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Pramipexole-Induced Somnolence and Episodes of Daytime Sleep

*†Robert A. Hauser, MD, *Lisa Gauger, BA, ‡W. McDowell Anderson, MD, and *Theresa A. Zesiewicz, MD

*Departments of *Neurology, †Pharmacology and Experimental Therapeutics, and ‡Medicine, University of South Florida, Tampa General Hospital, Tampa, Florida, U.S.A.*

Summary: Pramipexole is a non-ergot dopamine agonist used to treat Parkinson's disease (PD). Because of concern regarding driving safety, we evaluated the incidence and nature of somnolence experienced by patients receiving pramipexole in clinical trials at our center. A retrospective chart review was performed and structured interviews were conducted with patients who had reported moderate or severe somnolence. In addition, two patients underwent polysomnography (PSG) and multiple sleep latency tests (MSLT) while on and 2 weeks after discontinuation of pramipexole. Forty patients with PD participating in pramipexole clinical trials were identified. In the double-blind phases of the studies, 22 patients were randomized to pramipexole and 18 were randomized to placebo. Six patients assigned to pramipexole reported somnolence as an adverse event (1 moderate, 5 mild) compared with two patients assigned to placebo (1 severe, 1 moderate; $p = 0.19$, one-tailed Fisher's exact test). Thirty-seven patients participated in open-label extension studies. Twenty-one (57%) reported somnolence as an adverse event. Eleven (30%) patients reported moderate somnolence and three (8%) patients reported severe somnolence. For patients with moderate or severe somnolence, the onset of worst-reported somnolence occurred at a mean (± standard error) pramipexole dose of 4.0 ± 0.4 mg (range, 0.75–4.5 mg) per day. Patients had been taking pramipexole for a total of 10.0 ± 1.5 months (range, .03–22 mos) and at their maximal dose for 6.7 ± 1.5 months (range, .03–20 mos). During structured interviews with 12 of the 14 patients reporting moderate or severe somnolence, seven reported falling asleep while driving and two reported minor motor vehicle accidents caused by falling asleep. Most patients reported relatively continuous drowsiness that led to falling asleep without acute warning during periods of inactivity. Three patients reported discreet waves of irresistible sleepiness heralded by prodromal symptoms occurring against a background of normal wakefulness. MSLT in two of these patients revealed decreased latency to sleep without early onset of rapid eye movements. Sleep latency normalized after withdrawal of pramipexole. Intensive patient education is necessary to prevent motor vehicle accidents in patients taking pramipexole. We recommend that patients who are experiencing generalized drowsiness and falling asleep during periods of inactivity be instructed not to drive because these patients do fall asleep without acute warning. Somnolence usually resolves with pramipexole dose reduction or discontinuation. Patients should also be alerted to pull over and stop driving immediately if they feel a wave of sleepiness coming on. Patient education and compliance are critical to maximize safety. **Key Words:** Pramipexole—Somnolence—Parkinson's disease—Driving—Sleep—Polysomnography.

Pramipexole is a non-ergot dopamine agonist with strong specificity for D2/D3 receptors.[1,2] It is effective as monotherapy in early Parkinson's disease (PD) and as an adjunct to levodopa/carbidopa in later disease. Frucht et al.[3] recently described sleep attacks causing motor vehicle accidents in eight patients with PD who were taking pramipexole and one who was taking ropinirole. An important limitation of this report is that the incidence of such events cannot be determined because the size of the at-risk population being evaluated (denominator) is unknown.

We too were struck by the apparent high incidence of pramipexole-induced somnolence and the sudden irresistible waves of sleepiness experienced by some patients.[4] To determine the incidence of somnolence in patients taking pramipexole, we performed a retrospective chart review of patients participating in pramipexole clinical trials at our center. Because these studies were

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Address correspondence and reprint requests to Robert A. Hauser, MD, Parkinson's Disease and Movement Disorders Center, University of South Florida, 4 Columbia Drive, Suite 410, Tampa, FL 33606, U.S.A.

