



# Comorbid Depression Is Associated with a Negative Treatment Response in Idiopathic REM Sleep Behavior Disorder

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**Background and Purpose** The first-line medications for the symptomatic treatment of rapid eye movement sleep behavior disorder (RBD) are clonazepam and melatonin taken at bedtime. We aimed to identify the association between depression and treatment response in patients with idiopathic RBD (iRBD).

**Methods** We reviewed the medical records of 123 consecutive patients (76 males; age, 66.0±7.7 years; and symptom duration, 4.1±4.0 years) with iRBD who were treated with clonazepam and/or melatonin. Clonazepam and melatonin were initially administered at 0.25–0.50 and 2 mg/day, respectively, at bedtime, and the doses were subsequently titrated according to the response of individual patients. Treatment response was defined according to the presence or absence of any improvement in dream-enacting behaviors or unpleasant dreams after treatment.

**Results** Forty (32.5%) patients were treated with clonazepam, 56 (45.5%) with melatonin, and 27 (22.0%) with combination therapy. The doses of clonazepam and melatonin at follow-up were 0.5±0.3 and 2.3±0.7 mg, respectively. Ninety-six (78.0%) patients reported improvement in their RBD symptoms during a mean follow-up period of 17.7 months. After adjusting for potential confounders, depression was significantly associated with a negative treatment response (odds ratio=3.76, 95% confidence interval=1.15–12.32,  $p=0.029$ ).

**Conclusions** We found that comorbid depression is significantly associated with a negative response to clonazepam and/or melatonin in patients with iRBD. Further research with larger numbers of patients is needed to verify our observations and to determine the clinical implications of comorbid depression in the pathophysiology of iRBD.

**Key Words** rapid eye movement sleep behavior disorder, depression, clonazepam, melatonin.

## INTRODUCTION

Rapid eye movement sleep behavior disorder (RBD) is a parasomnia during rapid eye movement (REM) sleep characterized by dream-enacting behaviors (DEB) with vivid and unpleasant dreams.<sup>1</sup> Abnormal behaviors that occur in RBD vary in severity from limb jerks and sleep talking to complex and violent behaviors that can occasionally result in physical injury to patients and their bed partners.<sup>2</sup> Most RBD patients recall dreams that frequently have emotionally charged contents, such as fighting, arguing, and falling.<sup>3</sup> Idiopathic RBD (iRBD), which is also referred to as isolated RBD, is defined as RBD without any accompanying neurological disorders or triggering factors such as antidepressant medications and alcohol withdrawal.<sup>4</sup> Most importantly, iRBD is the strongest prodromal marker of neurodegenerative alpha-synucleinopathies, such as Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy.<sup>5</sup>

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Management strategies for iRBD should aim to minimize dream enactment, associated unpleasant dreams, and sleep-related injuries. Before starting pharmacotherapy, modifying the sleep environment is recommended for preventing potential sleep-related injuries to both patients and their bed partners.<sup>6</sup> The discontinuation of possible RBD-precipitating drugs, including selective serotonin reuptake inhibitor and other antidepressants, should also be considered. It has been well established that antidepressants can trigger DEB and the loss of muscle atonia that normally occurs during REM sleep.<sup>7</sup> Both depression and RBD are common prodromal nonmotor symptoms of alpha-synucleinopathies.<sup>8,9</sup> Accordingly, depression is common in patients with iRBD, with the risk being approximately sevenfold higher than that in controls.<sup>10</sup> One study found that patients with antidepressant-associated RBD exhibited significant abnormalities of neurodegenerative markers, such as mild motor dysfunction, olfactory dysfunction, and mild cognitive impairment.<sup>11</sup> These findings suggest that antidepressant-associated RBD is not a purely pharmacological side effect, instead representing the unmasking of pre-existing subclinical REM sleep without atonia in these patients.

