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Clonazepam for probable REM sleep behavior disorder in Parkinson's disease: A randomized placebo-controlled trial

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ABSTRACT

Background: Clonazepam is considered to be a first-line treatment for rapid eye movement sleep-related behavior disorder (RBD) in Parkinson's disease (PD). The purpose of this study was to determine the short-term efficacy and safety of clonazepam for the treatment of probable RBD (pRBD) in patients with PD.

Methods: We conducted a four-week, randomized, double-blind, placebo-controlled trial of clonazepam (0.5 mg/day at bedtime) compared to a placebo for RBD symptoms in patients with PD. Patients aged 30 years or older who had a caregiver that could observe RBD symptoms were recruited between April 2015 and February 2016. The primary outcome was the Clinical Global Impressions-Improvement (CGI–I) score at week four, and we compared scores between the clonazepam and placebo groups.

Results: A total of 40 patients were enrolled, with 20 assigned to receive clonazepam and 20 to receive the placebo. The CGI-I score at four weeks indicated an improvement in RBD symptoms in both the clonazepam (median score [minimum, maximum] = 2 [1,5]) and placebo (3 [1,6]) groups, with no significant difference between the groups (p = .253). The secondary outcomes were not significantly different between the clonazepam and placebo groups.

Conclusions: Both clonazepam and placebo tended toward improvement on pRBD symptoms in patients with PD. No firm conclusion on efficacy of clonazepam was drawn due to limitations in the study design. This study emphasized the importance of conducting future large-scale, randomized trials with better assessment tools and polysomnography to provide evidence for the benefit of clonazepam.

1. Introduction

Rapid eye movement (REM) sleep behavior disorder (RBD) is a common non-motor manifestation associated with Parkinson's disease (PD) and other synucleinopathies. Clonazepam is considered to be a first-line treatment for RBD [1]. However, the evidence for its efficacy was based on case series, case reports, and one prospective, open-label, follow-up study [1,2], not on randomized clinical trials. Furthermore, clonazepam can have negative side effects, such as daytime somnolence, cognitive decline, and falls, which can be problematic in elderly patients, especially in the Parkinsonian population. Evidence-based reviews of treatments for the non-motor symptoms of PD emphasized that there are insufficient evidences for all treatment options in RBD, yet clonazepam is still widely used in routine clinical practice [3,4]. This "state of the art" management of RBD was emphasized by the international RBD study group (IRBD-SG) in 2013, and they published a consensus statement on devising controlled clinical studies in RBD [5].

Even though physicians currently use clonazepam for their patients with some reported benefits, it remains unclear whether clonazepam is truly effective compared with placebo in a blinded clinical setting. We designed a randomized clinical trial in consideration of the proposals of the IRBD-SG [5]. The aim of the current study was to determine the efficacy and safety of clonazepam for the treatment of probable RBD (pRBD) in patients with PD.

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2. Methods

2.1. Trial design

This study was a four-week, randomized, double-blind, placebo-controlled, parallel group trial in patients with PD and pRBD who visited the Seoul National University Hospital (SNUH) in Korea.

2.2. Standard protocol approvals, registrations, and patient consent

This study was approved by the Institutional Review Board of the SNUH, and written informed consent was obtained from all participants. The study was registered at clinicaltrials.gov (NCT02312908).

2.3. Participants

All eligible subjects (aged 30 years or older) participated in the study at the SNUH. Inclusion criteria were as follows: subjects (1) were diagnosed with PD by experienced movement disorder specialists (H·K and B.J) using the United Kingdom Brain Bank Criteria [6]; (2) had a Hoehn and Yahr (HY) stage of less than four; (3) had caregivers who could observe RBD symptoms and provide information to investigators; (4) were enrolled voluntarily and understood the contents of the trial; (5) were diagnosed with pRBD by answering "yes" to the question "Have you ever been told, or suspected yourself, that you seem to 'act out your dreams' while asleep (for example, punching, flailing your arms in the air, making running movements, etc.)?" (RBD1Q) [7].