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completed prior to the report of Frucht et al.,[3] there should be no bias in ascertainment related to the heightened awareness it generated. Because there is concern as to whether it is safe for patients taking pramipexole to drive, we conducted structured interviews with patients who had reported moderate or severe somnolence as an adverse event. We sought to assess specifically whether patients fell asleep while driving, whether falling asleep caused motor vehicle accidents, and whether patients had warning that they were at risk of falling asleep while driving. The clinical resemblance to narcolepsy prompted us to evaluate patients who were experiencing sudden irresistible episodes of sleepiness with polysomnography (PSG) and multiple sleep latency tests (MSLTs) while on and then after withdrawal of pramipexole.

METHODS

A retrospective chart review of patients with PD who were participating in pramipexole clinical trials at our center was undertaken. Three separate trials were identified. One trial was a 10-week monotherapy tolerability study in which patients were randomized to placebo or pramipexole in doses escalating to 1.5, 3.0, 4.5, or 6 mg per day.[5] Another trial was a 36-week placebo-controlled safety and efficacy study of pramipexole in doses up to 4.5 mg per day as monotherapy in early PD. The third trial was a 24-week, placebo-controlled safety and efficacy study of pramipexole in doses up to 4.5 mg per day as an adjunct to levodopa/carbidopa in patients who were experiencing motor fluctuations. Each study was followed by an open-label extension. The studies have been completed and the placebo-controlled phases have been unblinded.

An investigator not involved in these studies (T.A.Z.) performed a chart review to determine the incidence of somnolence and episodes of irresistible sleepiness in this population. The reviewer identified somnolence (sleepiness, drowsiness) as an adverse event reported on case report forms and noted its severity. She also reviewed study visit notes to evaluate the description of the somnolence and identified those patients who reported episodes of irresistible sleepiness. Pramipexole doses and the duration of therapy at the onset of worst-reported somnolence and at the onset of episodes of irresistible sleepiness were recorded. The incidence of somnolence during the double-blind portions of the studies was assessed and compared between pramipexole and placebo groups using Fisher's exact test. The incidence, severity, and timing of somnolence during the open-label extension studies were then assessed. A comparison of the incidence of moderate or severe somnolence according to gender and levodopa use was performed using Fisher's exact test. A comparison of age and disease duration in patients experiencing moderate or severe somnolence to those who did not was performed using a Mann-Whitney U-test.

Another investigator (R.A.H.) conducted structured interviews with those patients who had reported moderate or severe somnolence as an adverse event while receiving pramipexole. These interviews were conducted shortly after publication of the report by Frucht et al.[3] Patients were asked whether they experienced continuous drowsiness or discreet episodes of sleepiness, whether they fell asleep in inappropriate situations including driving, if they had caused a motor vehicle accident by falling asleep, and whether they experienced a consistent warning or prodrome before falling asleep.

Patients who reported moderate or severe somnolence while receiving pramipexole were offered sleep evaluations including PSG and MSLT. Four episodes to sleep were evaluated for each MSLT. Following these tests, pramipexole was withdrawn while other medications were continued unchanged. Sleep tests were repeated 2 weeks after pramipexole withdrawal. Quantitative results of the sleep tests were compared for patients while on and then after withdrawal of pramipexole using a Wilcoxon signed rank test.

RESULTS

Forty patients with PD who were participating in pramipexole clinical trials were identified. At study entry, patients had a mean (± standard error) age of 61.0 ± 1.6 years and a mean disease duration of 3.4 ± 0.4 years. Twenty-two (55%) were men. Thirteen patients were taking levodopa at a mean dose of 530.8 ± 63.2 mg (range, 300—950 mg) per day.

