep efficiency $F(3,46)=6.50$, $p<.001$, number of awakenings $F(3,46)=3.75$, $p=.02$, and hot flashes $F(3,46)=2.99$, $p=.04$, improved over the course of the study. There was a trend towards improvement for WASO, $F(3,41)=2.05$, $p=.10$ (with an average improvement of 18 minutes).

Self-report questionnaires—Significant improvements were observed in patient-reported sleep quality (10-point Likert scale) $F(3,45)=23.39$, $p<.001$, daytime dysfunction (10-point Likert scale) $F(3,45)=4.98$, $p<.01$, daytime alertness (10-point Likert scale) $F(3,45)=8.27$, $p<.001$, global sleep impairment (SII) $F(3,45)=22.17$, $p<.001$, quality of life (MENQOL; $F(3,45)=13.71$, $p<.001$ & GCS; $F(3,45)=12.01$, $p<.001$), dysphoria (BDI) $F(3,45)=11.78$, $p<.001$ and anxiety (BAI) $F(3,45)=183.75$, $p<.001$. Means and standard deviations for self-report data, as well as the results of planned contrasts can be found in Table 2.

Clinician-rated scales—At the end of the trial, 55% of women ($n=11$) were considered “responders” as they were rated as a 1 (very much improved) or 2 (much improved) on the CGI-Improvement Scale (CGI-I). Severity of insomnia (CGI-Severity) also improved over the course of the study, with a baseline mean of 4.65 reduced to a mean of 3.14 at endpoint, $\chi^2=37.25$, $p<.001$.

Rebound and Tolerance—Data from the 14 women who completed the trial was used to assess rebound and tolerance. There was no evidence of rebound upon discontinuation of ramelteon. Total sleep time, $F(4,59)=7.58$, $p<.001$, and sleep latency, $F(4,59)=6.19$, $p<.001$, remained improved compared to baseline, despite discontinuation of the medication for one week. (However, higher rates of insomnia were reported at week 7 (1-week taper) than at week 6 (end of active treatment), based on an inspection of means). There was also no evidence of tolerance over the course of the trial (see Table 1 for planned contrasts).

Side Effects

Forty percent of women ($n=8$) reported side effects while participating in the study. The most frequently reported side effects included headaches (20%; $n=4$), daytime fatigue/fogginess (15%; $n=3$), dry mouth (5%; $n=1$), lightheadedness (5%; $n=1$), and dizziness (5%; $n=1$). The majority of side effects were mild and transient (i.e., resolved in 2–5 days), though one woman discontinued participation due to daytime fatigue/fogginess.

Discussion

This is the first study to evaluate ramelteon as an alternative treatment strategy for insomnia in menopausal women. The results of this study suggest that ramelteon may be an effective non-hormonal approach for the treatment of insomnia in menopause. Over the course of the study, women reported significant improvements in latency to sleep onset, total sleep time, subjective sleep quality, and daytime alertness/dysfunction, in addition to significant improvements in dysphoria, anxiety and quality of life. These gains were notable by week 4 of the trial and maintained for the remainder of the study. A trend was noted for WASO which is consistent with the mechanism of action of the drug, as the therapeutic impact of ramelteon

has been most clearly demonstrated in the early phases of sleep.^{19,20} Improvement in insomnia was also associated with a decreased frequency of hot flashes/night sweats. While this finding may be spurious, it is possible that improvements in fatigue made women less susceptible to the experience of additional vasomotor symptoms.

Although this is the first study to investigate ramelteon for menopausal insomnia, two randomized, placebo-controlled trials have been conducted in this population using the sedative hypnotics zolpidem²⁹ and eszopiclone.³⁰ Although both zolpidem and eszopiclone have generally been found to improve sleep onset in menopause and other populations,^{31,32,33,34,35} ramelteon's unique mechanism of action may be especially beneficial for menopausal women. In contrast to other medications, which produce their effect by depressing the central nervous system, ramelteon may serve to regulate the sleep-wake cycle by increasing melatonergic function, which may be particularly useful for menopausal women³⁶ who have been found to possess lower levels of melatonin.¹²

While ramelteon demonstrated a positive impact on sleep latency and TST in the current study, ramelteon had less of an impact on sleep maintenance. In the treatment studies for menopausal insomnia, both zolpidem²⁹ and eszopiclone³⁰ were found to produce significant improvements in WASO, whereas we found only a trend towards improvement. Other studies of ramelteon for general insomnia have also found a non-significant effect on sleep maintenance,^{19,20,36,37} which may be due, in part, to the drug's short half-life.³⁶

Consistent with the literature, ramelteon was well-tolerated, with 70% of participants completing the study. In published studies, this drug is quite safe with no evidence of next-day residual effects, no rebound or withdrawal effects, no abuse liability, and no tolerance.^{19,20,38} The most common side effects reported in other trials of ramelteon include headache (6–19% vs 2–18% for placebo), somnolence (4–8% vs 1–3% for placebo), dizziness (2–9% vs 1–7% for placebo), and fatigue (2–4% vs 0–3% for placebo).^{36,37,39,40,41}

While 40% of the women in the present study reported side effects, most events were transient and mild. Only one woman discontinued treatment due to the experience of daytime fatigue. Similar to the side effect profiles observed in other trials of ramelteon, the most frequently reported side effect in this pilot study was headache.^{37,40,41} Although the experience of headaches has ranged widely in the large randomized, controlled trials of ramelteon (for patients taking either ramelteon or placebo), the fact that 20% of our patients reported headache may be an artifact of our small sample size and not reflective of what is typically seen in clinical practice. Overall, the frequency of side effects observed in the current study is comparable to the rates found in the trials of zolpidem²⁹ and eszopiclone³⁰ for menopausal insomnia, which reported adverse event rates of 75% and 40%, respectively, as well as to the rates observed for trials of ramelteon in the general population^{36,37,39,40,41}.

