Serotonergic Antidepressants are Associated with REM Sleep Without Atonia

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Study Objectives: Rapid eye movement (REM) sleep behavior disorder (RBD) is generally observed in older men and in individuals with specific neurologic diseases. There are case reports of RBD in individuals taking serotonergic antidepressants. Our objective was to assess electromyogram (EMG) activity during REM sleep in individuals taking serotonergic antidepressants and in a matched control group not on such medication.
Design: Chart review of clinical and polysomnographic data.
Setting: Sleep laboratory affiliated with a general hospital.
Participants: 15 subjects taking a serotonergic antidepressant and 15 age-matched individuals not on such medication.
Measurements: Submental and anterior tibialis tonic and phasic EMG activity during REM sleep, REM latency, time in REM, apnea-hypopnea index, periodic leg movements of sleep index, and sleep-architecture measures.
Results: Tonic, but not phasic, submental EMG activity during REM sleep was significantly more common in the antidepressant-treated group than in the control group ($P < .02$). Tonic REM submental EMG activity correlated with REM latency ($r = .42$, $P = .02$) and inversely with REM time ($r = -.36$, $P = .05$). Subject age correlated with tonic REM submental EMG activity ($r = .58$, $P = .02$) in the antidepressant group There were also trends for more phasic activity in the anterior tibialis ($P = .09$) and submental ($P = .07$) EMG in REM sleep in the antidepressant group than in the control group.
Conclusions: Subjects taking serotonergic antidepressants had more EMG activity in the submental lead during REM sleep than did controls. This correlated with measures of REM suppression and age. Individuals taking such medications may be at increased risk of developing REM sleep behavior disorder, particularly with increasing age.
Key Words: REM sleep, antidepressants, serotonergic, REM sleep behavior disorder, EMG activity
Citation: Winkelman JW; James L. Serotonergic antidepressants are associated with REM sleep without atonia. *SLEEP* 2004;27(2):317-21.

INTRODUCTION

ATONIA OF SKELETAL MUSCLES IS ONE OF THE CARDINAL FEATURES OF RAPID EYE MOVEMENT (REM) SLEEP. Superimposed on this atonia is intermittent activity in both axial and limb muscles. REM sleep behavior disorder (RBD) is characterized by excessive motor activity during REM sleep with acting out of dreams.[1] The diagnosis of RBD is made by the appearance of elevated submental electromyogram (EMG) tone during REM and/or excessive phasic submental or anterior tibialis EMG activity, combined with polysomnographic documentation or a history of frank movements during REM sleep.[2] RBD is more common in elderly men, and at least half of those followed for 10 years develop Parkinson disease.[3]

Muscle-tone abnormalities in REM sleep may consist along a spectrum, with maintenance of full atonia at one end and full RBD at the other end. REM sleep without atonia has been described as an intermediate condition, in which REM sleep atonia is reduced on polysomnography, in the absence of reports of abnormal behaviors by the patient or bed partner. This polysomnographic finding has also been called "subclinical" RBD. Eisensehr's recent report[4] demonstrating that those patients with subclinical RBD have an intermediate reduction of striatal dopamine transporters, roughly halfway between normal individuals and those with RBD, establishes the potential importance of this disorder.

Antidepressants have substantial effects on REM sleep. Many studies show that they prolong REM sleep latency and suppress REM sleep time.[5] They are also associated with reports of "vivid" dreams.[6] In addition, case reports dating back 30 years show that antidepressants can induce RBD[7] or reduce REM sleep atonia.[8] In fact, medications with a wide variety of mechanisms of action have been implicated in producing loss of REM sleep atonia, including serotonergic reuptake blockers such as fluoxetine,[9] monoamine oxidase inhibitors,[10] β-adrenergic receptor blockers,[11] the noradrenergic and 5-HT_{1A}-mediated serotonergic enhancer mirtazapine,[12] and the tricyclic antidepressants.[13] However, no study has systematically assessed EMG tone during REM sleep in individuals chronically taking antidepressants. Given the number of individuals taking these medications, this issue is potentially of substantial public health importance.

