The Effectiveness of Prolonged-Release Melatonin in Primary Insomnia Patients with a Regular Sleep-Wake Cycle

Seockhoon Chung, MD, PhD, Soyoung Youn, MD, Boram Park, MD, Suyeon Lee, MD, Changnam Kim, MD

Department of Psychiatry, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Background and Objective Prolonged-release melatonin (PRM) might effectively increase patient satisfaction when administered to individuals older than 55 years old with primary insomnia who were not satisfied with their sleep even after their sleep-wake cycle schedule was set. We investigated patients' satisfaction rate with PRM when they took it after their sleep-wake cycle was set.

Methods Among 87 patients who were prescribed PRM at the sleep clinic, 44 patients with primary insomnia who complained of poor sleep quality even after adopting a set 7-hour sleep-wake schedule or taking sleeping pills 7 hours before wake-up time were selected. Their medical records were reviewed. We explored patients' satisfaction rates with PRM after 3–4 weeks.

Results Among the 35 subjects who completed follow-up, 23 (66%) reported an improvement in insomnia symptoms after taking PRM. Five subjects reported daytime sleepiness as treatment-emergent adverse events. Of the 25 subjects taking other sleeping pills at baseline and followed up, 11 (44%) reduced their sleeping pill dosage by at least 50%. Five subjects completely discontinued their previous sleeping pills after starting PRM.

Conclusions We observed a high satisfaction rate with PRM when prescribed to patients with a regular sleep-wake cycle. We believe that the results of this study will help to optimize hypnotic prescription to insomnia patients. **Sleep Med Res 2016;7(1):16-20**

Key Words Insomnia, Melatonin, Sleep, Hypnotics.

INTRODUCTION

The prevalence of both insomnia¹ and sleeping pill use² increases with age. The elderly population shows a decreased sleep efficiency and percentage of slow-wave sleep. In addition, any medical or psychiatric illness, circadian rhythm disruption, decreased physical activity, or medication used to treat illness can cause sleep disturbance in elderly people.³ Melatonin influences the sleep-wake cycle,⁴ sleep quality,⁵ and slow-wave sleep,⁶ and the nocturnal melatonin peak declines in elderly persons.⁷ Thus, exogenous melatonin therapy has been considered to be of benefit in promoting sleep in older patients.^{8,9}

Recently, a prolonged-release formulation of melatonin (PRM) was approved for the treatment of insomnia patients aged ≥ 55 years in South Korea. Patients are recommended to take PRM 1–2 hours before bedtime.¹⁰ When administered orally, the melatonin levels during the subsequent 8–10 hours can mimic the physiological profile of endogenous melatonin¹¹ without impairing daytime psychomotor performance.¹² However, recent studies of the effectiveness of PRM revealed a slightly lower response rate of 26–47%.^{11,13} A strict definition of a response, over a 10-mm improvement in the mean “quality of sleep” and “behavioral integrity the following morning” domains of the Leeds Sleep Evaluation Questionnaire,¹⁴ might have decreased the response rate. However, we also need to consider that the subjects' sleep-wake cycle might have influenced the results of these studies. For insomnia treatment, a set sleep-wake cycle is important and is one of the major components of cognitive behavioral therapy¹⁵ for insomnia. In particular, we previously reported that sleeping pill administration time may influence patient satisfaction with their sleeping pills.¹⁶ The administration time of the hypnotic agent

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Correspondence

Seockhoon Chung, MD, PhD
Department of Psychiatry,
Asan Medical Center, University of Ulsan
College of Medicine,
88 Olympic-ro 43-gil, Songpa-gu,
Seoul 05505, Korea
Tel +82-2-3010-3411
Fax +82-2-485-8381
E-mail chung@amc.seoul.kr

($p < 0.001$) and bedtime ($p < 0.001$), but not sleep onset or wake-up time, occurred later in the night in the satisfied group. Thus, we believe that the real effectiveness of a specific sleeping pill should be measured after the patient's sleep-wake schedule is set.

We hypothesized that PRM might effectively increase patient satisfaction when administered to individuals older than 55 years old with primary insomnia who were not satisfied with their sleep even after their sleep-wake cycle schedule was set. Thus, in the present study, we explored how many patients were satisfied with PRM when they took it after their sleep-wake cycle was set.