The first-line medications for the symptomatic treatment of RBD are clonazepam and melatonin taken at bedtime.<sup>6</sup> Both of these medications have been reported to be effective, although the supporting evidence has only come from case series, small clinical trials, and case reports, rather than from large double-blind placebo-controlled trials.<sup>12</sup> Clonazepam does not restore muscle atonia during REM sleep, but it suppresses increased phasic chin electromyography (EMG) activity.<sup>13,14</sup> In contrast, melatonin treatment was found to significantly improve muscle atonia during REM sleep compared to baseline.<sup>15</sup> Combination therapy of clonazepam and melatonin can be applied to patients with RBD who do not respond to the initial monotherapy.<sup>16</sup> Nevertheless, in a minority of patients either a worsening of RBD symptoms or no improvement is observed with these medications.<sup>17</sup> As a common psychiatric disorder in patients with iRBD, comorbid depression may affect their response to medical treatment. However, few studies have investigated the clinical characteristics of iRBD patients who did not respond to clonazepam and/or melatonin therapy. Therefore, this study aimed to identify the association between comorbid depression and the treatment response in patients with iRBD while adjusting for clinical and polysomnographic factors.

## METHODS

### Subjects

We reviewed the records of consecutive patients with iRBD

in whom treatment was initiated with clonazepam and/or melatonin from January 2015 to August 2018 at the Department of Neurology of the Seoul National University Hospital. Patients who fulfilled the following criteria were included: 1) having RBD but not previously treated with clonazepam or melatonin, 2) diagnosis of RBD confirmed by video-polysomnography (vPSG) according to the third edition of the International Classification of Sleep Disorders, 3) no defined neurodegenerative diseases such as parkinsonism and dementia, and 4) the treatment response followed up for at least 6 months. This study was approved by the Institutional Review Board of the Seoul National University Hospital (IRB No. 1507-100-689), and was performed in compliance with the Declaration of Helsinki and the Good Clinical Practice guidelines.

### Treatment response

We retrospectively reviewed the medical records of patients to identify the effects of clonazepam (Rivotril<sup>®</sup>, Roche, Basel, Switzerland, 0.5-mg tablets) and melatonin (Circadin<sup>®</sup>, Neurim Pharmaceuticals, Tel-Aviv, Israel, 2-mg prolonged-release tablets) in the symptomatic treatment of iRBD. The clinical evaluations of all iRBD patients included in this study were carried out by a single neurologist (K.Y.J.), as well as the treatment decisions. Clonazepam and melatonin were initially administered at dosages of 0.25–0.50 and 2 mg/day, respectively, at bedtime, and the doses were titrated according to how each patient responded during follow-up.

Treatment response was defined according to the presence or absence of any improvement in DEB or unpleasant dreams after treatment. Improvement of the RBD symptoms was primarily self-reported by patients, but also based on reports from bed partners or family members when this was feasible. Patients whose abnormal sleep behaviors and/or unpleasant dreams were completely or partially controlled were classified as the improvement group, whereas those who reported no improvement or worsening of DEB and unpleasant dreams after the medical therapy were classified as the no-response group. We also investigated the doses of clonazepam and melatonin prescribed initially and at follow-up.

### Investigations

We investigated demographic information such as age, sex, body mass index, and education level, and baseline characteristics of iRBD including disease duration, frequency of DEB, and history of sleep-related injury. A sleep-related injury was classified as a major injury when it required a medical intervention with or without hospitalization. We used the Korean version of the RBD Questionnaire–Hong Kong (RBDQ-KR) to measure the severity of RBD symptoms.<sup>18</sup> In

addition to the total RBDQ-KR score, we separately measured the subscores for factor 1 (dream related) and factor 2 (behavior related). We also used the Pittsburgh Sleep Quality Index and Epworth Sleepiness Scale (ESS) to assess sleep quality and excessive daytime sleepiness, respectively. Excessive daytime sleepiness was defined as an ESS score of >10.

Two depression scales were used to measure depressive symptoms: the Korean version of the Geriatric Depression Scale (GDS-K) and the Beck Depression Inventory-II (BDI-II).<sup>19</sup> Depression was defined as a GDS-K score of  $\geq 16$ , a BDI-II score of  $\geq 14$ , and/or current use of antidepressant medication.<sup>20</sup> We evaluated neurodegenerative markers of iRBD using the Scales for Outcomes in Parkinson's Disease for Autonomic Symptoms, Korean version of the Sniffin' sticks, Mini Mental State Examination (MMSE), and Unified Parkinson's Disease Rating Scale (UPDRS) part III.