Exclusion criteria were as follows: (1) subjects who had severe cognitive decline and were unable to participate in the trial; (2) subjects who had confusion or visual hallucinations; (3) subjects whose caregivers reported symptoms suggestive of obstructive sleep apnea or severe snoring; (4) subjects who had taken clonazepam within four weeks before study enrollment; (5) subjects who were being treated with benzodiazepines at bedtime; (6) subjects who were alcoholics, drug abusers, or had a drug dependency; (7) subjects who were lactating, pregnant, or possible pregnant; (8) subjects who had hypersensitivities to clonazepam or benzodiazepines; (9) subjects who had severe comorbidities (severe myasthenia gravis, liver dysfunction, or respiratory dysfunction) or cancer; (10) subjects who had acute close-angle glaucoma; (11) subjects who had genetic disorders, such as galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption; (12) subjects who had participated in other trials within three months; (13) subjects who was not eligible to participate in the study according to clinical judgement.

2.4. Interventions

Clonazepam tablets and matched placebos (identical in appearance, smell, and taste) were given to patients in identical packaging. Participants took either clonazepam (0.5 mg, 1 tablet) or a matched placebo (1 tablet) before sleep for four weeks. Other medications which may influence RBD, such as hypnotics, anticonvulsants, benzodiazepines, disulfiram, barbitals, hydantoin derivatives, cimetidine, and melatonin, were not allowed during the study period. Anti-parkinsonian medications were allowed if a stable dose was established $\geq$ 4 weeks prior to baseline data collection and during the study period; the dose of anti-parkinsonian medications could be changed if necessary by clinical judgement.

2.5. Outcomes and procedures

Baseline characteristics, included age, sex, severity of RBD evaluated using a validated questionnaire (RBD-HK) [8], onset of Parkinsonism motor symptoms, and levodopa-equivalent daily dose (LEDD). The Clinical Global Impression-Severity (CGI-S) scale score [9], Korean Epworth Sleepiness Scale (KESS) score [10], Korean version of the Parkinson's disease Sleep Scale (PDSS) score [11], Korean version of the Montreal Cognitive Assessment (MoCA-K) score [12], and scores for part I, part III, and item 13 (falling unrelated to freezing) of the Unified Parkinson's disease Rating Scale (UPDRS) [6] were assessed at baseline and after four weeks of treatment.

The primary outcome measure was the investigator-rated Clinical Global Impression-Improvement (CGI−I) scale [9] score at four weeks, for which the investigator evaluated the changes in frequency, severity, quality of RBD symptoms by interviewing the caregivers who were instructed to sleep with the patients every night, observe and record RBD symptoms during the study period. The CGI-I score is a 7-point scale to rate the improvement (1, very much improved; 2, much improved; 3, minimally improved) or worseness (4, no change; 5, minimally worse; 6, much worse; 7, very much worse) of the patient's illness relative at the beginning of the treatment. The responder rate was defined as the proportion of patients who had a CGI-I score of 1 to 3. For secondary outcomes, mean changes of in CGI−S, KESS, PDSS, MoCA-K, and UPDRS scores from baseline to four weeks were calculated. To reduce inter-rater differences, CGI−I, CGI−S, and UPDRS scores were measured by one movement disorder specialist (C.S), and all other measurements by another investigator (H·K).

Safety and tolerability were assessed by standard adverse event (AE) reporting, medication compliance, and dropout rates. AEs were evaluated for their duration, severity, seriousness, and causal relationship with the study drug. Serious AEs (SAEs) were defined as AEs that resulted in death, were life-threatening/disabling, or required hospitalization. Medication compliance was defined as the proportion of days in which a subject correctly followed the medication schedule. One investigator (H·K) interviewed the participants for safety assessment and medication adherence, and counted the remained pills at the endpoint visit. Participants could contact the investigators for reports of AEs via a cellular phone during the study period.