METHODS

Subjects and Assessments

Subjects were selected from patients who visited the sleep clinic in the Department of Psychiatry in Asan Medical Center, Seoul, South Korea, between November 2014 and December 2015. Among 99 patients who were prescribed PRM at the sleep clinic, we selected patients with primary insomnia according to the diagnostic criteria of the International Criteria for Sleep Disorders-2nd edition who complained of poor sleep quality even after adopting a set 7-hour sleep-wake schedule or taking sleeping pills, including benzodiazepine, and non-benzodiazepine gamma-aminobutyric acid (GABA) agonists, 7 hours before their wake-up time.¹⁶ In our present study, we defined the "regular sleep-wake cycle" as time in bed or duration from administration of pills to wake-up time within 8 hours.

We excluded patients who had 1) concurrent major psychiatric conditions such as major depressive disorder or anxiety disorder; 2) other concurrent sleep disorders such as circadian rhythm sleep disorder, restless legs syndrome, or periodic limb movements during sleep; 3) snoring, apneic symptoms, or severe daytime sleepiness suggestive of obstructive sleep apnea syndrome; 4) major medical or neurological diseases that can induce severe pain during the night or impair mobility and daily activities; 5) experience with cognitive behavioral therapy for insomnia prior to visiting our clinic; 6) usually spent over 30 minutes lying on their bed during daytime; or 7) use of other psychotropic medication, such as mirtazapine or antipsychotics, as sleeping pills.

When the patients visited our clinic, a psychiatrist specializing in sleep disorder (S.C.) obtained their full history, evaluated their sleep pattern, and performed a psychiatric examination. We usually asked the patients the following questions: 1) "How many tablets of sleeping pills per day are you taking now?"; 2) "What time do you usually take sleeping pills?"; 3) "When is your usual bedtime?"; 4) "What time do you usually actually fall asleep?"; and 5) "What time do you finally get out of bed in the morning? (wake-up time)".¹⁶ We retrospectively reviewed all medical records of the study patients to acquire the infor-

mation routinely obtained in our sleep clinic. The study protocol was approved by the Institutional Review Board of Asan Medical Center.

Calculating the time and duration variables

We calculated the time and duration variables (Table 1) using the subjects' answers to the above questions.¹⁶ The time variables were calculated by averaging the usual times reported (i.e., if a patient answered "I usually take hypnotics between 9:00 pm and 9:30 pm", we computed this as 9:15 pm). We transformed the time variables into numeric variables because minutes range from 0 to 60. Thus, 15 minutes (one quarter of 1 hour) was transformed into 0.25 (one quarter) and 30 minutes (a half of 1 hour) into 0.50, and 10:15 pm was transformed into 10.25 and 11:30 pm into 11.50, and so on. Using the data, we obtained new sleep indices (duration variables), namely, the 1) duration from administration of pills to bedtime (PTB), 2) duration from administration of pills to sleep onset time (PTS), and 3) duration from administration of pills to wake-up time (PTW).

Calculating the number of tablets of equivalent hypnotic agents

We have used the "number of tablets of equivalent hypnotic agents (TEQ)" as defined.¹⁶ The equivalent dosage of each medication was calculated as follows:¹⁷ alprazolam, 0.25 mg; bromazepam, 3 mg; clonazepam, 0.25 mg; diazepam, 5 mg; lorazepam, 0.5 mg; triazolam, 0.25 mg; and zolpidem, 10 mg of the

Table 1. Clinical characteristics of the study subjects at baseline

Total subjects at baseline (n = 44)	At baseline
Male, n (%)	27 (62)
Age, years (range)	65.9 ± 8.6 (55–95)
Sleep indices	
Bedtime	11:22 pm ± 0:43
Sleep onset time	11:36 pm ± 1:55
Wake-up time	6:02 am ± 0:54
Sleep latency, SOL (min)	29.8 ± 21.0
Time in bed, TIB (h)	6.8 ± 0.8
Patients currently taking sleeping pills (n = 31)	At baseline
Number of tablets of equivalent hypnotic drugs, TEQ (tablets)	1.9 ± 1.3
Sleeping pill administration time	11:13 pm ± 0:42
Duration from administration of pills to bedtime, PTB (min)	11.6 ± 14.6
Duration from administration of pills to sleep onset time, PTS (min)	37.2 ± 20.5
Duration from administration of pills to wake-up time, PTW (h)	6.9 ± 1.1

immediate-release form and 12.5 mg of the extended-release form. We calculated the TEQ by summing the number of sleeping pill tablets a patient was prescribed per day. For example, if a subject was prescribed 0.125 mg of triazolam, 5 mg of zolpidem immediate-release form, or 6.25 mg of zolpidem extended-release form, the TEQ would be 0.5. If a subject was prescribed 0.25 mg of triazolam and 5 mg of zolpidem immediate-release form at the same time, the TEQ would be 1.5.

