INTRODUCTION

REM sleep behavior disorder (RBD) is a parasomnia characterized by loss of the normal atonia of REM sleep, such that patients appear to act out their dreams.1 Behaviors include yelling, laughing or crying, complex voluntary movements, falling out of bed, and even violent behaviors with injury. RBD is not rare—the prevalence of severe and violent RBD is estimated to be approximately 1/200; milder forms may increase this estimate considerably. Most patients with RBD do not seek medical attention, and lack of awareness among physicians can exacerbate this under-recognition.1 RBD has received considerable recent attention because it is strongly associated with synuclein-mediated neurodegenerative syndromes; patients with idiopathic RBD have > 50% risk of developing neurodegenerative disease over 10 years.3-6 There-fore, the majority of idiopathic RBD patients in sleep clinics are falling out of bed, and even violent behaviors with injury. RBD is not rare—the prevalence of severe and violent RBD is approximately 1/200; milder forms may increase this estimate considerably. Most patients with RBD do not seek medical attention, and lack of awareness among physicians can exacerbate this under-recognition.1 RBD has received considerable recent attention because it is strongly associated with synuclein-mediated neurodegenerative syndromes such as Parkinson disease (PD), dementia with Lewy Bodies (DLB), and multiple system atrophy. Of special interest, RBD patients unique as windows into early stages of neurodegenerative disease, and as potential candidates for development and eventual use of neuroprotective therapy.7

Whereas RBD is often idiopathic, numerous studies have found that antidepressants can produce dream-enactment behavior and loss of normal REM sleep atonia. This is common; symptoms of dream enactment occur in up to 6% of patients prescribed antidepressants (prevalence is higher in older patients).8-17 The reason for this connection is unclear, particularly in relation to neurodegenerative disease. There are several potential mechanisms, each of which would have different effects upon neurodegeneration risk and the presence of neurodegenerative markers. These include:

1. Antidepressants independently cause an idiopathic-like RBD disorder that is completely independent of associated synucleinopathy. If this were the case, the risk of neurodegenerative disease would be low, and there would be few signs of neurodegenerative synucleinopathy in RBD patients taking antidepressants.

2. Antidepressants, among the most commonly prescribed medications, trigger symptoms of REM sleep behavior disorder (RBD) in up to 6% of users. Idiopathic RBD is a very strong prodromal marker of Parkinson disease and other synuclein-mediated neurodegenerative syndromes. It is therefore critically important to understand whether antidepressant-associated RBD is an independent pharmacologic syndrome or a sign of possible prodromal neurodegeneration.

3. Antidepressants disrupt the normal 10-20 ml rise in plasma growth hormone that occurs during REM sleep and may interfere with the protective effects of this hormone. Antidepressants, among the most commonly prescribed medications, trigger symptoms of REM sleep behavior disorder (RBD) in up to 6% of users. 1

4. Patients with idiopathic RBD, all with diagnosis confirmed on polysomnography, stratified to baseline antidepressant use, with 45 matched controls.

5. Measurements/Results: Of 100 patients, 27 were taking antidepressants. Compared to matched controls, RBD patients taking antidepressants demonstrated significant abnormalities of 12/14 neurodegenerative markers tested, including olfaction (P = 0.007), color vision (P = 0.004), Unified Parkinson Disease Rating Scale II and III (P < 0.001 and 0.007), timed up-and-go (P = 0.003), alternate tap test (P = 0.002), Purdue Pegboard (P = 0.007), systolic blood pressure drop (P = 0.029), erectile dysfunction (P = 0.002), constipation (P = 0.003), depression indices (P < 0.001), and prevalence of mild cognitive impairment (13% vs. 60%, P < 0.001). All these abnormalities were indistinguishable in severity from RBD patients not taking antidepressants. However, on prospective follow-up, RBD patients taking antidepressants had a lower risk of developing neurodegenerative disease than those without antidepressant use (5-year risk = 22% vs. 59%, RR = 0.22, 95%CI = 0.06, 0.74).

6. Conclusions: Although patients with antidepressant-associated RBD have a lower risk of neurodegenerative than patients with “purely-idiopathic” RBD, markers of prodromal neurodegeneration are still clearly present. Development of RBD with antidepressants can be an early signal of an underlying neurodegenerative disease.