2.6. Sample size

Because there has been no clinical trial for clonazepam to date, we used data from a previous study of melatonin in iRBD patients to guide our decisions regarding sample size [13]. Based on the reference, the expected mean difference between group was 1.2. However, for calculating sample size for this study, we assumed that mean difference would be 1 and its standard deviation be 1.2 rather than pooled standard deviation, which is a weighted average of two groups' standard deviation, to sufficiently obtain the expected power. We also considered that mean difference by 1 would be clinically effective. Therefore, we expected effect size of the CGI-I score between clonazepam and control group in the student's *t*-test as 1 ± 1.2. The sample size was calculated with the following formula:

$$n = \frac{2(Z_\alpha + Z_\beta)^2\sigma^2}{(\mu_c - \mu_t)^2}$$

As we expected that clonazepam would be effective, we set the one-tailed significance level at 0.05. It was calculated that 18 participants per group would provide 80% power to detect group differences in CGI-I scale scores. To compensate for an anticipated 10% withdrawal rate, the final sample size was 20 participants per group.

2.7. Randomization and blinding

A randomization sequence was developed and maintained by the Medical Research Collaborating Center in the SNUH. Patients were randomly assigned to receive clonazepam or placebo (1:1 ratio) by a centralized, web-based, blocked randomization schedule (four and six block size). All patients, investigators, and raters were blinded to the assigned treatment. Clonazepam and placebo tablets were given in identical packaging. Blinding was maintained until all study procedures

were completed.

2.8. Statistical analyses

An efficacy analysis was conducted in an intention-to-treat (ITT) population followed by a per-protocol (PP) population. The ITT population included all participants who took ≥1 dose of study medication after randomization. The PP population included all participants who completed the study procedure, had at least 80% medication compliance, and did not take other medications which were not allowed during the study period. We imputed missing data for the primary outcome (CGI-I score) to score four (no change) because since CGI-I is a bidirectional scale, from improvement to worsening, score four (no change) is the most reasonable and conservative substitution. Sensitivity analyses were conducted using other imputation methods (no imputation and imputation to score seven [very much worse]) and for comparing responder rate between groups. We did not impute missing data for secondary outcomes. A safety analysis was conducted in an ITT population.

Descriptive statistics (mean and SD, or median and minimum/maximum) were used to describe the patients' baseline characteristics. For comparison of group differences in baseline characteristics, we used Student's *t*-test for continuous variables and the Chi-squared test for categorical variables. When the required assumptions were not satisfied, the Wilcoxon rank-sum test and Fisher's exact test were used. For efficacy analysis of the primary outcome, we used the Wilcoxon rank-sum test. For secondary outcomes, changes from the baseline were compared using an analysis of covariance (ANCOVA) or a non-parametric ANCOVA adjusting for the baseline data. Normality assumption was evaluated with graphical methods, Q-Q plots and histograms, for residuals from ANCOVA. The significance level was set at one-tailed 0.05 for the primary outcome and two-tailed 0.05 for secondary outcomes, as previously defined.

3. Results

All participants were recruited between April 14, 2015 and March 3, 2016. Fig. 1 shows the flow diagram of participant selection. Of the 86 subjects who were screened for eligibility, 20 did not fulfil the eligibility criteria and 26 declined to participate. A total of 40 subjects were randomly assigned to either the clonazepam (20 subjects) or placebo (20 subjects) group. Three subjects in the clonazepam group withdrew after randomization; one withdrew informed consent before receiving the allocated intervention and was excluded from the ITT population, while two discontinued during the follow-up due to daytime sleepiness ($n = 1$) and dyskinesia aggravation ($n = 1$). Thirty-seven subjects completed the follow-up period. Thirty-nine subjects were included in the ITT analysis, and missing data were imputed as explained above. Three subjects (one in the clonazepam group and two in placebo group) were further excluded from the PP population due to major protocol violations (a drug compliance rate of under 80%).