### Video-polysomnography

We investigated vPSG data recorded at the time of an RBD diagnosis. All patients underwent single-night in-laboratory vPSG recording (Natus, Pleasanton, CA, USA). The recording system comprised six-channel EEG, two-channel electrooculography, EMG on the submentalis and tibialis anterior, and electrocardiography. Respiratory monitoring was conducted with a thermal airflow sensor, nasal pressure transducer, finger pulse oximeter, and thoracoabdominal piezoelectric belts. A body-position sensor and snore sensor were also employed. The time-synchronized video and audio recordings made during the overnight polysomnography were used to identify events related to REM-sleep behaviors. Sleep stages, periodic limb movements in sleep, and respiratory events including apnea, hypopnea, and respiratory effort-related arousal were scored in 30-s epochs according to the American Academy of Sleep Medicine (AASM) manual for the scoring of sleep and associated events.<sup>21</sup> REM sleep without atonia was also scored according to the AASM criteria for sustained muscle activity and excessive transient muscle activity during REM sleep.

### Statistical analysis

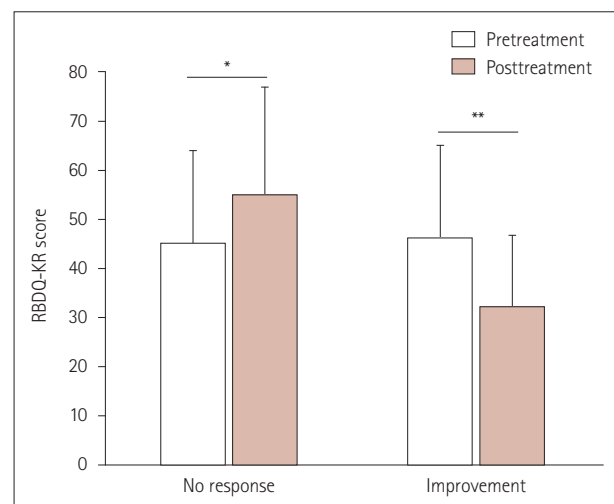
Data are presented as mean  $\pm$  standard deviation or number (percentage) values except where indicated otherwise. Statistical comparisons between the improvement and no-response groups were performed using Student's *t* test for continuous variables and Pearson's chi-square test or Fisher's exact test for categorical variables, as appropriate. Changes in the RBDQ-KR score after treatment were analyzed using repeated-measures analysis of variance, in which the within-subject variable was the treatment (before vs. after) and the between-subject variable was the group (no response vs. im-

provement). We also conducted a multiple logistic regression analysis to identify the factors that were independently associated with a treatment response in iRBD patients. In this model, the independent variable was "no response to medical treatment" while the predictor variables included factors for which the probability was  $p < 0.1$  in the univariate analyses. The multivariate model was also adjusted for potential confounding factors such as age, sex, symptom duration, and medication administered. The criterion for statistical significance was a two-tailed probability value of  $p < 0.05$ . All statistical analyses were carried out using SPSS software (version 18, SPSS Inc., Chicago, IL, USA).

## RESULTS

We identified 144 drug-naive patients with vPSG-confirmed RBD, of which 21 were excluded due to coexisting neurodegenerative diseases at the time of diagnosis of RBD ( $n=6$ ), a treatment or follow-up duration of less than 6 months ( $n=7$ ), or insufficient data ( $n=8$ ). We therefore finally analyzed 123 patients with iRBD who fulfilled all of the inclusion criteria [76 (61.8%) males; age,  $66.0 \pm 7.7$  years; and symptom duration,  $4.1 \pm 4.0$  years]. The RBDQ-KR score at diagnosis was  $49.0 \pm 19.1$ . Fifty-six (45.5%) patients were found to have depression.

For symptomatic treatment, 40 (32.5%) patients were treated with clonazepam, 56 (45.5%) with melatonin, and 27 (22.0%) with a combination of clonazepam and melatonin. Clonazepam and melatonin were initially administered at doses of  $0.4 \pm 0.2$  and  $2.0 \pm 0.0$  mg, respectively, while the cor-



**Fig. 1.** Pretreatment and posttreatment scores on the RBDQ-KR in patients with idiopathic REM sleep behavior disorder. These scores were available for 68 patients at both pretreatment and posttreatment. Error bars indicate standard deviations. \* $p < 0.05$ , \*\* $p < 0.001$ . RBDQ-KR: Korean version of the REM sleep Behavior Disorder Questionnaire-Hong Kong.

responding doses after a follow-up of  $17.7 \pm 6.6$  months were  $0.5 \pm 0.3$  and  $2.3 \pm 0.7$  mg. Ninety-six (78.0%) patients showed improvement in RBD symptoms after treatment (the improvement group), whereas 27 (22.0%) patients did not respond to clonazepam and/or melatonin (the no-response group). Changes in the RBDQ-KR score after treatment differed significantly between the two groups (interaction between treatment and group:  $F_{1,66}=30.5$ ,  $p<0.001$ ). The post-treatment RBDQ-KR score increased by  $9.9 \pm 8.3$  in the no-response group ( $p=0.014$ ) and decreased by  $14.1 \pm 15.0$  in the improvement group ( $p<0.001$ ) (Fig. 1). Bed partners or family members reported a treatment response in 58.1% of patients, while the remaining (41.9%) patients self-reported

symptom changes after treatment.