7. Keywords: REM sleep behavior disorder, antidepressants, Parkinson disease

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2. Antidepressants do not cause RBD per se, but augment/trigger an RBD that is subclinical, resulting in an earlier clinical presentation than would otherwise have occurred. If this were the case, risk of neurodegenerative disease would be lower than in pure idiopathic RBD, but markers of neurodegeneration would be present (although abnormalities may be less advanced than in other idiopathic RBD patients).

3. Within RBD, antidepressants are simply a proxy marker of another prodromal sign of neurodegeneration (i.e., depression\textsuperscript{18-20}). If this were the case, risk of disease may be higher than in idiopathic RBD, and markers would be present to at least the same degree (or more) than the rest of the idiopathic RBD cohort.

Given that antidepressants are commonly prescribed in the general population, and given the profound impact of synuclein-mediated neurodegenerative diseases, understanding the connection between antidepressants and RBD is of considerable clinical and scientific importance. Since 2004, we have been prospectively following a large cohort of patients with idiopathic RBD\textsuperscript{21-23} to assess risk of disease and test predictive markers of neurodegeneration. We therefore compared neurodegenerative markers in RBD patients taking antidepressants, and then prospectively assessed neurodegenerative disease risk over an 8-year follow-up.

**METHODS**

Patients with idiopathic RBD were recruited from the sleep disorders laboratory at the Hôpital du Sacré Coeur, Montreal, Quebec. Ethics approval was obtained from the research ethics board, and all patients provided written informed consent. RBD was defined according to standard ICSD-II criteria\textsuperscript{24} as excessive chin EMG activity during REM sleep,\textsuperscript{25} and either history of elaborate motor activity during sleep associated with dream content or documentation of behavioral manifestations occurring during REM sleep on polysomnographic recording. All patients were asked to hold all medications and substances used for sleep for 2 weeks before the recording, including sedating antidepressants used for insomnia (patients could continue other antidepressants). Controls were selected from the general population, and were frequency-matched for age and sex. All controls had a PSG documenting the absence of RBD.

Baseline characteristics, ancillary testing, and neurologic follow-up of the cohort have been described extensively elsewhere.\textsuperscript{26,27} All evaluations were performed by a movement disorders neurologist (RP) and a neuropsychologist (JAB, CD, or JFG), specifically testing markers of early neurodegenerative disease. All participants underwent a systematic medical history and a complete neurological examination that included all components of the Unified Parkinson Disease Rating Scale (UPDRS).\textsuperscript{28} Three additional quantitative motor indices were used\textsuperscript{29}: the alternate tap test,\textsuperscript{29} the Purdue Peg Board,\textsuperscript{30} and the “timed up and go” test.\textsuperscript{31} Olfaction was assessed with the brief 12-item Cross-Cultural Smell Identification Test (UPSIT-12).\textsuperscript{22,25} Color vision testing was performed using the Farnsworth-Munsell 100 (FM-100) Hue test.\textsuperscript{22,33,34} Symptoms of autonomic dysfunction were assessed with a structured clinical interview based upon the multiple system atrophy rating scale; orthostatic symptoms, urinary dysfunction, constipation, and erectile dysfunction were graded from 0-4.\textsuperscript{35} Blood pressure was measured in the supine position and after standing for one minute, and the orthostatic systolic blood pressure drop was calculated. Cognition was assessed with complete neuropsychological examination and diagnosis of mild cognitive impairment was made according to single or multiple domains, as described elsewhere.\textsuperscript{27,36} Depression was assessed with the UPDRS Part I (annually) the Beck Depression Inventory (baseline only), and by self-report of physician-diagnosed depression (annually).

Patients were then followed on an annual basis, with the same comprehensive protocol to assess development of a defined neurodegenerative disease (recruitment into the cohort is rolling, so maximum potential follow-up duration ranged from 1-8 years). On annual examinations, parkinsonism was diagnosed according to consensus criteria between the neuropsychologist (JFG) and the neurologist (RP), according to Movement Disorders Criteria for PD dementia and consensus criteria for DLB.\textsuperscript{38,39}

All patients who took antidepressants at baseline examination or were taking antidepressants at the time of RBD symptom onset were included in the antidepressant group. In the primary analysis, all patients with antidepressant use at baseline (i.e., “antidepressant-associated” RBD) were included, regardless of temporal relationship to RBD symptoms (because the time of RBD symptoms can be unreliable for many patients, and also to allow evaluation of a potential role of antidepressants as proxy disease marker). However, those with reported RBD symptom onset > 1 year before disease were excluded from a subgroup analysis assessing possible “antidepressant-triggered” RBD. For comparison of neurodegenerative markers, statistical analysis was performed using logistic regression, adjusting for age and sex (all analyses 2-tailed). For estimating risk of neurodegenerative disease, analysis was with Cox proportional hazards (antidepressant use as independent variable), also adjusting for age and sex.