The demographics and baseline characteristics of the clonazepam and placebo groups were similar (Table 1). The severity of depression (Q3 of UPDRS part I) was mild in placebo and clonazepam group. The severity of RBD as assessed with the RBDQ-HK was also similar between groups. Thirty-six subjects (92.3%) had dream enactment behaviors more than one-two times per week (the frequency of sleep talking in the Supplementary Table 1), which were sufficient for evaluation of change in RBD symptoms. Other medications of patients and controls during study period were summarized in Supplementary Table 3.

3.1. Efficacy analysis

The CGI-I score at four weeks, the primary outcome, tended toward improvement of symptoms in both the clonazepam and placebo groups, but there was no significant difference in scores between the two groups (Table 2). Sensitivity analyses also showed no differences between the two groups (Table 2). With regards to secondary outcomes, there were no differences in the mean changes in sleep-related scores (CGI−S, KESS, and PDSS), MoCA-K, or UPDRS scores between the clonazepam and placebo groups. In the efficacy analyses performed in the PP population (Supplementary Table 2), there were also no differences in the primary and secondary efficacy outcomes between the two groups.

3.2. Safety analysis

During the study period, 16 (41%) out of 39 subjects in the ITT population had 17 AEs, while six patients (30%) in the placebo group and 10 patients (52.6%) in the clonazepam group reported more than one AE (Table 3). No SAE was reported in either group. Only two patients in the clonazepam group (10.5%) withdrew from the study due to daytime sleepiness or dyskinesia aggravation. The most common AEs were daytime sleepiness (21.1%) in the clonazepam group, and daytime sleepiness and dizziness (both 10%) in the placebo group.

4. Discussion

This study was the first randomized, double-blind, placebo-controlled trial of clonazepam, which is the first-line treatment for RBD. There were no differences in primary and secondary efficacy outcomes between the two groups. There were only mild AEs in both the clonazepam and placebo groups.

The benefit of clonazepam in the treatment of RBD has been repeatedly reported, so the conflicting results of this study should be interpreted with caution. The primary outcome which was recommended by the IRBD-SG in 2013 was the CGI-Efficacy Index (CGI-EI) [5]. This index is a 16-point scale that can simultaneously evaluate the therapeutic benefit and side effect of a treatment. However, the index is not the sole efficacy scale because the score can be changed by the severity of the AE. Furthermore, there has been no previous study using the CGI-EI scale which could be used for estimating the sample size needed for our trial, whereas one melatonin trial used the CGI-I scale [13]. We selected the CGI-I scale as the primary outcome to focus on evaluating the efficacy of clonazepam, rather than weighing its efficacy and safety. The CGI-I score is a 7-point scale, but only four steps (no change, minimal, much, and very much improved) can be used for the assessment of clinical improvement and are not sensitive enough to assess improvements in RBD symptoms. There were also several RBD questionnaires which could have been used for screening of RBD, but these questionnaires were not designed for assessment of severity of RBD symptoms [5]. Objective evaluation or validated scales using a polysomnography (PSG) would have compensated the limitation of CGI-I score [14,15]. However, it was not applicable in this study because of the limited funding source. The use of more detailed and validated RBD severity assessment tools is recommended in future studies. For example, one study used the RBDQ-3 M scale to measure the severity of RBD during a three-month period by modifying the RBD-HK scale, which is designed to evaluate RBD symptoms over the course of one year [2]. The RBD episode frequency with an event diary by the bed partners is another quantitative outcome to be considered [16].