In the double-blind phases of the studies, 22 patients were randomized to pramipexole and 18 were randomized to placebo. The mean maximal dose for patients receiving pramipexole was 4.4 ± .3 mg (range, 1.5–6.0 mg) per day. Six patients assigned to pramipexole reported somnolence as an adverse event (1 moderate, 5 mild) compared with two patients assigned to placebo (1 severe, 1 moderate). The incidence of somnolence was not statistically different between groups ($p = 0.19$, one-tailed Fisher's exact test). Three patients withdrew from the studies during the double-blind phases, two on placebo (lack of efficacy, lost to follow up) and one on pramipexole (leg edema). No patient withdrew because of somnolence.

Thirty-seven patients participated in open-label extension studies. For these patients, total pramipexole use,

including both double-blind and extension phases, was 1508 patient-months.

During the open-label extension phases, 21 (57%) patients reported somnolence as an adverse event while receiving pramipexole. Eleven (30%) patients reported moderate somnolence and three (8%) patients reported severe somnolence (Table 1). For patients with moderate or severe somnolence, the onset of worst-reported som-

TABLE 1. *Demographics, severity of somnolence, and medications for 14 patients, and results of structured interviews for 12 patients, with moderate or severe somnolence in pramipexole clinical trials*

Patient no.	1	2	3	4*	5	6	7
Age at entry (yrs)	50	46	66	59	70	64	67
Gender	F	F	M	M	M	F	M
Disease duration at entry (yrs)	1	3	2	2	1	2	4
Pramipexole dose at onset worst somnolence	4.5	4.5	4.5	4.5	4.5	4.5	4.5
Levodopa dose at onset worst somnolence	—	300	—	—	—	—	50
Maximum severity of somnolence	Moderate	Severe	Severe	Moderate	Moderate	Moderate	Moderate
Continuous drowsiness?	No	No	No	No?	Yes	Yes	Yes
Episodes of sleepiness?	Yes	Yes	Yes	No	No	No	No
Consistent acute warning or prodrome?	Yes Yawning, drowsiness	Yes Yawning, tearing	Yes Yawning, blinking	?	No	No	No
Fell asleep in inappropriate situations?	Yes	Yes	Yes	No	Yes	Yes	Yes
Fell asleep while driving?	Yes	Yes	Yes	No	Yes	Yes	No
Car accidents caused by falling asleep?	No	No	No	No	Yes	No	No
Resolution?	Improved on lower dose	Resolved on discontinuation	Improved on lower dose	Persists with discontinuation	Resolved with amantadine	Resolved on discontinuation	Persists on medication
Concomitant neuropsych medications, daily dose	10 mg selegiline 50 mg sertraline 10 mg zolpidem prn§	— 4 mg trihexyphenidyl	10 mg selegiline	10 mg selegiline	—	10 mg selegiline	10 mg selegiline 6 mg benztropine
Other medications, daily dose	2 mg estradiol	10 mg fosinopril 30 mg nifedipine	180 mg verapamil 50 mg atenolol 325 mg aspirin	5 mg enlapril	20 mg propranolol 2 mg terazosin	40 mg fluvastatin 325 mg aspirin	

Patient no.	8	9	10†	11	12	13	14
Age at entry (yrs)	44	55	74	44	73	65	71
Gender	F	M	M	M	M	M	M
Disease duration at entry (yrs)	2	8	9	4	3	9	3
Pramipexole dose at onset worst somnolence	4.5	4.5	0.75	4.5	4.5	0.75	4.5
Levodopa dose at onset worst somnolence	—	250	750	400	—	700	—
Maximum severity of somnolence	Moderate	Moderate	Moderate	Severe	Moderate	Moderate	Moderate
Continuous drowsiness?	Yes	Yes	Yes	Yes	No	Unk	Unk
Episodes of sleepiness?	No	No	No	No	No‡	Unk	Unk
Consistent acute warning or prodrome?	N/A	No	?	No	Yes Drowsiness	Unk	Unk
Fell asleep in inappropriate situations?	No	Yes	No	Yes	Yes	Unk	Unk
Fell asleep while driving?	No	Yes	No	Yes	No	Unk	Unk
Car accidents caused by falling asleep?	No	No	No	Yes	No	Unk	Unk
Resolution?	Resolved on discontinuation	Persists on medication	Persisted with discontinuation	Improved on lower dose	Improved on lower dose	Unk	Unk
Concomitant neuropsych medications, daily dose	10 mg selegiline	10 mg selegiline 200 mg amantadine	—	— 100 mg sertraline	10 mg selegiline 7.5 clorazepate prn‖	10 mg selegiline 0.25 mg alprazolam	—
Other medications, daily dose		325 mg aspirin		300 mg nizatidine	5 mg lisinopril		

