REM Sleep Behavior Disorder and REM Sleep without Atonia in Patients with Progressive Supranuclear Palsy

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INTRODUCTION

RAPID EYE MOVEMENT (REM) SLEEP BEHAVIOR DISORDER (RBD), A DISABLING PARASOMNIA THAT INCLUDES ENACTED DREAMS AND REM SLEEP WITHOUT ATONIA, affects one third of patients with Parkinson disease (PD). RBD is even more common (80%-90%) in patients with multiple system atrophy and dementia with Lewy body disease,8,9 2 other neurodegenerative diseases characterized on postmortem examination, as is PD, by deposit of alpha-synuclein protein in the brain neurons. In addition, as many as one third to two thirds of patients with a diagnosis of idiopathic RBD may, in the subsequent decade after diagnosis, develop signs of parkinsonism.6,7 Lewy bodies have been found within the brain of a single patient presenting with no signs other than ‘idiopathic’ RBD.8 In contrast, RBD was reported to be rare in a series of patients with Alzheimer disease, progressive supranuclear palsy (PSP), frontotemporal dementia, and corticobasal degeneration.4 These 4 neurodegenerative diseases are characterized by tau-protein deposit in neurons. It has been suggested that RBD is a marker of synucleinopathy rather than of tauopathy and could be used as an additional diagnostic criteria to discriminate, in a patient with progressive cognitive impairment, a case of Lewy body disease rather than of Alzheimer disease.9

PSP, also known eponymously as Steele-Richardson-Olszewski syndrome, is a rare disease that affects 6.5 per 100 000 subjects,10 a prevalence 200 times lower than PD. Patients with PSP show a complex range of symptoms, including paralysis of vertical gaze, postural instability and falls,11 frontal cognitive impairment, dysarthria and dysphagia, parkinsonism, and dystonic rigidity of neck and upper trunk.12 Unlike those of PD, PSP motor symptoms are poorly levodopa responsive. The disease is progressive, and patients die from pulmonary embolism or aspiration pneumonia after a median of 7 years. Most patients with PSP complain of insomnia. Polysomnographic studies have reported reduced total sleep time and increased sleep fragmentation early in the course of the disease. With the progression of the disease, REM sleep is dramatically reduced.13-18 The velocity of
REM sleep may be reduced with occasional square-wave jerks, both during wakefulness and during REM sleep. Despite these extensive sleep studies in PSP, a specific study of RBD and its polygraphic correlates—REM sleep without atonia (RWA)—has been performed in only 2 patients, in whom it was normal.9 Furthermore, although sleep abnormalities may impair daytime vigilance, there has been no systematic study reporting on excessive daytime sleepiness in patients with PSP. To determine if patients with PSP have RBD, RWA, and abnormal daytime sleepiness, we conducted a prospective study of nighttime sleep and daytime vigilance in 15 patients with PSP, 15 control subjects, and 15 patients with PD, all matched for sex and age.

METHODS

Subjects

Between February 2001 and February 2002, 23 patients with PSP were followed at the movement disorder clinics of 2 university hospitals. They were prospectively offered a sleep study. Two patients refused to take part, and 1 patient died before the sleep study. Five other patients completed the sleep study but their data were removed from the analysis because they were treated with antidepressant drugs, which could disturb the analysis of muscle tone during REM sleep. Finally, 15 patients, 8 women and 7 men, completed the study, which was approved by the local ethics committee. All patients met clinical diagnostic criteria for probable PSP, including parkinsonism, early occurrence of falls, saccade abnormalities on electrooculography, and levodopa responsiveness lower than 50% (their motor score on Unified Parkinson’s Disease Rating Scale-part III [UPDRS-III] was decreased by less that 50% during a standardized acute levodopa challenge).12 They were aged 68 ± 8 years (mean ± SD, range 55-80 years). The disease course ranged from 1 to 8 years, with a mean of 4 ± 2 years (Table 1). They had a mild cognitive defect, as demonstrated by a Mini Mental State Examination score of 24 ± 5 (range 14-30).19 They were severely disabled, with a mean 29 ± 14 (range 4-49) motor score on the UPDRS-III while optimally treated,20 a score that has also been validated in patients with PSP.21 Nine patients were treated with levodopa, and 1 of them also received a dopamine agonist (ropinirole). Four patients took an evening dose of a benzodiazepine or benzodiazepine-related drug (clonazepam 0.2 mg/day, prescribed for alleviating RBD, bromazepam 1.5 mg/day, nitrazepam 5 mg/day, and zopiclone 7.5 mg/day). None of these 15 patients with PSP received antidepressant therapy.