There were no differences in the secondary efficacy outcomes, such as the mean changes in CGI−S, KESS, and PDSS scores, between the two groups. An unexpected inflation of placebo effect in the placebo group may be a significant factor for the negative results found in this study. Compared with the results of the melatonin study we used for our sample size calculation [13], the average CGI-I score in the clonazepam group was only slightly better in our study (mean ± SD: 2.5 ± 1.2 vs. 3.3 ± 1.2, respectively), but the CGI-I score in the placebo group was much better (3.0 ± 1.4 vs. 4.5 ± 0.8, respectively). Because CGI scores were reported by caregivers in this study, they may have been influenced by their expectation of medication and biased recall of the patients' symptoms before and after the study.

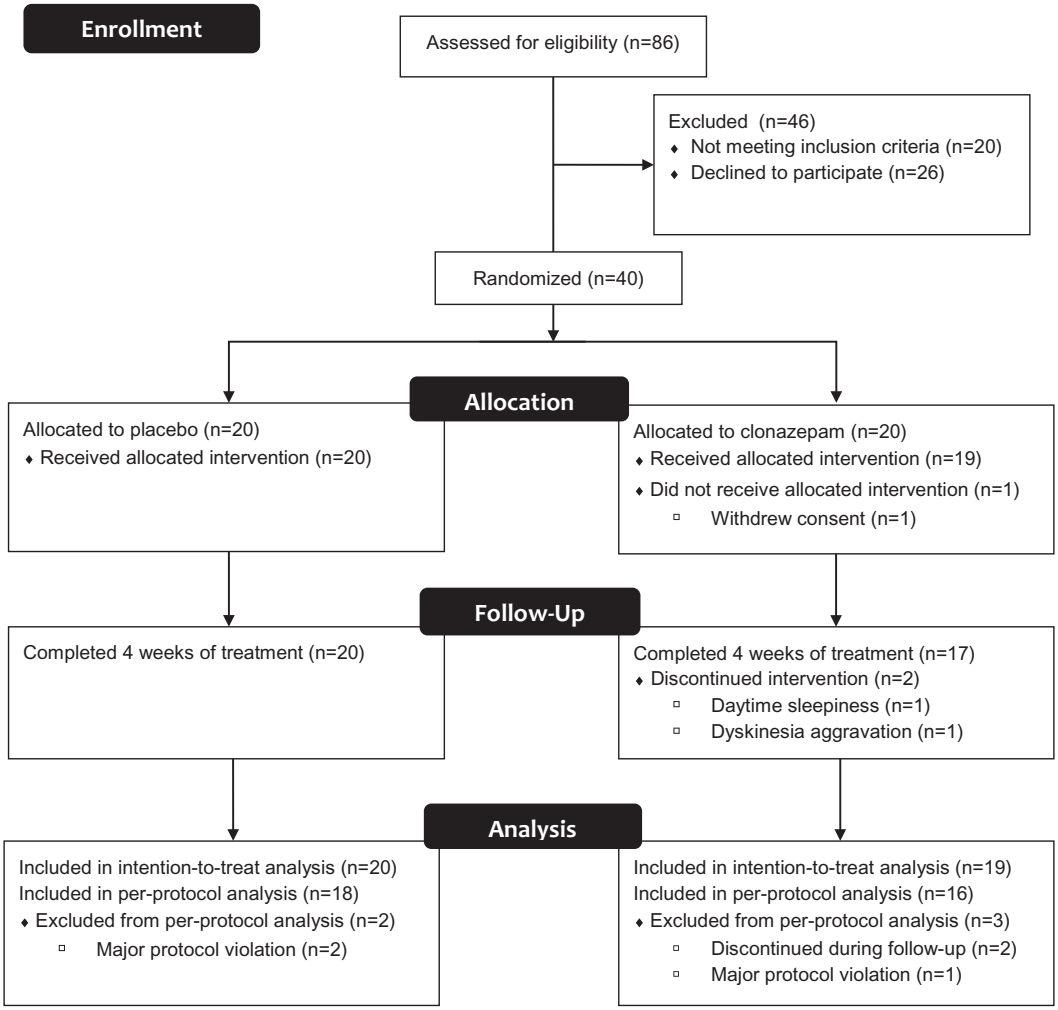

Fig. 1. Flow diagram of subject selection.