When comparing the clinical characteristics of iRBD patients according to the treatment response, we found no significant intergroup differences in age, sex, symptom duration, DEB frequency, history of sleep-related injuries, RBDQ-KR score, UPDRS part III score, MMSE score, dose of medications, and follow-up duration (Table 1). However, depression was significantly more common in the no-response group than in the improvement group (66.7% vs. 39.6%,  $p=0.013$ ). Six (10.7%) of 56 patients with comorbid depression were taking antidepressants: 5 in the no-response group and 1 in the improvement group. The frequency of excessive daytime sleepiness was 22.2% in the no-response group, which ap-

**Table 1.** Clinical characteristics according to the presence or absence of a treatment response

Variable	No response (n=27)	Improvement (n=96)	p
Age, years	65.7±8.5	66.1±7.5	0.849
Sex, male	15 (55.6)	61 (63.5)	0.451
Symptom duration, years	4.4±6.2	4.1±3.2	0.753
BMI, kg/m <sup>2</sup>	24.8±3.4	24.2±3.0	0.331
Education			0.962
Elementary school or lower	5 (18.5)	18 (19.3)	
Middle school	7 (25.9)	18 (19.4)	
High school	6 (22.2)	24 (25.8)	
College or higher	9 (33.3)	33 (35.5)	
DEB frequency, per week	4.4±2.3	3.8±2.5	0.306
Sleep-related injury			0.433
Minor	6 (22.2)	34 (35.4)	
Major	1 (3.7)	3 (3.1)	
RBDQ-KR score	49.3±17.0	49.0±19.6	0.941
Factor 1 (dream related)	15.7±7.2	15.2±7.1	0.769
Factor 2 (behavior related)	33.6±12.7	33.8±15.0	0.963
UPDRS part III score	1.3±2.7	1.2±2.8	0.960
MMSE score	27.1±3.1	27.1±2.4	0.930
Medication			0.496
Clonazepam	7 (25.9)	33 (34.4)	
Melatonin	12 (44.4)	44 (45.8)	
Both	8 (29.6)	19 (19.8)	
Dose at follow-up, mg			
Clonazepam	0.5±0.4	0.4±0.2	0.496
Melatonin	2.5±0.9	2.2±0.6	0.140
Follow-up, months	15.1±6.3	18.4±6.5	0.106
Excessive daytime sleepiness	6 (22.2)	7 (7.5)	0.071
Depression	18 (66.7)	38 (39.6)	0.013
PSQI score	7.9±4.5	6.8±3.9	0.225
SCOPA-AUT score	14.1±7.4	11.9±6.8	0.170
KVSS score	18.0±5.6	18.5±5.8	0.756

Data are mean±standard deviation or n (%) values.

BMI: body mass index, DEB: dream-enacting behavior, KVSS: Korean version of the Sniffin' stick, MMSE: Mini Mental State Examination, PSQI: Pittsburgh Sleep Quality Index, RBDQ-KR: Korean version of the REM sleep Behavior Disorder Questionnaire-Hong Kong, SCOPA-AUT: Scales for Outcomes in Parkinson's Disease for Autonomic Symptoms, UPDRS: Unified Parkinson's Disease Rating Scale.

peared to be higher than that of 7.5% in the improvement group, but the difference was not significant ( $p=0.071$ ). The scores for olfactory function and autonomic symptoms did not differ significantly between the two groups.