The objective of this study was to compare tonic and phasic EMG during REM sleep in individuals without a complaint of abnormal behavior during sleep who were taking serotonergic antidepressants with the REM characteristics of matched controls not taking such medications. We hypothesize that serotonergic antidepressants will increase tonic and phasic submentalis and anterior tibialis EMG activity during REM sleep compared to the control population not taking such medications.

METHODS

Subjects were recruited from the polysomnography database of Sleep Health Centers, Newton Center, Mass. All sleep studies between June 2001 and August 2003 were reviewed and excluded if any of the following features were present: apnea-hypopnea index > 15 per hour; REM-related apnea-hypopnea index > 10; continuous positive airway pressure use during the sleep study; complaint of abnormal behavior during sleep or abnormal behavior on polysomnogram; duration of REM sleep < 20 minutes; active neurologic disease (other than migraine); or benzodiazepine, antipsychotic, or anticonvulsant use.

All subjects who met these criteria and were taking a serotonergic antidepressant were included as the antidepressant group (n = 15). Five subjects were taking fluoxetine (20-50 mg per day), 3 were taking paroxetine (15-40 mg per day), 3 were taking citalopram (20-40 mg per day), 3 were taking sertraline (100-225 mg per day), and 1 was taking venlafaxine (400 mg per day). Two subjects in the antidepressant group were taking bupropion (200 mg) in the morning in addition to their sero-

Disclosure Statement
No significant financial interest/other relationship to disclose.

Submitted for publication October 2003
Accepted for publication December 2003
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tonergic antidepressant. Duration of antidepressant treatment was unknown, though subjects had been taking such medications for at least 2 weeks (based upon questionnaire data). Four of the 15 subjects in the antidepressant group reported a history of depression only, and 4 described a history of an anxiety disorder only; 7 described a history of both an anxiety and a depressive disorder. Fluoxetine equivalents were calculated for antidepressant doses of all subjects by the following equation[14]: fluoxetine = 5; sertraline = 1.2; paroxetine = 5; citalopram = 3.33; venlafaxine = 1.

An age- and sex-matched sample fulfilling the inclusion and exclusion criteria and not taking an antidepressant or any other centrally acting agent was identified as the control group. No subjects in the control group reported a history of either depressive or anxiety disorders. Fifty-three percent (8/15) of subjects in the control group and 40% (6/15) in the serotonergic antidepressant group were women. All subjects were referred to rule-out obstructive sleep apnea. Data from an extensive sleep, psychiatric, and medical history questionnaire were entered into a database for all subjects.

All polysomnograms were performed in the same laboratory using Alice 3 and 4 digitizing software (Respironics, Murrysville, Penn) according to the following standard methods: left and right central and occipital electroencephalogram (EEG) leads referenced to the opposite ear; bilateral electrooculogram, submental EMG, bilateral anterior tibialis EMG, and cardiorespiratory recordings consisting of nasal pressure monitoring, nasal-oral thermistors, abdominal and chest effort, pulse oximetry from the digit, and electrocardiogram.

Sleep staging was performed according to standard criteria,[15] though scoring of REM sleep was modified according to the method of Lapierre and Montplaisir.[16] In this modification, a REM epoch is terminated for an EEG arousal but not as a result of increased EMG submental tone. Each REM period for each subject was assessed for both tonic and phasic EMG activity. REM epochs in which an EEG arousal (scored according to standard guidelines), snore artifact in the submental EMG, periodic leg movement (in a group of 4, with a stable intermovement interval), or a hypopnea was present were eliminated from all further analyses. Tonic EMG activity for each 30-second REM epoch was scored as present (or put another way, was scored as absence of atonia) if greater than 50% of the epoch had submental EMG activity greater than 4 times the lowest level in that REM period. The percentage of epochs without atonia was computed for each REM period and averaged for each subject.