The responder rate of the clonazepam group was 76.5% (13/17) in this study. This is a slightly lower rate compared with the responder rates in previous studies (range of total responder rates: 87–90%) [17–20]. The clonazepam dose was fixed at 0.5 mg in this study, while larger doses (1.0 mg or more) could be used in previous studies. In one study, the mean dose of clonazepam was initially 0.65 ± 0.47 mg, but was gradually increased in 64% of the patients, for a final average of 1.4 ± 1.37 mg [17]. Therefore, the responder rate of this study is not an unusual finding considering the low dose of clonazepam. The lack of effect on secondary outcomes may be also influenced by the low dose. In the guideline of the treatment of RBD, the recommended dose of clonazepam is 0.25–2.0 mg [1]. It is necessary to determine the efficacy and safety of higher doses (1.0 mg or more) of clonazepam in placebo-controlled trials.

Is clonazepam a drug that has no effect on RBD? It is still inconclusive, although our study showed negative results. In a study of electroencephalogram (EEG) changes with clonazepam treatment in iRBD patients, < 15 Hz EEG band suppression was reduced in drug-naïve iRBD patients, which was partially recovered after clonazepam treatment [21]. In addition, clonazepam has been shown to reduce aggressive behaviors in RBD patients, yet does not change the degree of REM sleep without atonia [22,23]. Considering these objective studies, clonazepam seems to reduce the negative effects from the supratentorial network rather than acting directly on the infratentorial pathology of RBD [21]. Therefore, although the efficacy of clonazepam was not demonstrated in our study, we recommend continuing studies to reveal whether there is objective improvement of RBD clonazepam treatment when compared with a placebo.

In this study, no SAE was reported in either group during the study period. The most common AE was daytime sleepiness, which has already been associated with clonazepam treatment [17–20]. Some AEs were uncertain to be related to clonazepam or placebo treatment, such as dyskinesia aggravation, because anti-parkinsonian medications were also used. Clonazepam may increase the risk of falls in PD patients, so the related UPDRS score (Q13) was evaluated separately, with no difference observed between the groups. Clonazepam was a safe and tolerable medication for short-term treatment of pRBD in PD patients with an HY stage < 4.

There are some limitations to be considered in this study. First, the sample size was small, which could have contributed to the lack of statistical power. As we discussed above, the sample size was calculated based on a previous study of iRBD using melatonin [13]. Moreover, the CGI-I score was not the primary outcome in that study, which would affect the power of the statistical analysis on the primary outcome in this study. Second, we used a one-tailed statistical test on the primary outcome. Although a two-tailed test is more conservative and neutral, the sample size was calculated for the one-tailed test in this study. The result was already negative in a one-tailed test, hence we did not re-analyze using a two-tailed test because it is meaningless. Third, only subjective scales were used, although we strictly selected only those participants with caregivers who could observe and report changes in RBD symptoms. Finally, we recruited pRBD patients without confirmation of PSG. Although RBD is very common in PD patients, with a prevalence of up to 60% [24], a clinical history and the simple

Table 1
Baseline characteristics (intention-to-treat population).