Comparisons of vPSG data revealed that patients with a negative response had shorter sleep latency than those with improvement ( $10.4\pm 9.0$  vs.  $17.9\pm 23.5$  min,  $p=0.012$ ). However, there were no other significant intergroup findings, including in the total sleep time, sleep efficiency, proportion of sleep stages, REM sleep latency, periodic limb movement index, apnea-hypopnea index (AHI), and arousal index (Table 2). The severity of obstructive sleep apnea, which was classified into mild (AHI=5–15 events/h), moderate (AHI=15–30 events/h), and severe (AHI >30 events/h), did not differ between the two groups ( $p=0.592$ ). When we further analyzed the AHI during REM sleep and non-REM (NREM) sleep separately, we found no significant difference between the no-response ( $n=23$ ) and improvement ( $n=69$ ) groups (AHI during REM sleep,  $8.8\pm 10.5$  vs.  $10.3\pm 13.4$ ,  $p=0.628$ ; AHI during NREM sleep,  $8.5\pm 8.0$  vs.  $10.2\pm 10.0$ ,  $p=0.456$ ).

We subsequently performed a multiple logistic regression analysis to identify factors independently associated with a response to symptomatic treatment in iRBD. After adjusting for potential confounders, depression was significantly associated with a negative response to treatment [odds ratio (OR)=

$3.76$ , 95% confidence interval (CI)= $1.15-12.32$ ,  $p=0.029$ ] (Table 3). None of the other analyzed factors showed an independent association with a treatment response. Additionally, we excluded from the analysis those patients who were taking antidepressants in order to remove their potential confounding effect on REM sleep without atonia and DEB. This resulted in the association between depression and negative treatment response no longer being significant (OR=2.71, 95%

**Table 3.** Results of multiple logistic regression analysis of a negative treatment response in iRBD patients

Variable	OR	95% CI	<i>p</i>
Depression	3.76	1.15–12.32	0.029
Age, years	0.97	0.90–1.04	0.336
Sex, male	0.68	0.21–2.17	0.509
Symptom duration, years	1.02	0.91–1.14	0.757
RBDQ-KR score	0.98	0.95–1.01	0.223
Excessive daytime sleepiness	5.08	0.99–26.04	0.051
Sleep latency, min	0.97	0.93–1.02	0.216
AHI, events/h	0.99	0.93–1.07	0.875
Medication (vs. melatonin only)			0.489
Clonazepam only	1.21	0.31–4.82	0.782
Clonazepam and melatonin	2.54	0.54–11.91	0.236

AHI: apnea-hypopnea index, CI: confidence interval, iRBD: idiopathic REM sleep behavior disorder, OR: odds ratio, RBDQ-KR: Korean version of the REM sleep Behavior Disorder Questionnaire–Hong Kong.

**Table 2.** Comparison of video-polysomnography findings at the diagnosis of iRBD

Variable	No response ( $n=27$ )	Improvement ( $n=96$ )	<i>p</i>
Total sleep time, min	$371.4\pm 70.7$	$363.5\pm 70.2$	0.608
Sleep efficiency, %	$79.1\pm 15.2$	$76.5\pm 13.7$	0.397
WASO, min	$93.1\pm 75.8$	$96.5\pm 63.3$	0.814
Sleep latency, min	$10.4\pm 9.0$	$17.9\pm 23.5$	0.012
REM sleep latency, min	$139.2\pm 99.3$	$112.7\pm 70.4$	0.124
Sleep stage, %			
N1	$21.2\pm 14.9$	$20.9\pm 10.3$	0.913
N2	$47.3\pm 11.8$	$48.5\pm 12.0$	0.634
N3	$9.2\pm 8.0$	$8.5\pm 10.0$	0.758
R	$19.9\pm 6.7$	$20.8\pm 7.4$	0.572
AHI, events/h	$7.2\pm 6.3$	$9.0\pm 10.4$	0.398
AHI severity, events/h			0.592
<5	13 (48.1)	44 (45.8)	
5–15	10 (37.0)	35 (36.5)	
15–30	4 (14.8)	11 (11.5)	
>30	0 (0)	6 (6.3)	
RDI, events/h	$9.6\pm 7.5$	$10.8\pm 11.6$	0.623
PLM index, events/h	$22.0\pm 27.6$	$17.3\pm 25.8$	0.415
PLM arousal index, events/h	$6.5\pm 15.7$	$1.9\pm 4.5$	0.173
Total arousal index, events/h	$12.9\pm 12.2$	$9.9\pm 10.5$	0.210

Data are mean±standard deviation or *n* (%) values.

AHI: apnea-hypopnea index, iRBD: idiopathic REM sleep behavior disorder, PLM: periodic limb movement, RDI: respiratory disturbance index, WASO: wakefulness after sleep onset.