Phasic EMG was scored in 2-second bins separately for the submental and bilateral anterior tibialis leads according to the method of Lapierre and Montplaisir.[16] Each 2-second bin containing EMG activity lasting 0.1 to 5.0 seconds, which exceed 4 times the lowest EMG activity in that epoch, was counted as a bin with phasic activity. The percentage of bins with phasic activity in the anterior tibialis and submental leads was computed for each REM period and then averaged for each subject. Phasic activity was also scored by the method of Eisensehr,[4] in which "long" EMG phasic activity was quantified. EMG bursts were defined as "long" when they exceeded 0.5 seconds. A 10-second epoch of REM was considered to have "long" EMG activity when the total of such long bursts exceeded 1.0 seconds (eg, either at least 2 bursts lasting 0.5 seconds or 1 burst exceeding 1.0 seconds). The percentage of such 10-second epochs was determined for each subject for each REM period and then averaged for each subject.

Statistical analyses were performed with the Student *t* test in normally distributed data. The rank-sum test was used for variables that were not normally distributed.

RESULTS

The 2 study groups did not differ in age, sex, body mass index, or complaint that initiated the sleep study (see Table 1). On polysomnography, subjects taking antidepressants had less REM time, longer REM latency, greater sleep latency, a higher percentage of stage 2 sleep, and a higher periodic limb movements of sleep index (see Table 1). No statistically significant differences in apnea-hypopnea index (total or REM-related) or arousal index were noted between groups.

Subjects taking antidepressants had significantly more 30-second REM epochs without submental atonia (with submental tone) than control subjects ($P = 0.02$) (Table 2). There were significant correlations between the submental EMG tone during REM and the degree of REM suppression in the total sample, such that REM latency was positively correlated with submental EMG tone ($r = .42$, $P = .02$) (see Figure 1), and REM time was negatively correlated with submental EMG tone ($r = -.36$, $P = .05$). There was a significant correlation between age and submental EMG tone during REM in the antidepressant group ($r = .58$, $P = .02$) (see Figure 2). This association was not significant in the control group. There was no correlation between submental EMG tone during REM and antidepressant dose (in fluoxetine equivalents).

There were trends for the subjects taking antidepressants to have more 2-second epochs in REM with phasic EMG activity in both the submental ($P = .07$) and anterior tibialis ($P = .09$) leads than the control group (see Table 2). There was a negative correlation between such phasic activity in the anterior tibialis and REM time ($r = -0.42$, $P = .02$). There was no correlation between either phasic submental or anterior tibialis EMG activity in REM and medication dose (in fluoxetine equivalents).

Table 1—Demographic and Polysomnographic Features of Antidepressant and Control Groups

Demographic or Polysomnographic Feature	Control	Serotonergic Antidepressant	*P* value
No.	15	15	
Age (range), y	42.0 ± 14.1 (18-63)	45.5 ± 10.8 (26-60)	
Men, no. (%)	8 (53)	6 (40)	
BMI, kg/m^2	25.0 ± 3.4	27.1 ± 5.5	
Arousal index, arousals/h	15.3 ± 4.8	18.9 ± 9.7	
Sleep efficiency, %	84.9 ± 11.9	81.7 ± 9.3	
Sleep latency, min	13.0 ± 12.7	24.7 ± 14.4	.03
REM latency, min	68.8 ± 20.1	185.7 ± 73.7	< .001
PLM index, PLM/h	3.6 ± 6.3	18.8 ± 19.8	.08
Sleep stage, %			
1	8.3 ± 5.9	9.05 ± 5.4	
2	62.6 ± 6.8	69.6 ± 9.5	.03
3	6.1 ± 4.0	5.3 ± 3.7	
4	7.2 ± 7.8	4.9 ± 7.4	
REM	21.0 ± 4.8	14.4 ± 5.3	.001
REM time, min	79.1 ± 26.5	49.4 ± 21.3	.002
AHI, events/h	4.0 ± 2.5	4.7 ± 2.7	
AHI during REM, events/h	5.6 ± 4.4	7.1 ± 5.4	

Data are presented as mean ± SD, unless otherwise noted. All *P* values are not significant unless otherwise noted.
BMI refers to body mass index; REM, rapid eye movement; PLM, periodic leg movement, AHI, apnea-hypopnea index.