Measurement[a]	Placebo (n = 20)	Clonazepam (n = 19)	p-value[b]
Age, years	70.0 (56.0,77.0)	66.0 (48.0,73.0)	0.147
Sex			
Male	9 (45.0)	10 (52.6)	0.634[d]
Female	11 (55.0)	9 (47.4)	
Symptom onset for PD, years	59.0 (48.0,74.0)	56.0 (36.0,70.0)	0.272[c]
Duration of PD, years	6.0 (1.0,21.0)	8.0 (0.0,20.0)	0.778
Current use of anti-PD medication	19 (95.0)	19 (100)	0.323[d]
LEDD, mg/d	675 (0,2578)	1000 (150,2102)	0.491
RBDQ-HK score	45.5 (13.0,88.0)	44.0 (23.0,72.0)	0.686
CGI-S score	5 (2,7)	4 (2,7)	0.367
KESS score	7 (1,12)	6 (1,20)	0.480
PDSS score	106 (50,133)	101 (61,149)	0.911
MoCA-K score	25.5 (18.0,30.0)	25.0 (18.0,29.0)	0.843
UPDRS scores			
Part I	2.0 (0.0,7.0)	1.0 (0.0,4.0)	0.748
Part III	23.5 (12.0,45.0)	24.0 (12.0,49.0)	0.789
Depression (Q3)	0 (0.0,2.0)	1 (0.0,1.0)	0.369
Falling unrelated to freezing (Q13)	1.0 (0.0,3.0)	1.0 (0.0,3.0)	0.801
H&Y stage (min, max)	2.5 (1.5,3.0)	2.0 (1.5,3.0)	0.261

Abbreviations: SD = standard deviation, RBDQ-HK = Rapid Eye Movement Behavior Disorder Questionnaire – Hong Kong, PD = Parkinson's disease, LEDD = levodopa equivalent daily dose, CGI-S = Clinical Global Impression - Severity, KESS = Korean Epworth Sleepiness Scale, PDSS = Parkinson's disease Sleep Scale, MoCA-K = Korean Version of the Montreal Cognitive Assessment, UPDRS = Unified Parkinson's Disease Rating Scale, H&Y = Hoehn and Yahr.

[a] Median (minimum, maximum) values were used as summary statistics for continuous variables because the normality assumption was not satisfied by any variable except for PD symptom onset. Frequency (%) was used for categorical variables.

[b] The Wilcoxon rank-sum test was used for group comparisons unless otherwise specified.

[c] The Student's t-test was used for group comparison.

[d] The Chi-squared test was used for group comparison.

Table 2
Efficacy results (intention-to-treat population).

Outcome measure[a]	Placebo (n = 20)	Clonazepam (n = 17)	p-value[b]
Primary outcome: CGI-I score			
Week four, median (min, max)[c]	3 (1,6)	2 (1,5)	0.253
Week four, mean (SD)	2.95 (1.36)	2.47 (1.23)	
Interquantile range (25th, 75th quantile)	(2,4)	(2,3)	
Sensitivity analyses			
No imputation[d], median (min, max)	3 (1,6)	2 (1,5)	0.144
Imputation (score 7)[e], median (min, max)	3 (1,6)	2 (1,7)	0.344
Responder rate[f]	13 (65.0)	13 (76.5)	0.447
1: Very much improved	3 (15.0)	4 (23.5)	
2: Much improved	5 (25.0)	6 (35.3)	
3: Minimally improved	5 (25.0)	3 (17.7)	
4: No change	5 (25.0)	3 (17.7)	
5: Minimally worse	1 (5.0)	1 (5.9)	
6: Much worse	1 (5.0)	0 (0.0)	
7: Very much worse	0 (0.0)	0 (0.0)	
Secondary outcomes			
CGI-S score, median change (min, max)	−1 (−5,1)	−1 (−4,0)	0.181
KESS score, mean change (SD)	2.3 (2.6)	−1.8 (3.0)	0.452
PDSS score, mean change (SD)	14.1 (19.9)	18.9 (13.3)	0.138
MoCA-K score, mean change (SD)	1.2 (1.8)	1.6 (1.8)	0.485
UPDRS scores			
Part I, median change (min, max)	0.0 (−2.0,1.0)	0.0 (−2.0,1.0)	0.589
Part III, mean change (SD)	−0.7 (4.1)	−1.2 (4.1)	0.764
Falling unrelated to freezing (Q13), median change (min, max)	0.0 (−2.0,1.0)	0.0 (−1.0,0.0)	0.899

Abbreviations: SD = standard deviation, CGI-I = Clinical Global Impression - Improvement, CGI-S = Clinical Global Impression - Severity, KESS = Korean Epworth Sleepiness Scale, PDSS = Parkinson's Disease Sleep Scale, MoCA-K = Korean Version of the Montreal Cognitive Assessment, UPDRS = Unified Parkinson's Disease Rating Scale, H&Y = Hoehn and Yahr.