We selected 15 age- and sex-matched patients with PD from a series of PD patients who had sleep interviews, overnight video-polysomnography, and Multiple Sleep Latency Tests in our program of the systematic study of sleep in patients with PD. Their demographic, clinical, and treatment characteristics are provided in Table 1. They were treated with levodopa alone (7/15), ropinirole alone (1/15), and a combination of levodopa and a dopamine agonist (7/15: pergolide [2]; bromocriptine: [2]; ropinirole [3]). In addition, 4 patients took a benzodiazepine or benzodiazepine-related drug at bedtime (clonazepam 0.5 mg/day, flunitrazepam 1 mg, zopiclone 7.5 mg/day, zolpidem 20 mg/day). None of the patients took any antidepressant drugs.

We selected age- and sex-matched controls from a series of 104 subjects seen in the department of internal medicine who had a potential diagnosis of venous thromboembolism, not subsequently confirmed, who were systematically studied, after signed agreement, with a sleep interview and a polysomnogram within 1 month (Table 1). They had no neurologic disease. Three subjects took a benzodiazepine at bedtime (lorazepam 0.5 mg, bromazepam 1.5 mg, oxazepam 25 mg), and none of them took any antidepressant drugs.

Study Design

Each patient was studied in the sleep laboratory for 24 hours. The protocol included (1) motor disability scale,20 (2) interview of patient and caregiver about sleep disorders, (3) Mini Mental State Examination,19 (4) Epworth Sleepiness Scale,22 (5) class-II HLA phenotype (only in the PSP group), (6) nighttime sleep recordings from lights off (ad lib) to 6:30 AM (all patients woke up spontaneously before that time); and (7) 5 clinical Multiple Sleep Latency Tests.23 The controls underwent only the sleep interview, the Mini Mental State Examination, and the nighttime recordings.

Nighttime polysomnographic recordings included frontocentral and occipitocentral bipolar electroencephalography, electrooculogram, chin and bilateral tibialis anterior surface electromyography (EMG; arriving through a Y montage to the same amplifier), nasal pressure cannula, tracheal sounds through a microphone, thoracic and abdominal belts to measure respiratory movements, pulse rate, and oximetry (Cidelec Ltd, France). Patients were under the constant supervision of a sleep technologist, who monitored the recordings. The sleep stages, arousals, periodic leg movements, and respiratory events were scored visually according to standard criteria.24,25-27 The alpha rhythm was measured during an evening period of quiet wakefulness, on the occipitocentral lead, using fast Fourier transformation. Tonic muscle activity was quantified second per second during REM sleep on the chin EMG as a muscle activity with an amplitude at least equal to the amplitude observed during quiet wakefulness. It was then divided by the total duration of REM sleep to obtain the percentage of RWA. Leg muscle activity was measured second per second on the leg muscle EMG as a transient and frank elevation of muscle tone. The duration of leg muscle activity was also divided by

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**Table 1—Clinical Characteristics of Patients with Progressive Supranuclear Palsy, Patients with Idiopathic Parkinson Disease, and Age- and Sex-Matched Control Subjects**