Several limitations to this study should also be acknowledged. As this was an uncontrolled pilot trial, the role of chance as well as non-specific treatment factors could not be explored. It is possible that factors other than the study medication (e.g., time, patient expectations, clinician's attention, demand characteristics, frequency of assessments) were responsible for the observed improvement in sleep. Another limitation may have resulted from our use of sleep diaries to measure the main outcome variables. Rather than obtaining objective polysomnograms, which would have required the participants to stay overnight at a sleep center on several occasions, women kept a daily record of their sleep patterns. While the use of ramelteon was not likely to negatively impact the participants' abilities to recall sleep and wake times, as published studies have found no effect on cognition the morning after dosing,^{19,20,38} it is possible that the record could have been completed inaccurately due to the biases inherent in self-report measures (i.e., wanting to provide responses that please the investigator).

However, despite this subjective measurement of sleep, improvements in sleep latency and total sleep time observed in this study are consistent with those found in controlled, polysomnographic trials of ramelteon.^{37,39,41} Larger, randomized, placebo-controlled trials of sleep in menopausal women, using both sleep diary data and polysomnograms, are needed to further evaluate the efficacy of this intervention.

In sum, our findings suggest that ramelteon may be a safe and effective non-hormonal treatment option for insomnia associated with menopause. The reduction in sleep latency and improvement in total sleep time produced by ramelteon in this study are comparable to the effects observed in trials of the sedative hypnotics for menopausal insomnia.^{29,30} Furthermore, ramelteon lacks both the sedating side effects and the abuse potential of these traditional sleeping agents.³⁸ The favorable side effect profile, combined with the improvements in latency to sleep onset and total sleep time observed in this study, suggest that ramelteon may be a good treatment option for menopausal insomnia. However, it is important to consider that ramelteon's non-significant effect on WASO may be one limitation to its use in the subgroup of menopausal women whose primary complaint is middle insomnia due to hot flashes/night sweats. Because the majority of women in this study were post, rather than perimenopausal, these findings may be most relevant to women experiencing insomnia postmenopause.

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Table 1

Means, Standard Deviations, and Significance Levels of Planned Contrasts for Sleep Measures Across Time

	Baseline	Week 2	Week 4	Week 6
Sleep latency (in minutes)	46.2 (19.8)	42.6(30.6)	27.6(17.0)**	24.0(15.0)***
Total sleep time (in minutes)	336(62)	378(79)*	422(62)***	420(38)***
WASO (in minutes)	38.4(36.6)	25.8(25.2)	25.7(24.9)	20.4(21.0)
Sleep efficiency	.80(.10)	.83(.15)	.90(.06)**	.91(.06)***
Nighttime awakenings	2.32(1.36)	2.06(1.35)	1.83(1.09)**	1.86(1.53)*
Hot flashes	2.31(1.95)	1.80(1.45)	1.69(1.52)	1.52(1.32)*

Key: Change from baseline significant at * $p < .05$, ** $p < .01$, *** $p < .001$ in planned contrast analyses with Bonferroni adjustment.

Table 2

Means, Standard Deviations, and Significance Levels for Planned Contrasts for Self-Report Questionnaires Across Time

	Baseline	Week 2	Week 4	Week 6
Sleep quality	3.30(1.30)	5.30(2.23)***	5.93(1.98)***	7.36(1.34)***
Daytime dysfunction	6.15(2.13)	7.35(2.62)	7.93(1.27)**	8.21(1.48)**
Daytime alertness	5.60(1.79)	6.70(2.20)*	7.21(1.72)**	7.93(1.33)***
SII	65.65(31.99)	33.55(8.17)***	29.00(9.82)***	27.86(11.02)***
MENQOL	108.35(31.99)	131.75(26.38)***	137.21(26.84)***	137.14(35.74)***
GCS	43.55(11.93)	49.70(9.90)***	50.14(10.48)***	50.64(12.66)***
BDI	11.35(7.30)	6.50(6.32)***	5.00(4.85)***	4.07(5.59)***
BAI	41.30(6.03)	7.95(9.68)***	7.79(10.16)***	9.00(12.81)***

Key: Sleep Impairment Index (SII), Menopause Quality of Life Scale (MENQOL), Greene Climacteric Scale (GCS), Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI)

Change from baseline significant at * $p < .05$, ** $p < .01$, *** $p < .001$ in planned contrast analyses with Bonferroni adjustment.