Statistical Analysis

Statistical analyses were performed using SPSS version 19.0 for Windows (IBM Corp., Armonk, NY, USA). A Student t-test and paired t-test for continuous variables and chi-square test for categorical variables were performed. The level of significance was defined as $p < 0.05$ in two-tailed tests for all analyses.

RESULTS

A total of 44 subjects were selected and their medical records were reviewed. After the prescription of PRM to the subjects, 35 subjects completed follow-up; 9 were lost to follow-up. At baseline, the subjects' mean age was 65.9 ± 8.6 years old (Table 1). Their mean bedtime was 11:22 pm, mean sleep onset time was 11:36 pm, and mean wake-up time was 6:02 am. Their mean sleep latency was 29.8 ± 21.0 minutes and mean time in bed was 6.8 ± 0.8 hours. Of the 44 subjects, 31 (70%) were currently taking sleeping pills within 8 hours of PTW. They were taking 1.9 tablets of sleeping pills per day, their mean sleeping pill administration time was 11:13 pm, mean PTB was 11.6 minutes, mean PTS was 37.2 minutes, and mean PTW was 6.9 hours.

After taking PRM 2 hours before bedtime, their bedtime, sleep onset time, and wake-up time was not significantly

Fig. 1. Subject sleep schedules and time at which they took prolonged-release melatonin.

changed at follow-up (Fig. 1). Among the 35 subjects who completed follow-up, 23 (66%) reported an improvement in insomnia symptoms after taking PRM (Table 2). Their mean duration of PRM use was 26.4 ± 10.5 days, the mean PRM administration time was 9:31 pm, mean PTB of PRM was 1.9 ± 0.4 hours, mean PTS of PRM was 2.3 ± 0.5 hours, and mean PTW of PRM was 8.5 ± 0.9 hours. Five subjects reported daytime sleepiness as treatment-emergent adverse events. Of the 25 subjects taking other sleeping pills at baseline and followed up, 11 (44%) reduced their sleeping pill dosage by at least 50%. Five subjects completely discontinued their previous sleeping pills after starting PRM. There were no significant differences in clinical characteristics between subjects who were satisfied and dissatisfied with PRM at the endpoint (Table 3).

DISCUSSION

We observed a 62% satisfaction rate after PRM use for 3–4 weeks in subjects with a regular sleep-wake cycle schedule was set. Although we simply estimated the satisfaction rate based on patients' medical records, we believe that PRM effectively reduced their insomnia symptoms. Previous studies revealed a relatively low response rate,^{11,13} but we believe that the real effects of sleeping pills can be assessed when the patients have a regular sleep-wake cycle schedule. A lower satisfaction rate is likely to be seen in patients without a regular sleep-wake cycle who take sleeping pills. We previously reported that patients who were satisfied with their sleeping pills tended to take the pills later than those who were dissatisfied.¹⁶ We also found a duration of around 7 hours from sleeping pill administration

Table 2. Subjects who were prescribed PRM (n = 35)

	At follow-up
Are you satisfied with PRM? (yes)	23/35 (66%)
Duration of PRM use (days)	26.4 ± 10.5
No. of patients who reduced sleeping pills disease by at least 50% (n)	11/25 (44%)
No. of patients who discontinued previous sleeping pills (n)	5/25 (20%)
Treatment-emergent adverse events	
Daytime sleepiness (n = 5), dizziness (n = 2), headache (n = 1)	
PRM-related sleep indices	
PRM administration time	9:31 pm $\pm$ 0:34
Duration from PRM to bedtime, PTB (h)	1.9 ± 0.4
Duration from PRM to sleep onset time, PTS (h)	2.3 ± 0.5
Duration from PRM to wake-up time, PTW (h)	8.5 ± 0.9

PRM: prolonged-release melatonin.