<table>
<thead>
<tr>
<th>Patients</th>
<th>PSP</th>
<th>PD</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Sex</td>
<td>7</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Age, y</td>
<td>68 ± 8</td>
<td>67 ± 6</td>
<td>67 ± 10</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.5 ± 4.1</td>
<td>24.2 ± 4.8</td>
<td>26.1 ± 5.4</td>
</tr>
<tr>
<td>ESS Score</td>
<td>6.7 ± 5.0</td>
<td>8.2 ± 3.5</td>
<td>6.9 ± 4.2</td>
</tr>
<tr>
<td>MMSE Score</td>
<td>24 ± 7</td>
<td>28 ± 1</td>
<td>29 ± 1</td>
</tr>
<tr>
<td>Clinical RBD, no. (%)</td>
<td>2 (13)</td>
<td>3 (20)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Disease duration, y</td>
<td>4 ± 2</td>
<td>12 ± 9</td>
<td>NA</td>
</tr>
<tr>
<td>Motor disability, UPDRS-III</td>
<td>29 ± 14</td>
<td>19 ± 10</td>
<td>NA</td>
</tr>
<tr>
<td>Levodopa dose, mg/d</td>
<td>290 ± 290</td>
<td>521 ± 260</td>
<td>NA</td>
</tr>
<tr>
<td>Use of dopamine agonists, no.</td>
<td>2 ± 0</td>
<td>2 ± 0</td>
<td>NA</td>
</tr>
<tr>
<td>Dopa-equivalent dose, mg/d</td>
<td>295 ± 297</td>
<td>775 ± 339</td>
<td>NA</td>
</tr>
</tbody>
</table>

*P < .05 for a difference between patients with Parkinson disease (PD) and control subjects.

*BMI refers to body mass index; ESS, Epworth Sleepiness Scale; MMSE, Mini Mental State Examination; RBD, REM (rapid eye movement) sleep behavior disorder; UPDRS, Unified Parkinson Disease Rating Scale.
total REM sleep to obtain the percentage of leg muscle activity during REM sleep. The EMG measures were performed both by scorers aware of the patient’s diagnosis (IA, MMA) and by an independent scorer blinded to the diagnosis, with similar results.

Statistics were performed using analyses of variance for comparison of continuous variables between the 3 groups. When the significance level \(P < .05\) was obtained, we performed posthoc analysis using Bonferroni corrected \(t\) tests, at the significance level of \(P < .01\). Unpaired \(t\) tests were performed for comparisons limited to the PSP and PD groups or for intragroup comparisons. Results are reported as mean ± SD, except for the daytime mean sleep latencies (mean ± SEM).

RESULTS

Clinical Interview

As expected by matching, age and sex of the patients were identical between groups. Body mass index was not different between groups. Although PSP patients had a shorter disease course than PD patients, they were as equally motor disabled, more cognitively impaired, and received lower daily levodopa-equivalents doses (Table 1). Six PSP patients, 5 PD patients, and 6 control subjects complained of difficulties initiating or maintaining sleep. Two PSP patients, 2 PD patients, and 2 control subjects met the clinical criteria of restless legs syndrome. Clinical RBD was reported by 2 men (13% of the group) with PSP, 3 men (20%) with PD, and no controls. The Epworth Sleepiness Scale score was not different between groups (Table 1). Two PSP patients, 2 PD patients, and 3 controls had an Epworth Sleepiness Scale score greater than 10.

Nighttime Sleep

Nighttime sleep measures are shown in Table 2. Electroencephalographic abnormalities were found only in PSP patients. Alpha rhythm was slower than 8 Hz during the waking electroencephalogram in 4 patients. Isolated frontal spikes were also observed in 4 patients, and although this was not formally quantified, spindles were rare. The alpha rhythm during wakefulness was slower in PSP patients than in controls, but the difference did not reach significance when compared with PD patients (Table 2).