**RESULTS**

One hundred patients were evaluated and met full criteria for RBD (Table 1). Of these, 27 reported antidepressant use at or before baseline examination and 73 did not. Seven took paroxetine, 4 sertraline, 5 citalopram, 1 escitalopram, 5 venlafaxine, 1 mirtazapine, 1 phenelzine, 3 buspirone (2 of whom took other antidepressants), 1 clomipramine, 1 amitriptyline, 1 trazodone, and 1 desipramine. There was no difference in age or sex between those taking or not taking antidepressants; mean age of those taking antidepressants was 64.5 ± 10.5 years. Of the 27 with reported antidepressant use, 8 reported probable onset of RBD symptoms > 1 year before initial prescription of antidepressant—these were removed in a separate subgroup analysis. All 100 were evaluated in a full baseline neuropsychological evaluation; in addition, 84 completed additional prospective follow-up ≥ 1 year (mean = 4.5 years to September 2012, range = 1-8 years). For comparison of markers of neurodegeneration, 44 age- and sex-matched controls were also evaluated.

Are antidepressants associated with neurodegenerative markers in RBD?

If antidepressants cause an RBD syndrome unrelated to underlying synucleinopathy, then other markers of neurodegenerative
synucleinopathy should be absent (i.e., similar to age-matched controls). However, patients with antidepressant-associated RBD demonstrated significant abnormalities of neurodegenerative markers compared to controls (see Figure 1). Patients demonstrated mild motor slowing on all quantitative tests of motor function (UPDRS Part III = 3.5 ± 2.8 vs. 1.8 ± 2.1 [P = 0.007], alternate tap test 179.1 ± 30.9 vs. 199.5 ± 28.9 taps [P = 0.002], Purdue Pegboard 11.3 ± 2.5 vs. 12.3 ± 2.1 pegs [P = 0.007], and timed up-and-go 6.6 ± 1.1 vs. 6.1 ± 1.0 seconds [P = 0.002]). Olfactory function, possibly the most well-established non-motor predictor of Parkinson disease,[24,43] was decreased compared to controls (UPSAT-12 = 8.1 ± 2.5 vs. 9.7 ± -2.3, P = 0.007). Consistent with RBD as a predictor of DLB, patients had a higher prevalence of mild cognitive impairment on neuropsychological examination (60% vs. 13%, P < 0.001). Color vision, a predictor of neurodegenerative disease in RBD—taking evidence of prodromal neurodegenerative synucleinopathy, was also abnormal compared to controls (FM-100 error score = 144.4 ± 54.8 vs. 98.5 ± 74.2, P = 0.004). Rating scales of constipation, a known prodromal marker of PD,[45-47] were increased (symptom score = 0.81 ± 0.99 vs. 0.16 ± 0.45, P = 0.003), as was orthostatic blood pressure drop (0.29), and erectile dysfunction symptom scores (1.8 ± 1.6 vs. 0.40 ± 0.96, P = 0.002). RBD patients taking antidepressants had increased depressive symptoms (Beck Depression Inventory = 15.2 ± 7.3 vs. 5.1 ± 3.8, P < 0.001). Notably, there were no significant differences in any variable between RBD patients taking vs. not taking antidepressants, with the exception of orthostatic symptoms (more severe in patients taking antidepressants [P = 0.042]) and depression symptoms (more severe in patients taking antidepressants). Removing patients with an unlikely temporal relation for antidepressant-triggered RBD did not alter results (Table S1). Patients taking antidepressants had higher percentage of phasic (but not tonic) REM sleep EMG activity (P = 0.007), consistent with a direct effect of antidepressants upon phasic REM.