CI=0.77–9.52,  $p=0.119$ ).

## DISCUSSION

In this study, 78% of the patients with iRBD reported subjective improvements in abnormal sleep behaviors and dream symptoms after treatment with clonazepam and/or melatonin during a mean follow-up period of 17.7 months. Overall, 45.5% of the patients with iRBD had depression. We found that after adjusting for potential confounding factors, iRBD patients with depression were 3.76-fold more likely to exhibit a negative response to treatment compared to those without depression. However, it is worth noting that polysomnographic characteristics—especially the severity of obstructive sleep apnea and periodic limb movement during sleep—did not significantly affect the treatment response.

To the best of our knowledge, this is the first study to show that comorbid depression has a negative effect on the response to treatment in patients with iRBD. In contrast to our results, a previous study found that less-optimal treatment outcomes were related to an early onset of iRBD and comorbid obstructive sleep apnea, but not to psychiatric illness.<sup>22</sup> These inconsistent results may arise from the present study applying less-stringent criteria for a treatment response (e.g., including partial improvement) and a higher rate of melatonin therapy. Additionally, despite the advantage of the prospective design of the previous study, the smaller sample size ( $n=39$ ) might have reduced the statistical power in detecting the influence of comorbid depression.

A possible explanation for the link between depression and poor treatment response in our study is that comorbid depression in iRBD, which is a potential predictor of phenocopy, reflects a more-advanced stage of neurodegeneration than iRBD without depression.<sup>23</sup> In agreement with this, iRBD patients with depression were previously found to have smaller gray-matter volumes in the caudate nucleus, calcarine cortex, and cuneus compared with iRBD patients without depression.<sup>24</sup> Moreover, depressed Parkinson's disease patients showed a significant loss of dopaminergic and noradrenergic innervation in the locus coeruleus and limbic system compared with non-depressed patients.<sup>25</sup> However, an international multicenter observational study found that depression does not significantly predict the subsequent development of neurodegenerative diseases in iRBD patients.<sup>26</sup> Therefore, further investigations are needed into whether prodromal depression is directly involved in the neurodegenerative pathophysiology of iRBD or manifests as an epiphenomenon.

Depression per se contributes to REM-sleep dysregulation,<sup>27</sup> which is another possible explanation for our obser-

vations. Sleep-related changes in patients with depression include decreases in the total sleep time, sleep efficiency, and slow-wave sleep, as well as disinhibition of REM sleep manifesting as a decreased REM latency and increases in the proportion of REM sleep and the REM density.<sup>28</sup> Moreover, antidepressant drugs mostly exert REM-sleep-suppressing effects and normalize the REM-sleep dysregulation in depressed patients.<sup>29</sup> The altered REM sleep in depression is partially caused by the overactivation of REM-on cholinergic neurons. This is supported by the finding that cholinergic stimulation leads to more pronounced REM-sleep disinhibition in depressed patients than in healthy controls.<sup>30</sup> The results of the aforementioned study are consistent with a previous positron emission tomography study showing increased glucose uptake in the brainstem reticular formation during REM sleep in depressed patients.<sup>31</sup> Cholinergic neurons in the pedunculopontine nucleus, laterodorsal tegmental nucleus, and basal forebrain are responsible for cortical activation during REM sleep.<sup>32</sup> Moreover, we previously found that iRBD patients showed increased activation of the motor cortex during phasic REM sleep compared to controls.<sup>33</sup> It is therefore possible that cholinergic hypersensitivity or overdrive during REM sleep in iRBD patients with comorbid depression contributes to increased cortical activation, abnormal sleep behaviors, and unpleasant dreams, which consequently increases their resistance to symptomatic treatment. However, polysomnographic parameters of REM-sleep disinhibition, such as the REM sleep latency and the proportion of REM sleep, did not differ with the treatment response in the present study. These findings do not support the hypothesis that poor treatment response in depressed iRBD patients is mediated by REM-sleep dysregulation. Furthermore, the association between depression and a treatment response failed to reach significance after excluding patients who were taking antidepressant medications. Accordingly, we cannot rule out the possibility that the use of antidepressants affected the DEB symptoms and REM tonic and phasic EMG activities, and consequently biased the association between depression and a treatment response. McCarter et al.<sup>34</sup> demonstrated that psychiatric patients taking antidepressants exhibited elevated REM sleep without atonia, whereas the level of REM sleep without atonia did not differ significantly between psychiatric patients not taking antidepressants and controls. This finding suggests that antidepressant therapy rather than depression itself induces REM sleep without atonia. Further prospective research involving sufficiently large numbers of patients is needed to determine whether comorbid depression or antidepressant therapy affects the treatment response in patients with iRBD.