Total sleep time was less than 300 minutes in 7 PSP patients, in 6 PD patients and in 0 controls but was not significantly different between groups. PSP patients tended to have lower sleep efficiency and a had longer duration of wakefulness after sleep onset, longer REM sleep latency, higher percentage of stage 1 sleep, and almost twice as great an arousal index as the PD patients and controls. REM sleep percentage was lower in PSP and PD patients than in controls. There were no differences in apnea-hypopnea indexes between the 3 groups. The apnea-hypopnea index was greater than 15 in 9 (60%) PSP patients, in 9 (60%) PD patients, and in 6 (40%) controls (no significant difference in frequencies).

Motor Activity During Sleep

The mean percentages of RWA were higher in PSP patients and in PD patients than in controls (Table 2). In 4 PSP patients (27% of the group; 2 men, 2 women) and 4 PD patients (27% of the group; 2 men, 2 women), RWA represented more than 50% of REM sleep duration, while this was never observed in the controls.

### Table 2

<table>
<thead>
<tr>
<th>Sleep Measures</th>
<th>PSP</th>
<th>PD</th>
<th>Controls</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occipital alpha waking rhythm, Hz</td>
<td>8.9 ± 1.5(^†)</td>
<td>10.4 ± 2.0</td>
<td>11.1 ± 2.5</td>
<td>.01</td>
</tr>
<tr>
<td>Nighttime sleep</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total sleep period, min</td>
<td>541 ± 52(^*)</td>
<td>429 ± 88</td>
<td>477 ± 58</td>
<td>.0002</td>
</tr>
<tr>
<td>Total sleep time, min</td>
<td>347 ± 87</td>
<td>323 ± 76</td>
<td>372 ± 73</td>
<td>.24</td>
</tr>
<tr>
<td>Wakefulness after sleep onset, min</td>
<td>194 ± 82(^*)</td>
<td>114 ± 53</td>
<td>105 ± 69</td>
<td>.0016</td>
</tr>
<tr>
<td>Sleep efficiency, %</td>
<td>64 ± 15</td>
<td>77 ± 23</td>
<td>78 ± 13</td>
<td>.053</td>
</tr>
<tr>
<td>Latency, min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep onset</td>
<td>22 ± 19</td>
<td>20 ± 26</td>
<td>38 ± 29</td>
<td>.12</td>
</tr>
<tr>
<td>REM sleep</td>
<td>202 ± 122(^†)</td>
<td>134 ± 60</td>
<td>87 ± 44</td>
<td>.0018</td>
</tr>
<tr>
<td>Sleep duration, % total sleep time</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>21 ± 12(^*)</td>
<td>11 ± 11</td>
<td>9 ± 7</td>
<td>.005</td>
</tr>
<tr>
<td>Stage 2</td>
<td>44 ± 15</td>
<td>52 ± 16</td>
<td>48 ± 15</td>
<td>.39</td>
</tr>
<tr>
<td>Stages 3-4</td>
<td>26 ± 13</td>
<td>25 ± 13</td>
<td>20 ± 13</td>
<td>.44</td>
</tr>
<tr>
<td>REM sleep</td>
<td>8 ± 6(^†)</td>
<td>10 ± 4(^†)</td>
<td>20 ± 6</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>REM sleep without atonia, % total REM sleep</td>
<td>33 ± 36(^†)</td>
<td>28 ± 35(^†)</td>
<td>0.5 ± 1</td>
<td>.008</td>
</tr>
<tr>
<td>Chin muscle activity</td>
<td>4 ± 3</td>
<td>2 ± 3</td>
<td>2 ± 3</td>
<td>.24</td>
</tr>
<tr>
<td>Legs muscle activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep fragmentation, per hour</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arousals</td>
<td>47 ± 28(^*)</td>
<td>22 ± 14</td>
<td>28 ± 26</td>
<td>.018</td>
</tr>
<tr>
<td>Periodic legs movements</td>
<td>30 ± 27</td>
<td>19 ± 25</td>
<td>11 ± 24</td>
<td>.15</td>
</tr>
<tr>
<td>Apnea-hypopnea</td>
<td>25 ± 18</td>
<td>19 ± 16</td>
<td>21 ± 23</td>
<td>.65</td>
</tr>
<tr>
<td>Daytime sleepiness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean sleep latency</td>
<td>11.0 ± 6.4</td>
<td>11.1 ± 4.7</td>
<td>—</td>
<td>.95</td>
</tr>
<tr>
<td>Less than 8 min, no.</td>
<td>4</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The \(P\) value is derived from the analysis of variance between the 3 conditions: \(^*\)Progressive supranuclear palsy (PSP) group different from both Parkinson disease (PD) and control groups; \(^†\)PSP and PD groups different from control group; \(^‡\)PSP group different from control group; \(^§\)PSP group different from PD group. REM refers to rapid eye movement.
(Figure 1). The percentage of leg EMG activity during REM sleep was not different between the 3 groups. The 4 PSP patients with RWA had an alpha rhythm (8.2 ± 1.3 Hz) that was not different from that of the 11 PSP patients without RWA (9.1 ± 1.6 Hz, \( P = .38 \)). This was also the case for the PD patients with RWA (n = 4, alpha rhythm: 9.5 ± 1.0 Hz) and without RWA (n = 11, alpha rhythm: 10.3 ± 2.4 Hz, \( P = .60 \)). The indexes of periodic leg movements during sleep were not significantly different between the 3 groups. Seven PSP patients had more than 25 periodic leg movements per hour of sleep, versus 5 PD patients and 2 controls.