Therefore, there was clear evidence of abnormalities of numerous markers of synuclein-mediated neurodegeneration in our patients with antidepressant-RBD. These were indistinguishable from RBD patients without associated antidepressant use.

Do RBD patients taking antidepressants have the same risk of neurodegeneration?

Although RBD patients with antidepressant use might have evidence of prodromal neurodegenerative synucleinopathy,
this does not necessarily imply that disease risk would be the same. It is possible that antidepressants triggered a clinical presentation of RBD that occurred earlier than it would have if antidepressants were not used. If so, risk of disease would remain, but might be lower than in those without this symptomatic trigger.

Over 8 years follow-up, 36 patients developed a defined neurodegenerative syndrome. Eighteen developed primary parkinsonism (PD = 15, possible multiple system atrophy = 3), and 18 developed dementia (all 18 met possible DLB criteria, 13 met probable DLB criteria). Over the total prospective period, 32/61 (52%) patients not taking antidepressants

*Figure 1—Selected prodromal markers of synuclein-mediated neurodegeneration in controls and in idiopathic RBD patients according to antidepressant use. Olfaction (A), color vision (B), orthostatic blood pressure drop (C), motor speed (alternate tap test) (D). For figure legibility, individual results have been rounded to the nearest integer. *Significant difference compared to controls (there were no significant differences between RBD patients taking vs. not taking antidepressants).
developed neurodegenerative disease, compared to 4/23 (17%) of those taking antidepressants (P = 0.006, Fischer exact test). On Kaplan-Meier survival analysis, the estimated 5-year risk of developing neurodegeneration in patients not taking antidepressants was 59%, compared to 22% if taking antidepressants (RR = 0.22, 95% CI = 0.06, 0.74 - see Figure 2). The 7-year risk was 84% compared to 22%; however, numbers at these longer intervals were low (7 and 5 in each group). Removal of those who reported RBD symptom onset > 1 year before first prescription of antidepressants did not appreciably change results (59% vs. 32%). Self-report of diagnosed depression did not significantly predict risk of developing defined neurodegeneration (5-year risk with depression = 41%, without depression = 53%, P = 0.23). Cox proportional hazards analysis, adjusting for age and sex, found a significant association between antidepressants and a lower risk of developing defined neurodegeneration (adjusted RR = 0.30, 95% CI = 0.10, 0.86, P = 0.026).

Therefore, although some RBD patients taking antidepressants eventually developed a defined neurodegenerative synucleinopathy, risk was lower than for other idiopathic RBD patients.

**DISCUSSION**

An association between antidepressants and RBD has been documented by numerous groups. Given the vast number of antidepressants prescribed worldwide, it is of critical clinical importance to understand whether RBD occurring with prescription of antidepressants is a relatively benign side effect, or is a marker of prodromal neurodegenerative disease that requires further evaluation and follow-up. The existence of a large RBD cohort extensively evaluated for neurodegenerative markers, combined with a prospective longitudinal follow-up, allowed us to test possible explanations for the association between RBD and antidepressants. If antidepressants were associated with a separate “purely pharmacologic” syndrome, we would have anticipated a lower risk of neurodegeneration (observed), but also few ancillary signs of neurodegeneration (not observed). If antidepressants simply marked depression or anxiety as a prodromal marker of neurodegeneration, we would have anticipated ancillary signs of neurodegeneration (observed), but also a higher (or at least equal) risk of developing neurodegenerative disease (not observed). The finding of a lower risk of neurodegenerative disease, yet combined with clear evidence of markers of neurodegeneration suggests that antidepressants primarily trigger early clinical presentation of an RBD that is nonetheless still due to underlying neurodegeneration.

Our finding is consistent with previous observations that although clinical RBD can be triggered by antidepressants, withdrawal of antidepressants may not reverse the loss of REM sleep atonia. Therefore, these studies suggest that antidepressants unmask an already-present subclinical loss of REM sleep atonia (which persists after antidepressant withdrawal). It is also consistent with the fact that only a minority of patients taking antidepressants present with clinical RBD, and that this is more common in older individuals (who would be more likely to have an underlying neurodegenerative disease). Studies systematically assessing emergence of dream enactment with new antidepressant prescription would be of considerable interest, to assess the true risk of RBD and risk factors for its development.