REM sleep has been implicated in emotional memory pro-

cessing, and it depotentiates neural and behavioral response to emotional experiences during the daytime.<sup>35</sup> Disinhibited REM sleep in depressed patients may disrupt sleep-dependent emotional regulation and disproportionately amplify the strength of negative memories.<sup>36</sup> This is consistent with depressed patients showing increased activation of the hippocampus, amygdala, and anterior cingulate cortex—which are associated with emotional response and memory—during REM sleep, compared to controls.<sup>31</sup> We can therefore speculate that comorbid depression in patients with iRBD can contribute to emotional dysregulation during REM sleep and dreaming that has more affectively intense and negative content that is then enacted during RBD episodes. It is also possible that depression biased self-evaluation in a negative way and consequently led to a spurious association between comorbid depression and a poor treatment response. This concern can be addressed in future studies by using objective measures of RBD symptoms.

The doses of clonazepam ( $0.5 \pm 0.3$  mg) and melatonin ( $2.3 \pm 0.7$  mg) used in this study were lower than those used in previous studies. Fernández-Arcos et al.<sup>2</sup> reported that clonazepam therapy at a mean dose of 1.0 mg resulted in complete and partial responses in 55.1% and 31.1% of patients with iRBD, respectively. Similarly, another study found that a mean clonazepam dose of 0.98 mg completely eliminated sleep-related injurious behaviors in 66.7% of patients.<sup>22</sup> However, low-dose clonazepam at 0.5 mg per night also resulted in a response rate of 76.5% in Parkinson's disease with probable RBD, although with no significant difference between the clonazepam and placebo groups.<sup>37</sup> The most commonly used dose for melatonin therapy in clinical trials involving RBD is 3 mg, although higher doses up to 12 mg have been found in retrospective studies.<sup>38</sup> Therefore, although the doses of clonazepam and melatonin during the follow-up period were slightly higher than the initial doses in our study, further increases in the dose could have led to additional improvements in some patients. However, the overall response rate of 78% indicates that the medication doses used in this study were substantially effective over the 1.5-year follow-up period. It is also worth mentioning that clonazepam therapy in elderly patients can cause dose-dependent side effects such as daytime somnolence, increased risk of falls, and aggravation of obstructive sleep apnea,<sup>6</sup> although these side effects are uncommon at doses less than 1.0 mg.<sup>39</sup> Moreover, melatonin therapy is excluded from health insurance coverage in Korea, which hinders the use of higher doses of melatonin in clinical practice.

This study was subject to several limitations. Its retrospective design meant that the data sources used to assess the treatment response may have been less accurate than those in a prospective study. Furthermore, the treatment response

was evaluated subjectively without using quantitative measures. Another important limitation is that the assessment of symptom changes by bed partners was unavailable in approximately 40% of the patients. Since about half of patients with iRBD are unaware of their abnormal behaviors during sleep,<sup>2</sup> changes in DEB might not be properly evaluated in the iRBD patients who are not reported on by bed partners. It is likely that the treatment response in those patients was mainly determined by improvement in unpleasant dreams. Moreover, we did not conduct a quantitative analysis of REM sleep without atonia, which might have been associated with the response to symptomatic treatment in patients with iRBD. In addition, the small sample size and recruiting patients from a single center restrict the generalizability of our results. Finally, causal relationships cannot be confirmed in the retrospective case-control study. These limitations mean that the results obtained in this study should be interpreted with caution.

In conclusion, our results demonstrate that comorbid depression is significantly associated with poor responses to clonazepam and/or melatonin in patients with iRBD. However, it cannot be concluded from this study whether the effect of comorbid depression on the negative treatment response is attributable to depression itself or to the antidepressant therapy. Further research is needed to determine the clinical implications of comorbid depression in the pathophysiology of dream enactment and unpleasant dreams in iRBD.

#### Author Contributions

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#### Conflicts of Interest

Carlos H. Schenck is a consultant for Axovant Sciences, Inc. The other authors have no potential conflicts of interest to disclose.

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