Table 2—Submental and Anterior-Tibialis Characteristics in Antidepressant and Control Groups

Epochs, %	Control (n = 15)	Serotonergic Antidepressant (n = 15)	*P* value
30-second with submental EMG tone*	2.36 ± 3.88	9.54 ± 9.06	.02
2-second with phasic EMG†			
Submental	5.63 ± 5.31	10.74 ± 9.16	.07
Anterior tibialis	9.72 ± 8.64	16.82 ± 14.69	.09
10-second with long EMG‡			
Submental	6.71 ± 6.06	13.39 ± 11.62	.03
Anterior tibialis	2.98 ± 2.63	8.94 ± 12.59	.06

Data are presented as mean ± SD, unless otherwise noted.
*Electromyogram (EMG) tone considered present if more than 50% of the epoch had submental EMG activity greater than 4 times the lowest level in that rapid eye movement (REM) period.
†Phasic EMG considered present if EMG activity lasted 0.1 to 5.0 seconds and exceeded 4 times the lowest EMG activity in that epoch.
‡EMG considered present if the total of "long" bursts (> 0.5 seconds) exceeded 1.0 seconds.

The antidepressant group had significantly more 10-second REM epochs with "long" phasic activity than the control group in both the submental (P = .03) and anterior tibialis (P = .06) leads. REM latency correlated with submental "long" EMG activity for the entire sample (r = .52, P = .003).

The REM-period number (ie, 1 vs 2 vs 3) did not influence the degree of EMG tone during REM in the submental lead or the extent of phasic activity in the anterior tibialis or submental recordings.

DISCUSSION

Our results demonstrate that serotonergic antidepressants are associated with a statistically significant and persistent reduction in REM-sleep atonia, even in individuals without overt clinical features of RBD. We have also demonstrated that the degree of REM sleep without atonia is correlated with other evidence of antidepressant effects on REM sleep (suppression of REM time and prolongation of REM latency). Previous case reports have described RBD in individuals taking antidepressants for depression,[17-18] narcolepsy,[19] or Parkinson disease.[12] Two previous reports describe absence of atonia in REM sleep with the use of the tricyclic antidepressant clomipramine.[20-21] Guilleminault[20] reported that EMG atonia was "generally absent" in his narcoleptic subjects taking clomipramine. Niyama[21] identified this sleep stage as 1-REM in his normal control subjects given single doses of 25 to 50 mg of clomipramine.