? = unsure; N/A, not applicable; unk, unknown.
* Patient demented, history from spouse.
† Patient deceased, history from spouse.
‡ Patient denied continuous drowsiness but fell asleep during periods of relative inactivity.
§ Approximatley one every other month.
‖ Approximately one every 2 weeks.

nolence occurred at a mean pramipexole dose of 4.0 ± 0.4 mg (range, 0.75–4.5 mg) per day. These patients had been taking pramipexole for a total of 10.0 ± 1.5 months (range, .03–22 mos) and at their maximal dose for 6.7 ± 1.5 months (range, .03–20 mos) at the onset of worst-reported somnolence.

There was no difference in the incidence of moderate or severe somnolence based on gender ($p = 0.31$), levodopa use ($p = 1.0$), or selegiline use ($p = 1.0$, two-tailed Fisher's exact tests). There was also no difference in age (60.6 ± 2.9 vs 61.9 ± 2.1, $p = 0.83$) or disease duration (3.8 ± .7 vs 3.3 ± .5, $p = 0.80$, Mann-Whitney U-test) comparing patients experiencing moderate or severe somnolence with those who did not.

Additional concomitant medications are presented in Table 1. We did not identify a temporal relationship between the onset of worst-reported somnolence and the introduction of or a change in concomitant medications except in one case. This patient (no. 7) was receiving 4.5 mg pramipexole, 10 mg selegiline, and 6 mg benztropine per day. He experienced an increase in severity of somnolence from mild to moderate with the introduction of levodopa/carbidopa beginning at a daily dose of 50 mg and escalating to 250 mg. Somnolence later resolved on discontinuation of benztropine despite continuing other medications unchanged.

Five patients reported episodes of irresistible sleepiness during clinical trials. All had reported somnolence (2 moderate, 3 severe) as an adverse event. Patients experiencing episodes of irresistible sleepiness had a mean age of 56.4 ± 5.5 years and a mean disease duration of 3.2 ± 0.7 years. Three (60%) were men. Two of these patients were also taking 150 and 400 mg levodopa/carbidopa per day at the time. The onset of episodes of irresistible sleepiness occurred at a mean pramipexole dose of 4.5 ± 0.0 mg per day. Patients had been taking pramipexole for a total of 10.4 ± 1.7 months (range, 5–15 mos) months and at their maximal dose for 8.5 ± 1.7 months (range, 3–13 mos).

We were able to conduct structured interviews with 12 of the 14 patients who reported moderate or severe somnolence (Table 1). These interviews took place a mean of 22.9 ± 4.7 months (range, 2–55 mos) after patients had completed the studies. None of the patients had a known sleep disorder. Nine patients reported falling asleep in inappropriate situations and seven reported falling asleep while driving. Seven of the patients reported relatively continuous drowsiness that led to falling asleep during periods of inactivity. Five of these patients reported that they did not consistently experience an acute warning that they were about to fall asleep. Three patients reported discreet waves of irresistible sleepiness occurring against a background of normal wakefulness. All three consistently experienced prodromal symptoms that evolved over several minutes. Symptoms included the emergence of subjective drowsiness usually accompanied by yawning, eye blinking, or tearing. One patient denied continuous drowsiness in that he felt fully awake while engaged in activities but fell asleep during periods of relative inactivity. These included episodes of falling asleep while eating alone and during group conversation. One patient reported no background drowsiness or waves of sleepiness but he did not fall asleep at inappropriate times. For most patients, somnolence improved with dose reduction or discontinuation. One patient reported resolution of somnolence with the introduction of amantadine. One patient (no. 2) who noted severe somnolence and episodes of irresistible sleepiness on 4.5 mg pramipexole and 300 mg levodopa/carbidopa per day noted resolution of somnolence with pramipexole discontinuation. She was later placed on pergolide and while receiving 3 mg pergolide and 600 mg levodopa/carbidopa per day she experienced occasional episodes of mild sleepiness although somnolence was still markedly improved.