These results have important clinical implications. Antidepressants are among the most commonly-prescribed medications in clinical medicine, commonly used for both depression and anxiety. Symptoms of RBD will usually not be mentioned by patients, and even when reported may be dismissed by health professionals as a benign or “normal” phenomenon. Our findings suggest that the dream enactment behavior occurring with antidepressant use may be an important signal of an impending neurodegenerative disease, especially in older individuals (significance in young individuals is unclear, as they were not represented in this cohort). Therefore, surveillance for this side effect is warranted, and if detected, requires diagnostic evaluation by referral to a qualified sleep center. If RBD is confirmed, referral to a neurologist for prospective clinical follow-up may be recommended to detect and treat early manifestations of disease (although no established neuroprotective therapy to prevent PD is available, early symptomatic treatment can considerably improve quality of life). Among sleep centers already treating patients with RBD, patients taking antidepressants might be advised that their risk of neurodegenerative disease is lower than in other RBD patients (possibly simply because their antidepressants triggered earlier clinical presentation of their prodromal disease). Nevertheless, clinical follow-up is still warranted, given that a neurodegenerative etiology for their symptoms may still be present. As a final clinical point, since antidepressants also substantially reduce REM sleep time, they can also paradoxically reduce RBD or withdrawal of antidepressants can augment symptoms (note that all patients in our study had full clinical symptoms of RBD).

Some limitations should be noted. We used a broad panel of markers of neurodegenerative disease to assess underlying synucleinopathy; although olfactory, color vision, constipation, and motor markers are established markers of prodromal synucleinopathy, some autonomic and cognitive markers have not yet been proven to mark disease. Therefore the significance of these latter abnormalities is less certain. Our study
analyzed overall outcomes and neurodegenerative markers in the aggregate—we aimed to assess the predominant pattern of antidepressant-associated RBD, without assuming that all patients have the same underlying pathophysiology. The interaction between depression, antidepressants and RBD is complex,\textsuperscript{4,6,52} and it is certainly plausible that our cohort contained a smaller subset of individuals with a “pure antidepressant-caused” RBD that was not associated with synucleinopathy, or a small subset of patients for whom antidepressants marked depression as a prodromal symptom. Note that patients taking antidepressant still had higher Beck scores despite treatment—this may not be surprising, considering that medications may not be completely efficacious. It does raise the possibility that depression may have confounded the cognitive examination (which, however, would have resulted in a higher likelihood of dementia). Of note, our cohort was older and male-predominant (as are most cohorts with idiopathic RBD\textsuperscript{6,52}), and did not include the young, predominantly female antidepressant users reported by other groups\textsuperscript{8,10} (we had 5 patients under 50, only one of whom was female); such a subgroup certainly may have a separate pathophysiology. Again, it would be of considerable interest in the future to prospectively evaluate patients in psychiatry clinics to systematically assess the prevalence and risk factors for emergence of RBD symptoms with new antidepressant prescription. Mainly for compliance and ethical issues, we did not systematically evaluate results of polysomnography with and without antidepressants. Finally, the sample size was too small to provide sufficient power to assess subgroups such as those with young-onset RBD, women, or patients taking different types of antidepressants.

Although patients with antidepressant-associated RBD have a lower risk of neurodegeneration than those without antidepressants, markers of prodromal neurodegeneration are still clearly present. This suggests that antidepressants predominantly trigger clinical presentation of a previously subclinical loss of REM sleep atonia due to an underlying synucleinopathy. Dream-enactment behavior occurring with antidepressants may be an important early signal of neurodegenerative disease.

**DISCLOSURE STATEMENT**

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Table S1—Neurodegenerative markers in patients with antidepressants according to temporal relation to RBD symptoms