Table 3. Clinical characteristics of the study subjects who were satisfied or dissatisfied with prolonged-release melatonin

Variables at study endpoint	Satisfied (n = 23)	Dissatisfied (n = 12)	p-value
Male, n (%)	13 (57)	7 (58)	0.60
Age (years)	64.7 ± 7.0	63.3 ± 6.4	0.57
Mean duration of PRM use (days)	27.4 ± 12.0	23.1 ± 7.1	0.26
Time variables			
PRM administration time	9:36 pm ± 0:32	9:28 pm ± 0:40	0.47
Bedtime	11:28 pm ± 0:47	11:30 pm ± 0:34	0.91
Sleep onset time	11:45 pm ± 0:51	11:56 pm ± 0:41	0.50
Wake-up time	6:12 am ± 0:58	5:54 am ± 0:48	0.40
Duration variables			
Sleep latency (min)	25.8 ± 22.7	32.5 ± 15.4	0.37
Time in bed (h)	6.7 ± 0.9	6.4 ± 0.9	0.33
Duration from administration of PRM to bedtime, PTB (h)	1.8 ± 0.5	2.0 ± 0.3	0.25
Duration from administration of PRM to sleep onset time, PTS (h)	2.1 ± 0.6	2.5 ± 0.4	0.07
Duration from administration of PRM to wake-up time, PTW (h)	8.6 ± 1.0	8.5 ± 0.9	0.36
Sleeping pill ingestion			
Number of patients who are currently using other sleeping pills, n (%)	18 (78)	7 (58)	0.20
Number of tablets of equivalent hypnotic drugs, TEQ (tablets)	1.2 ± 0.3	1.8 ± 0.7	0.23

PRM: prolonged-release melatonin.

to wake-up time (i.e., PTW). From the results, we proposed a new sleeping pill administration instruction of “take your sleeping pills 7 hours before your wake-up time”. When we applied the instruction to insomnia patients, we found increased satisfaction with sleeping pills and sleep quality and decreased insomnia symptoms (manuscript under consideration). Based on these results, we hypothesized that PRM needs to be taken 9 hours before the usual wake-up time and that patients should go to bed 2 hours after taking the PRM. We believe that this instruction could improve satisfaction with PRM.

In previous studies, PRM helped to reduce the dosage of sleeping pills,^{18,19} and a 31% sleeping pill discontinuation rate was observed after taking PRM.²⁰ In our present study, of the 25 subjects who had been using benzodiazepine or non-benzodiazepine GABA agonists as sleeping pills, 44% reduced and 20% completely discontinued their previous sleeping pill use after starting PRM. Patients who were taking sleeping pills for insomnia usually feel anxious about long-term hypnotic use, dependency, tolerance, or memory disturbance. Melatonin is generally regarded as a safer medication than benzodiazepine or Z-class drugs, and patients tried to reduce their sleeping pill use while taking PRM. Treatment-emergent adverse events included daytime sleepiness after PRM use in five subjects. In a previous study, pharyngitis, back pain, asthenia, upper respiratory tract infection, and bronchitis were reported adverse effects during 26 to 52 weeks of PRM treatment.¹⁷ Because our observation period lasted just 3–4 weeks, our results are not comparable. However, PRM can be used safely without any se-

rious adverse events.

We could not determine why some subjects were satisfied with PRM and some were not (Table 3). There were no significant differences in clinical variables between the two groups. One possible explanation is that the patients' basal melatonin level rather than clinical variables might influence the effectiveness of PRM. We hypothesize that subjects whose peak melatonin level was high might be more likely to be dissatisfied with PRM. To explore this theory, the melatonin level should be measured in future studies.

This study had a number of limitations of note. First, we simply analyzed data from medical records gathered retrospectively. Patient sleep indices were measured based on subjective responses and the satisfaction rates were also obtained from subjective responses from these subjects rather than objective findings. Objective findings such as nocturnal polysomnography or melatonin level measurement would help when investigating the real effectiveness of PRM in future studies. Second, we could not estimate the effectiveness of PRM when prescribed to patients whose sleep-wake cycle was not set. When we selected patients whose medical records could be reviewed in our clinic, we could not easily determine which cases had a regular sleep-wake cycle. In our sleep clinic, we usually instruct the patients to take their prescribed sleeping pills based on their desired wake-up time. Third, we had a relatively small sample size and short observation period.

In conclusion, we observed a high satisfaction rate with PRM when prescribed to patients with a regular sleep-wake

cycle. We believe that the results of this study will help to optimize hypnotic prescription to insomnia patients.

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Conflicts of Interest

The authors have no financial conflicts of interest.

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