Two patients (nos. 5 and 11) reported motor vehicle accidents caused by falling asleep. Both had relatively continuous drowsiness and would fall asleep during times of inactivity. While stopped at a traffic signal, each dozed off and rolled into the vehicle waiting in front of him. In both cases the patient was driving alone in the early afternoon (noon and 1:30 PM) and the accident was unwitnessed. Both were wearing seatbelts and no one was injured. Neither patient was sleep-deprived nor had taken a sedative-hypnotic medication the night before.

Two women (nos. 1 and 2), 48 and 51 years old, underwent sleep evaluations while on and 2 weeks after discontinuation of pramipexole. Each reported discreet, irresistible waves of sleepiness superimposed on a background of normal wakefulness. Both were taking 4.5 mg pramipexole per day and one (no. 2) was also taking 300 mg levodopa per day. Subjective somnolence improved after pramipexole withdrawal. PSG revealed decreased but normal sleep efficiency (95% vs 87%) and increased but unchanged arousal index (17 vs 18 events per hr). Mean sleep latency (normal, >10 mins) increased significantly (6.8 vs 18.0 mins, $p < 0.05$, Wilcoxon signed rank test). No sleep-onset rapid eye movements (REM) were seen. There was no evidence of medication-induced narcolepsy, sleep apnea, or other sleep disruptions.

DISCUSSION

Somnolence is a common side effect of pramipexole. In a 10-week safety and efficacy study of pramipexole as monotherapy in early PD, somnolence was the most fre-

quently reported adverse event, occurring in 30% to 31.5% of patients assigned to 3.0 to 6.0 mg pramipexole per day.[5] In contrast, somnolence occurred in only 13.7% of patients assigned to placebo and 16.7% of patients assigned to 1.5 mg pramipexole per day. This suggests that somnolence is dose-related. Another trial of pramipexole in mild to moderate de novo PD patients also found a higher incidence of somnolence in the pramipexole-treated group (18.3%, mean daily dose 3.8 mg per day) than the placebo group (8.8%, $p = 0.015$).[6] Some studies did not find somnolence to be a common adverse event.[7,8]

Other dopamine agonists can also cause somnolence. Ropinirole is a non-ergot dopamine agonist with a receptor binding profile similar to pramipexole. In a 6-month study of ropinirole as monotherapy in early disease, 36% of ropinirole-treated patients experienced somnolence compared with 4.8% in the placebo group.[9] For both ropinirole and pramipexole the reported incidence of somnolence is lower in trials of advanced PD than early PD.[8,10] In a 6-month study of pergolide as adjunctive therapy in advanced PD, somnolence occurred in 10% of pergolide-treated patients compared with 3% in the placebo group.[11] It is not currently possible to determine if the incidence of somnolence differs significantly among dopamine agonists. Differences across studies may reflect the duration of the study, the doses used, the study population under evaluation, or concomitant medications. Even for a given agonist, the reported incidence of somnolence varies greatly among studies for reasons that are not clear.[4–10,12–15] It is also not known whether the character or nature of the somnolence differs among agonists.