**Daytime Sleepiness**

During Multiple Sleep Latency Tests, the mean sleep latency was not different between PSP and PD patients. Four PSP patients and 1 PD patient had an abnormal (< 8 minutes\( \frac{28}{28} \)) mean sleep latency. These 4 PSP patients had arousal indexes similar to those of the 11 PSP patients with normal daytime mean sleep latencies (40.4 ± 21.6 vs 48.8 ± 31.3, \( P = .69 \)) but slept longer during the night (total sleep time: 442 ± 14 minutes vs 312 ± 74 minutes, \( P = .004 \)). Except for 1 isolated sleep-onset REM period observed in a PSP patient, no narcolepsy-like pattern [ie, 2 or more sleep-onset REM periods among 5 latency tests] was found in PSP or PD patients. In the PSP group, the HLA-class II allele was DQB1-0201 in 4 of 30 (13%) alleles, DQB1-03 (0301, 0302, 0307, 0309) in 8 of 30 (27%) alleles, DQB1-0501 in 5 of 30 (17%) alleles, and DQB1-0602 in 3 of 30 (10%) alleles. These percentages were not different from those found in French controls. 29

**DISCUSSION**

The main finding is that 27% of patients with PSP, a tauopathy with parkinsonism, had a large percentage of RWA and 13% had RBD. These frequencies were similar to those of age- and sex-matched patients with PD, a synucleinopathy, while RBD and RWA were not found in controls. Furthermore, although PSP patients had a more fragmented sleep, they were as sleepy during the day as PD patients, but neither had a narcolepsy-like phenotype.

Boeve et al have suggested that RBD is a hallmark of synucleinopathies, since it is very rare in tauopathies. 8 However, only 2 patients with PSP were interviewed and recorded in that series. Our results challenge this hypothesis and demonstrate that RBD and RWA may affect as many as one third of patients with PSP and should not preclude this diagnosis.

There are several limitations to our findings. We did not record arm movements or the video images. This limited the opportunity to record speech and hands movements, which are frequently found in patients with RBD. Interestingly, the patients with PSP had percentages of tonic EMG activity during REM sleep similar to those of matched PD patients. The 60% to 100% RWA in our PSP and PD patients resemble the more than 50% RWA observed in one third of PD patients recorded by Gagnon et al. 2 The abnormal muscle activity was mainly observed on the chin muscle, however, since PSP had the same small amount of leg muscle activity that patients from the other groups had. Again, the arm muscles were not recorded, preventing further interpretation of phasic muscle activity during REM sleep.