[a] Mean (SD) values were used as summary statistics for continuous variables that satisfied the normality assumption; otherwise, median (minimum, maximum) values were used. Frequency (%) was used for the responder rate.

[b] The Wilcoxon rank-sum test was used for the primary outcome; the Chi-squared test was used for the responder rate. For the secondary outcomes, an analysis of covariance (ANCOVA) or non-parametric ANCOVA was used according to whether a given variable satisfied the normality assumption.

[c] The missing CGI-I scores (two in the clonazepam group) were classified as "4 = no change".

[d] The missing CGI-I scores were not imputed.

[e] The missing CGI-I scores were classified as "7 = very much worse".

[f] The responder rate was defined as the proportion of patients who had a CGI-I score of 1 to 3 (very much improved to minimally improved).

screening questionnaire (RBD1Q) would not be sufficient to confirm RBD in the PD population [25]. The positive predictive value of RBD1Q is 48% for REM atonia index positive in PD [25]. Moreover, patients with other RBD-mimicking conditions such as obstructive sleep apnea and snoring were excluded by only caregiver's report, not PSG evaluation. Therefore, the results can be interpreted only for PD patients with pRBD symptoms, which may be other sleep-related disorders, and should not be generalized to patients with PSG-confirmed RBD. The assistance of PSG for the diagnosis and objective evaluation of RBD is important in clinical trials. However, evaluation with PSG was not feasible in this study. We recommend a multi-center, randomized trial to reduce the burden to participants and investigators to apply PSG evaluation.

4.1. Conclusion

Both clonazepam and placebo tended toward improvement on pRBD symptoms in patients with PD. No firm conclusion on efficacy of clonazepam was drawn due to limitations in the study design. This study emphasized the importance of conducting future large-scale, randomized trials with better assessment tools and polysomnography to provide evidence for the benefit of clonazepam.

Conflicts of interest

All authors have no conflicts of interest.

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Author contributions

1. Research project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript: A. Writing of the first draft, B. Review and Critique.

C.S.: 1A, 1C, 2C, 3A, 3B.
H.P.: 1C, 3B.
W.L.: 1C, 3B.
Hyun.K.: 1C, 3B.
Han.K.: 1A, 1B, 1C, 2A, 3A, 3B.

Table 3
Adverse events.

Adverse event	Subjects reporting an AE, n (%)		No. (%) of AEs	
	Placebo (n = 20)	Clonazepam (n = 19)	Placebo (total events *n* = 7)	Clonazepam (total events *n* = 10)
Subjects with an AE	6 (30.0)	10 (52.6)		
Subjects with a SAE	0 (0.0)	0 (0.0)		
Subjects with an AE leading to discontinuation	0 (0.0)	2 (10.5)		
Daytime sleepiness	2 (10.0)	4 (21.1)	2 (28.6)	4 (40.0)
Dizziness	2 (10.0)	3 (15.8)	2 (28.6)	3 (30.0)
Postural instability	0 (0.0)	1 (5.3)	0 (0.0)	1 (10.0)
Headache	0 (0.0)	1 (5.3)	0 (0.0)	1 (10.0)
Dyskinesia aggravation	0 (0.0)	1 (5.3)	0 (0.0)	1 (10.0)
Partial seizure	1 (5.0)	0	1 (14.3)	0
Erectile dysfunction	1 (5.0)	0	1 (14.3)	0
Tremor	1 (5.0)	0	1 (14.3)	0

Abbreviation: AE = adverse event, SAE = serious adverse event.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2019.04.029.

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