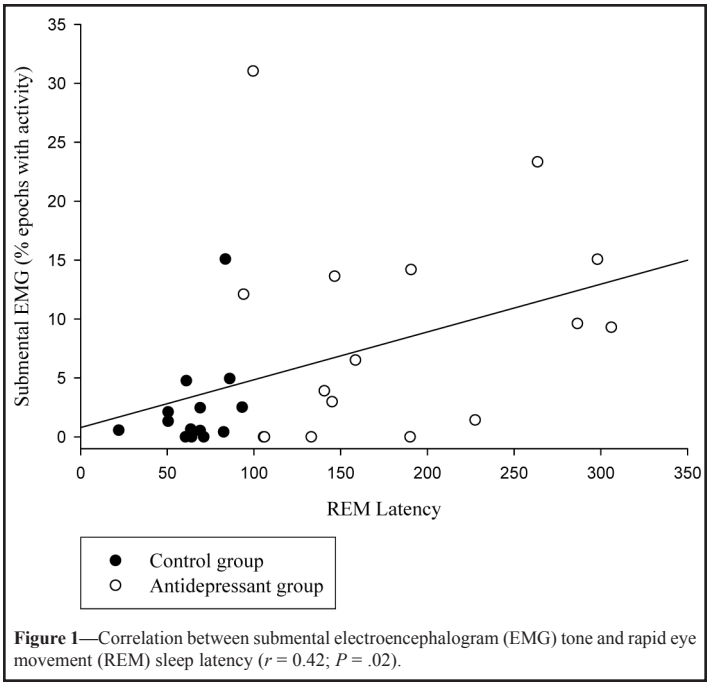

Figure 1—Correlation between submental electroencephalogram (EMG) tone and rapid eye movement (REM) sleep latency (r = 0.42; P = .02).

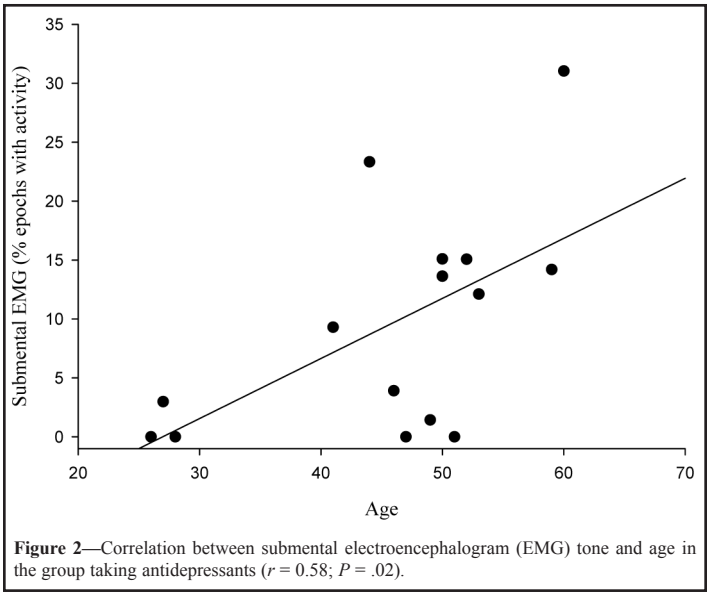

Figure 2—Correlation between submental electroencephalogram (EMG) tone and age in the group taking antidepressants (r = 0.58; P = .02).

This is a retrospective study, and future studies of EMG tone after medication treatments should address issues that we were unable to, given this design. For instance, data on length of antidepressant treatment and details regarding dream emotional quality and motor activity would be of great interest. Further, increased numbers of subjects, preferably in an age range that might be more vulnerable to REM sleep without atonia (over 60 years), would also increase the power of such studies. In addition, prospective studies of EMG tone before and after chronic administration of a single serotonergic antidepressant are recommended to confirm our findings and to better establish the precise nature of this relationship.

A number of limitations of our data exist, which should be considered. We did not evaluate the sleep of individuals prior to medication administration and, thus, cannot definitely conclude that the serotonergic antidepressants were responsible for the elevation in EMG activity during REM sleep. Three of the subjects in the antidepressant group were taking medication with effects beyond the serotonergic system: 2 were taking bupropion, which enhances dopaminergic neurotransmission, and 1 was taking venlafaxine, which, in addition to its serotonergic properties, produces noradrenergic reuptake blockade. It is possible that some of our results may be a consequence of these other biologic effects. It is also possible that depression or anxiety disorders themselves produced these findings. It should be noted, however, that these findings have been demonstrated acutely in normal volunteers.[21] Similarly, these findings were observed in our subjects treated for both depression and anxiety disorders. Our subjects were not a random sample of individuals taking serotonergic antidepressants but were recruited from individuals referred for sleep study. To minimize this referral bias, we excluded individuals with a description of behavioral abnormalities during sleep. All of our subjects were referred to rule-out sleep apnea. Finally, we excluded subjects taking medications such as benzodiazepines and anticonvulsants to eliminate the potential effects of these medications on the polysomnogram and to avoid a potential referral bias, as these medications may have been used to treat sleep disruption resulting from the use of antidepressants. This restriction may thus in fact have reduced the observed prevalence of REM sleep abnormalities.