Our PSP patients had low amounts of REM sleep, which is a common abnormality in PSP, but this reduction of REM sleep was not different from that of matched PD patients. This is probably because our PSP patients had a mean 4-year disease duration, allowing the observation of sufficient REM sleep amounts to measure the level of atonia. We think that the selection of PD patients of the same age, but with longer disease duration and similar motor disability, provides a more adequate parkinsonian control group than adjustment of disease durations because PD patients are as disabled during the night as PSP patients, thereby allowing comparison of sleep measures not biased by impaired nocturnal mobility. As REM sleep progressively disappears with the rapid course of the disease, it is probable that RBD disappears too, thereby explaining why RBD has not been previously reported in patients with advanced PSP.

The observation of RBD and RWA in PSP patients raises the question of RBD in other tauopathies. Large series of patients with Alzheimer disease have been recorded during the night, but sleep has rarely been studied in frontotemporal dementia and in corticobasal degeneration. Evidence is accumulating that symptomatic RBD can be observed in various neurodegenerative diseases, whatever the nature of the lesions. Indeed, patients with spinocerebellar ataxia, a polyglutamine disease, may have RBD and RWA, whether they had spinocerebellar ataxia type 3/Machado-Joseph disease or spinocerebellar ataxia type 1 or 2. 32 Patients with the parkin mutation, a mutation that leads to early-onset parkinsonism without intraneuronal alpha-synuclein deposits, can also exhibit RBD and RWA. 33 This suggests that it is the location of the lesion, rather than the type of lesion, that is important in the genesis of RBD. PSP, synucleinopathies, and spinocerebellar ataxia are diseases characterized by brain, especially brainstem, neuronal death. All 3 diseases involve, to various degrees, the dopaminergic system. None is limited to that system, however, thereby precluding further attempts to localize the lesions responsible for RBD. The cholinergic system may also be involved. In animal studies, it has been shown that REM-sleep executive cholinergic and cholinceptive neurons, located in the pedunculopontine tegmentum (locus coeruleus alpha and perialpha in the cat), are inhibited by monoaminergic (serotonin, histamine, norepinephrine, known to be preserved in PSP) and hypothalamic hypocretinergic descending systems and activated
by cholinergic descending systems. In PSP, the severe loss of cholinergic neurons previously observed in the pedunculopontine tegmentum may progressively and directly affect the REM-sleep executive and activating systems. This would explain the abnormalities in both duration and quality (ie, absence of normal atonia) of REM sleep in our patients with PSP.

We found that 27% of PSP patients had an abnormal mean daytime sleep latency. Previous measures of Multiple Sleep Latency Tests have been performed, to the best of our knowledge, in only 3 patients with PSP. There has been increased concern about people with PD having excessive daytime sleepiness and potential motor vehicle accidents when driving. Since PSP patients are disabled earlier and more severely than PD patients, one would imagine that they would stop driving earlier and be less affected by excessive daytime sleepiness when activities of daily living are also limited. This assertion should, however, be determined in individual cases, at least at the beginning of the disease. In our study, patients with excessive daytime sleepiness had similar sleep fragmentation but longer nocturnal sleep than those with normal alertness, suggesting that sleepiness was caused by a primary central hypersomnia. The number of patients is limited here, however, preventing further speculations. Excessive daytime sleepiness was as severe as in our patients with PD, but the narcolepsy-like pattern that has been reported in PD patients was not observed here. Our data suggest that the mechanism underlying excessive daytime sleepiness differs in PD and in PSP. REM-sleep executive systems may be too damaged to produce sleep onset in REM periods during daytime naps. On the other hand, since 60% of our patients with PSP had an obstructive apnea-hypopnea index greater than 15, excessive daytime sleepiness may be partly caused by sleep-disordered breathing. This has not been previously reported, possibly because nocturnal respiratory events have not been monitored or were monitored with methods (oximetry or naso-oral thermistance) now known to produce false-negative results. The prevalence of sleep apnea was not different, however, between age- and sex-matched PD patients and controls, suggesting, rather, that sleep apnea reflects common risk factors such as aging and male sex. The possibility of sleep apnea in PSP patients should, however, be kept in mind by neurologists before they prescribe drugs that may promote sleep apnea, such as benzodiazepines, or apnea-promoting position, such as the supine sleep position.