<table>
<thead>
<tr>
<th></th>
<th>RBD - no antidepressant n = 73</th>
<th>Antidepressant unlikely temporal relation, n = 8</th>
<th>Antidepressant, Possible temporal relation, n = 19</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>67.8 ± 9.7</td>
<td>69.3 ± 7.7</td>
<td>62.0 ± 10.9</td>
<td>0.03</td>
</tr>
<tr>
<td>Sex, % male</td>
<td>74%</td>
<td>88%</td>
<td>69%</td>
<td>0.54</td>
</tr>
<tr>
<td>RBD symptom duration, years</td>
<td>10.2 ± 10.2</td>
<td>9.4 ± 6.4</td>
<td>9.9 ± 12.5</td>
<td>0.95</td>
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<tr>
<td>Duration follow-up, years</td>
<td>4.3 ± 2.1</td>
<td>5.1 ± 2.3</td>
<td>4.1 ± 2.6</td>
<td>0.74</td>
</tr>
<tr>
<td>Tonic REM, %</td>
<td>46.3 ± 31.5</td>
<td>54.3 ± 32.3</td>
<td>43.6 ± 27.9</td>
<td>0.87</td>
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<tr>
<td>Phasic REM, %</td>
<td>28.8 ± 14.1</td>
<td>38.6 ± 25.0</td>
<td>38.0 ± 16.4</td>
<td>0.10</td>
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<tr>
<td>Olfaction (UPSIT), % normal</td>
<td>72.0 ± 27.0</td>
<td>95.6 ± 35.6</td>
<td>76.4 ± 24.4</td>
<td>0.85</td>
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<tr>
<td>Color vision (FM-100), % normal</td>
<td>129.7 ± 57.6</td>
<td>114.6 ± 40.4</td>
<td>121.4 ± 56.9</td>
<td>0.74</td>
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<tr>
<td>UPDRS Part II</td>
<td>2.0 ± 2.2</td>
<td>0.88 ± 0.88</td>
<td>1.4 ± 1.2</td>
<td>0.65</td>
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<td>UPDRS Part III</td>
<td>4.3 ± 4.5</td>
<td>2.6 ± 1.9</td>
<td>3.8 ± 3.1</td>
<td>0.49</td>
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<td>Timed up and go, seconds</td>
<td>6.7 ± 2.0</td>
<td>6.9 ± 0.62</td>
<td>6.5 ± 1.3</td>
<td>0.53</td>
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<tr>
<td>Purdue peg board</td>
<td>11.0 ± 2.0</td>
<td>10.9 ± 1.3</td>
<td>11.5 ± 2.9</td>
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<tr>
<td>Alternate tap test</td>
<td>176.0 ± 35.3</td>
<td>187.1 ± 36.7</td>
<td>175.8 ± 28.5</td>
<td>0.24</td>
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<td>Orthostatic symptoms</td>
<td>0.22 ± 0.46</td>
<td>0.38 ± 0.52</td>
<td>0.47 ± 0.61</td>
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<td>Systolic blood pressure drop, mmHg</td>
<td>14.0 ± 14.6</td>
<td>14.0 ± 18.0</td>
<td>9.4 ± 14.6</td>
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<td>Urinary symptoms</td>
<td>0.39 ± 0.59</td>
<td>0.13 ± 0.35</td>
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<td>Erectile symptoms</td>
<td>1.7 ± 1.4</td>
<td>1.7 ± 1.4</td>
<td>1.8 ± 1.7</td>
<td>0.20</td>
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<tr>
<td>Constipation</td>
<td>0.63 ± 0.88</td>
<td>0.50 ± 0.76</td>
<td>0.95 ± 1.07</td>
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<tr>
<td>Depression - UPDRS Part I</td>
<td>0.21 ± 0.48</td>
<td>0.63 ± 0.74</td>
<td>1.26 ± 0.99</td>
<td>&lt; 0.001</td>
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<td>Beck Depression Inventory</td>
<td>8.9 ± 6.6</td>
<td>13.0 ± 8.8</td>
<td>16.3 ± 6.5</td>
<td>&lt; 0.001</td>
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<tr>
<td>Mild Cognitive Impairment (yes/no)</td>
<td>41/32 (56%)</td>
<td>5/3 (62%)</td>
<td>12/7 (63%)</td>
<td>0.14</td>
</tr>
<tr>
<td>Mild Cognitive Impairment (none/single/multiple domain)</td>
<td>32/33/8</td>
<td>3/3/2</td>
<td>7/8/4</td>
<td>0.20</td>
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</table>

*P value is for the comparison between the “antidepressant with possible temporal relation” and all other RBD patients, analyzed with logistic regression adjusting for age and sex. UPRDS, Unified Parkinson Disease Rating Scale; RBD, REM Sleep Behavior Disorder; UPSIT, University of Pittsburgh Smell Identification Test (Cross-Cultural 12-item version); FM-100, Farnsworth Munsell 100 Hue Test. Data in bold type indicates significant difference (P < 0.05).