For a diagnosis of RBD, the *International Classification of Sleep Disorders*[2] requires both (1) abnormal behavior and (2) "excessive" submental EMG tone or "excessive" phasic submental or limb twitching during polysomnography. Although the behavioral markers for RBD may be relatively clear,[22] the polysomnographic criteria for what constitutes "excessive" submental or anterior tibialis EMG tone during REM sleep have not been established. Gagnon et al[23] suggested that absence of atonia (requiring 50% of the epoch with elevated tone) in greater than 20% of REM epochs is abnormal. In their study, 19 of 33 (57%) subjects with Parkinson disease exceeded this degree of REM sleep without atonia, whereas only 1 of 16 (6%) normal subjects exceeded this threshold. By comparison, 2 of our 15 (13.3%) subjects taking antidepressants exceed this criterion, whereas none of our control subjects did.

Eisensehr[4] defined the upper limit of normal motor activity during REM sleep as 15% of 10-second REM epochs containing at least 1 second of elevated submental EMG activity (counting only "long" EMG bursts, as described above). No unselected normative data were cited to support the validity of this figure. Nevertheless, 8 of our 15 subjects taking antidepressants (53%) exceeded this threshold in either the anterior tibialis or submental lead, compared to only 1 of our 15 controls (7%).

Gagnon et al[23] recently demonstrated the increased sensitivity of submental EMG tone compared to anterior tibialis EMG tone in distinguishing patients with Parkinson disease with RBD from both patients with Parkinson disease without RBD and controls. In our data as well, submental EMG tone over 30-second REM epochs was more sensitive than either submental or anterior tibialis leads over shorter REM epoch durations in distinguishing antidepressant from control groups. When 2-second REM epochs were used, submental and anterior tibialis phasic

EMG were roughly equivalent in distinguishing subjects taking antidepressants from the control subjects.

Integrity of motor atonia during REM sleep is maintained by a number of neuronal systems and, thus, may be disrupted by lesions or biochemical interventions at a variety of sites.[24] In fact, based on animal experiments, separate systems, potentially colocalized at some points, have been postulated to control the atonia and phasic locomotor aspects of REM.[25] Gilman et al's[26] recent demonstration of anatomic distinctions between areas subserving atonia and those underlying phasic motor activation in REM in subjects with RBD associated with multiple system atrophy is further evidence of this. Our data demonstrating an effect of serotonergic antidepressants on submental motor tone, in the absence of robust effects on phasic activity, are consistent with other clinical reports indicating a similar dissociation.[7] The absence of reported abnormal nocturnal behaviors in the majority of individuals taking serotonergic antidepressants (including our subjects) may thus be due to the fact that serotonergic antidepressants primarily disrupt tonic rather than phasic components of motor activity during REM sleep.

The pathophysiology of RBD and REM sleep without atonia, as suggested above, are likely complex. Dopaminergic mechanisms have recently been suggested by imaging studies in patients with RBD and Parkinson disease or multiple system atrophy.[4,26-27] On the other hand, basic research on motor control during REM sleep implicates glycinergic, GABAergic, noradrenergic, and serotonergic transmitter systems.[28-30] In an animal model of RBD, Trulson et al[28] found that raphe neurons, which are usually quiet in REM, became tonically active. Similarly, Lai's[30] recent finding that electrical or acetylcholine stimulation of the pontine inhibitory area produces both motor-tone suppression and reductions in serotonergic (and noradrenergic) activity further emphasizes the importance of serotonergic inputs on spinal motor units in REM sleep. Serotonergic antidepressants could thus influence motor tone during REM sleep indirectly at brainstem levels (pedunculopontine nucleus or pontine inhibitory area), or directly at spinal levels, producing REM sleep without atonia.

