REM Sleep Behavior Disorder in Psychiatric Populations

To the Editor: Rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia characterized by a loss of REM-related muscle atonia and abnormal motor activities during REM sleep with consequent sleep-related injuries.[1,2] It has been increasingly reported among psychiatric populations and has a potential association with use of psychotropics, particularly selective serotonin reuptake inhibitor (SSRI), tricyclic, and serotonin and noradrenergic reuptake inhibitor (SNRI) antidepressants.[3–8]

A previous case report[5] found that cessation of SSRI treatment did not result in complete resolution of clinical RBD symptoms and polysomnographic (PSG) abnormalities. Our recent clinical epidemiologic study[8] found that 3.8% of psychiatric outpatients might have RBD features over the past year. The prevalence is 10 times more common than that of the typical RBD in the elderly general population.[9] In addition, the RBD features could result in sleep-related injuries and violence, with potential medicolegal repercussions.[8,10]

In the current study, we conducted a comprehensive evaluation of clinical and PSG features as well as follow-up response to an open intervention of antidepressant regimen modification.

Method. Fifteen depressed subjects with concurrent antidepressant treatment and features suggestive of RBD were included in this case series, which spans from December 2006 to March 2009. They were interviewed by experienced psychiatrists and neurologists for a thorough clinical evaluation, which included a semistructured psychiatric interview and physical examination with Hoehn and Yahr staging for parkinsonism.[11] They also underwent video-polysomnographic assessments at baseline and follow-up.

Modification of their current antidepressant regimen was suggested to all subjects. Bupropion was offered as the treatment of choice in this open intervention, as it has rarely been associated

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Table 1. Clinical and Polysomnographic Features of RBD Patients Who Modified (group A) and Did Not Modify (group B) Their Antidepressant Regimens

	Group A (n = 6)			Group B (n = 9)		
	Baseline	Follow-Up		Baseline	Follow-Up	
Female gender, n (%)	5 (83.3)			5 (55.5)		
Age, mean ± SD, y	34.0 ± 9.4			43.7 ± 7.9*		
Nightmares, n (%)						
> 3 nights/wk	2 (33.3)	0		4 (44.4)	6 (66.7)*	
> 1 night/wk	5 (83.3)	2 (33.3)		8 (88.9)	7 (77.8)	
Dream enactment, n (%)	6 (100.0)	3 (50.0)		9 (100.0)	9 (100.0)*	
Sleep-related injuries, n (%)	4 (66.7)	0		6 (66.7)	3 (33.3)	
Benzodiazepine use						
n (%)	4 (66.7)	1 (16.7)		7 (77.8)	6 (66.7)	
Equivalent daily dosage, mean ± SD	16.25 ± 16.01	40.0		17.86 ± 10.75	12.5 ± 6.12	
Clonazepam use						
n (%)	3 (50.0)	0		4 (44.4)	4 (44.4)	
Daily dosage, mean ± SD	0.42 ± 0.14	0		0.56 ± 0.47	0.75 ± 0.29	
Hoehn and Yahr[10] stage for parkinsonism (n = 12)	0			0		
	Baseline	Follow-Up	Change From Baseline	Baseline	Follow-Up	Change From Baseline
BDI score, mean ± SD[a]	12.3 ± 5.4	10.3 ± 6.1	−2.0 ± 4.1	20.8 ± 11.0	18.9 ± 11.6	−2.1 ± 9.9
REMREEA score, mean ± SD[a]	4.9 ± 4.1	6.7 ± 3.9	1.7 ± 5.2	10.8 ± 5.6*[b]	3.9 ± 2.8[b]	−7.0 ± 6.5[b]
REM density, mean ± SD[a]	32.7 ± 3.2	25.2 ± 12.4	−7.5 ± 12.1	41.4 ± 5.3*	33.5 ± 11.3	−7.9 ± 12.6[b]

[a]Mann-Whitney *U* test; other categorical data by Fisher exact test.
[b]n = 5.
*$P < .05$ vs group A at the same timepoint.
Abbreviations: BDI = Beck Depression Inventory, RBD = rapid eye movement sleep behavior disorder, REM = rapid eye movement, REMREEA = REM-related electromyogram activities.

with RBD in previous reports. The subjects' prescription history of benzodiazepines was also recorded, as benzodiazepines, especially clonazepam, are a common treatment option for RBD.