CONCLUSION

The definitive observation of RBD and RWA in PSP patients, at the same frequency as in PD patients, suggests that RBD is not limited to synucleinopathies but also affects at least 1 type of tauopathy with parkinsonism. Our observation also suggests that RBD is dependent on the site of the lesion rather than on the type of pathologic neuronal inclusions. In addition, some patients suffer from excessive daytime sleepiness that may be caused by a primary PSP-related hypersomnia.

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24. Rechtschaffen A, Kales A. A Manual of Standardized Terminology,


PROVIGIL—the first and only wake-promoting agent—is indicated to improve wakefulness in patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea/hypopnea syndrome (OSAHS), and shift work sleep disorder.

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There was no evidence of tumorigenesis associated with PROVIGIL administration in these studies, but because the pharmacokinetics of PROVIGIL may be altered by CYP3A4 inducers (eg, carbamazepine, phenobarbital, rifampin) or inhibitors of CYP3A4 (eg, ketoconazole, itraconazole) could alter the metabolism of some tricyclic antidepressants, a reduction in tricyclic dose may be needed. PROVIGIL may elevate tricyclics in this patient subset. A reduction in tricyclic dose may be needed. PROVIGIL should be administered cautiously to patients taking tricyclic antidepressants for the potential to increase tricyclic plasma levels.

AUC0-24

Coadministration of a single dose of clomipramine 50 mg with PROVIGIL 200 mg/day did not affect the pharmacokinetics of PROVIGIL, but resulted in decreased absorption of clomipramine by approximately 1 hour.

From post-marketing experience, there have been no reports of fatal overdoses involving PROVIGIL alone (doses up to 1000 mg/day) or in combination with other CNS stimulants. Overdoses, including accidental ingestion/overdose or intentional overdose, have been reported in adults and children. The child remained stable. The symptoms associated with overdose in children were

In human hepatocytes, PROVIGIL produced a dose-related suppression of CYP2C9 activity suggesting a potential for increased serious adverse events in patients with abnormal levels of sleepiness who take PROVIGIL. Patients should be advised about the availability of a patient information leaflet, and they should be advised to exercise discretion when driving or operating machines requiring a high degree of psychomotor activity. Patients should be advised to avoid driving or any other potentially dangerous activities. Procerin should also be aware that patients may not acknowledge sleepiness or drowsiness until directly questioned about drowsiness or sleepiness during specific activities.

In human liver microsomes, PROVIGIL and modafinil sulfone reversibly inhibited CYP2C19. Both compounds combined could produce sustained partial effect in animals. Drugs primarily eliminated via CYP3A9 metabolism, such as demerol, pemoline, propoxyphene, or S-citalopram (S-citalopram may be metabolized by CYP3A9) may be affected by PROVIGIL. In clinical trials, a total of 151 protocol-specified doses of PROVIGIL (up to 1000 mg/day) have been administered to 32 subjects, including 13 subjects who received a single dose of PROVIGIL. In clinical trials, PROVIGIL has been found to be generally well tolerated and most adverse experiences were mild to moderate.

The most commonly observed adverse events (AEs) associated with the use of PROVIGIL were headache and sleepiness, which were at least 1 dose of PROVIGIL. In clinical trials, PROVIGIL has been found to be generally well tolerated and most adverse experiences were mild to moderate.