The clinical status of REM sleep without atonia is ambiguous. Although it is not listed in the *International Classification of Sleep Disorders* nosology, it appears to be common in populations vulnerable to RBD. In a recent study, 58% of patients with Parkinson disease demonstrated atonia in REM sleep on polysomnography, 42% of whom had no history of behavioral manifestations.[31] In our series of consecutive subjects without RBD taking antidepressants, 15% to 53% had evidence of REM sleep without atonia, depending upon the definition. REM sleep without atonia may be a "sentinel" finding on polysomnography, expressing a vulnerability to overt RBD.[31] From this perspective, it may be a form fruste of early or evolving RBD. The evolution of RBD into Parkinson disease in a high percentage of patients suggests that EMG activity during REM sleep may be a sensitive indicator of early central nervous system dysfunction. Finally, the distinction between REM sleep without atonia and RBD may be blurred, as some individuals with the former may in fact have behavioral manifestations of RBD that are missed or ignored by patients and their bed partners and/or are not present on a single night of polysomnography. In summary, it is unclear whether elevated REM tone is just a polysomnographic finding or whether it represents an important clinical prognostic finding. Longitudinal studies of patients with Parkinson disease probably represent the best opportunity to address this question scientifically.

If REM sleep without atonia is an early stage of RBD, it will be important to understand the mediators of this response to antidepressants. Our data suggests that age, in agreement with the increase in idiopathic RBD in the elderly,[1] is one such potential mediator. Older subjects taking serotonergic antidepressants were more vulnerable to antidepressant-related disinhibition of submental EMG tone in REM sleep. It is unclear whether age is a surrogate for other factors that mediate this relationship (central nervous system damage, antidepressant-receptor binding or metabolism, etc.). However, we are aware of no other data that demonstrate an influence of age on antidepressant effects on sleep.

Serotonergic antidepressant suppression of REM sleep (increased REM latency and decreased REM time) was also a marker of the degree of REM sleep without atonia in our subjects. Although no such correlations have been demonstrated for patients with idiopathic (or Parkinson-related) RBD, percentage of REM time is no different between those with idiopathic RBD and normal controls.[16] This may suggest that the mechanisms producing abnormalities in EMG tone in REM sleep are different in patients with idiopathic RBD and those given serotonergic antidepressants. In both RBD and "idiopathic" REM sleep without atonia (subclinical RBD), there are striatal presynaptic dopamine-transporter deficits.[4] On the other hand, serotonergic agonism may be more relevant to REM suppression and increased EMG tone in our antidepressant group.[32-34]

Other potential vulnerability markers were not of value in predicting REM sleep without atonia. For instance, male sex is an important risk factor for idiopathic RBD.[1] We did not find an increased vulnerability to REM sleep atonia with male sex in our antidepressant group. Similarly, we did not find a relationship between antidepressant dose (in fluoxetine equivalents) and inhibition of REM sleep atonia. The relationship between REM latency and antidepressant serum level has only been documented for discontinuation of fluoxetine after subchronic use.[35] Whether this is true at steady state after chronic dosing is unclear. One important mediator on which we did not have data was length of treatment. It is not clear whether length of time on an antidepressant may predispose the individual to developing REM sleep without atonia. Future studies of antidepressant effects on sleep should address this issue.

Although the clinical significance of REM sleep without atonia has not been established, there are substantial potential public health implications of REM sleep abnormalities in individuals taking serotonergic antidepressants. Nearly 10 million people in the United States are taking these medications on a routine basis. Increased awareness of RBD among physicians who see individuals with sleep disorders, and among those who prescribe serotonergic antidepressants, will allow for an accurate estimate of sleep-related behavioral abnormalities observed as a result of serotonergic antidepressants.

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