Electromyogram (EMG) activities during REM sleep were determined by a quantitative criterion of REM-related EMG activities (REMREEA) on chin muscles. Details of this quantitative scoring method have been described elsewhere.[2] In brief, REMREEA is the summation of the percentage of both tonic and phasic chin EMG activities during REM sleep. EMG activities associated with respiratory events, periodic leg movements, spontaneous arousal, and signal artifacts were excluded from the analysis. The scorer of the REMREEA muscle activities was blind to the sleep diagnoses. The study was approved by the institutional ethics committee, and informed consent was obtained from all study subjects.

Results. At baseline, the majority of subjects (n = 12) were taking an SSRI, and 3 were taking an SNRI. The dosages of antidepressants were all within therapeutic range. None of the subjects had any clinical neurologic disorder or sign of parkinsonism. Six of the subjects (group A) agreed to alter their treatment, including switching to bupropion (n = 3) and discontinuing antidepressant use (n = 3) (in view of clinical remission). The remaining 9 subjects (group B) opted to keep their usual treatments, and only 5 completed the follow-up PSG. The mean duration of the follow-up period was 13 months (range, 9–19 months), with similar duration between the 2 groups.

For patients who continued their usual antidepressant treatments, there was no significant difference in the mean equivalent daily dosage of antidepressants between baseline and follow-up. Eleven patients were receiving benzodiazepine treatment at baseline (group A, n = 4, mean equivalent dosage of diazepam = 16.25 ± 16.01; group B, n = 7, mean equivalent dosage of diazepam = 17.86 ± 10.75). Among them, 7 subjects were prescribed clonazepam at a mean dosage of 0.5 mg/d (group A, n = 3; group B, n = 4). At follow-up, only 1 subject in group A continued to receive benzodiazepine treatment (same dosage as at baseline), while 6 subjects in group B continued to receive benzodiazepine treatment (including 4 subjects taking clonazepam). Their mean equivalent dosage of benzodiazepine did not differ from baseline.

At baseline, both groups had comparable clinical features of RBD with respect to frequency of nightmares, dream enactments, and sleep-related injuries (Table 1). However, group B subjects were older and had slightly more REMREEA. At follow-up, group A showed improvement in clinical symptoms of RBD, especially in frequency of nightmares and dream enactments (Table 1). They also had a nearly significant reduction in sleep-related injuries. However, their PSG still showed residual REMREEA.

This study provides further insights about RBD in psychiatric populations. First, the hypothesis of antidepressant treatment as the sole cause of RBD among psychiatric patients was not fully supported. Upon withdrawal or switch of antidepressants, the clinical symptoms improved, but the PSG features persisted. Although the study was limited by a small sample size and open intervention, the preliminary findings implied that, among vulnerable subjects, antidepressants might serve as precipitating agents for RBD symptoms instead of being the sole causative agent. A recent study of a series of patients with early-onset RBD reported a rather similar demographic background: female subjects with psychiatric morbidities and psychotropic usage.[12] In particular, the longitudinal course of early-onset RBD and its relationship with typical RBD, especially with respect to a neurodegenerative etiologic basis, are unclear.[8] In light of these distinct demographics of early onset and female predominance, and the potentially complex etiologic basis of the symptoms, we suggested that RBD in psychiatric populations would be better labeled as "atypical RBD" instead of "drug-induced RBD."

Second, our study suggested a possible synergistic mechanism of serotonergic antidepressants in precipitating RBD symptoms by modulation of the dream mechanism and REM sleep–related muscle atonia. Previous postulation of the mechanism focused on the effects of antidepressants on REM-related muscle atonia, including enhancement of EMG activities by SSRIs during REM sleep.[13]

However, both our study and a previous study[5] found that REM-related muscle atonia was not completely restored after withdrawal of the antidepressants. The authors of the other study proposed an inhibitory role of antidepressants on extrapyramidal dopaminergic neurons,[5] but our neurologic examination detected no clinical parkinsonism or other extrapyramidal side effects. Nonetheless, subtle dopaminergic transmission disturbance could not be excluded, and further neuroimaging study will be needed.[14]

As seen in the typical RBD cases, nightmares are a consistent and dominating feature that may act as an emotional drive for dream enactment.[1,15] Changes in dream content with more vivid and intense dreams and nightmares have been reported among subjects taking serotonergic antidepressants.[16–18] In our study, there was a parallel diminution of clinical RBD symptoms and severity of nightmares and dream enactments upon amendment of the antidepressant regimen. Thus, a distinct possibility remained that a serotonergic antidepressant could partially exert its effect by the modulation of dream mechanism. In addition, nightmares have been closely associated with mental states and psychiatric disorders (especially depression and posttraumatic stress disorder).[19,20] In this regard, further study will be needed to examine the etiologic role of nightmares in both typical and atypical RBD as well as their associations with mental states and antidepressants.

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