At our center, six of 22 patients (27%) receiving pramipexole during double-blind studies reported somnolence. However, this difference was not statistically different from placebo and, in fact, placebo patients reported a worse severity of somnolence. Thus, the double-blind portions of these studies did not suggest that somnolence was a major side effect.

In contrast, in open-label extension studies, 21 of 37 patients (57%) reported somnolence as an adverse event and 14 of 37 patients (38%) reported moderate or severe somnolence. It is not clear why the incidence of somnolence we observed is higher than that reported in previously published studies. This may be the result of random chance, differences in our study population demographics, concomitant medications, reporting tendencies, length of studies, pramipexole doses, or our rigor in identifying adverse events in general or somnolence in particular. The incidence data we report is derived directly from case report forms and was not affected by recall bias or influenced by the report of Frucht et al.[3]

Because there were no comparison placebo groups in the long-term extension studies, we do not know what proportion of the somnolence we observed is directly related to the use of pramipexole. We also do not know how the observed incidence of somnolence would compare with that associated with other antiparkinsonian medications.

We found that patients who experienced moderate or severe somnolence in the open-label extension studies had been taking pramipexole for a total of 10 months and at their maximal dose for over 6 months at the onset of worst-reported somnolence. This suggests that somnolence may be a "delayed" side effect of pramipexole and may explain the low incidence of moderate and severe somnolence observed during the double-blind phases of the trials.

We were able to conduct structured interviews with 12 of the 14 patients reporting moderate or severe somnolence. These interviews were a relatively long time from the completion of the studies and patients' responses may be subject to recall bias or may have been influenced by the report of Frucht et al.[3] However, patients did not seem to have difficulty recalling their experience in the studies and seven patients were still receiving pramipexole at the time of the interviews.

Seven patients reported falling asleep while driving and two reported that they had caused a motor vehicle accident by falling asleep at the wheel. Both accidents were minor and were caused by falling asleep while stopped at a traffic signal.

Patients generally provided one of two descriptions for their excessive daytime sleepiness (EDS). Most patients (seven of 12) reported that they were drowsy all of the time and would fall asleep during periods of inactivity. Most of these (five of seven) reported that they did not consistently experience an acute warning before falling asleep. This type of sleepiness caused the two motor vehicle accidents resulting from falling asleep in this population. In contrast, other patients (three of 12) reported discreet waves of irresistible sleepiness occurring against a background of normal wakefulness. All three of these individuals reported that they experienced consistent prodromal symptoms of sufficient duration to avoid dangerous situations. If driving, they would pull over to the side of the road. Whether these two types of EDS are distinct or a continuum remains to be determined. Our experience indicates that distinctions regarding characteristics of EDS were not made when recording adverse events in clinical trials.

Sleep tests performed in two patients who reported irresistible waves of sleepiness on what they felt was a normal background of wakefulness revealed early onset of sleep but not early onset of REM. This suggests that pramipexole can induce central hypersomnolence by a mechanism distinct from narcolepsy. Early onset of sleep on MSLT is thought to represent objective evidence of sleepiness and suggests that these patients' background wakefulness was not normal. This might indicate that the somnolence they experienced was similar to those patients who described generalized drowsiness and falling asleep during periods of inactivity. However, "sleep attacks" were not captured during these evaluations. Electroencephalographic monitoring during a sleep attack is required for a more definitive conclusion.

Improvement observed in time to sleep onset in two patients with the discontinuation of pramipexole is consistent with our clinical observation that somnolence usually improved with medication dose reduction or discontinuation. We speculate that patients who experienced persistent somnolence despite discontinuation of pramipexole have a different etiology for their somnolence.

Intensive patient education is necessary to prevent motor vehicle accidents in patients taking pramipexole. Our patients had warning signs that indicated that they were at risk for falling asleep in potentially dangerous situations. Patients who fell asleep while driving either experienced generalized drowsiness or waves of sleepiness heralded by prodromal symptoms. We recommend that patients who are experiencing generalized drowsiness and falling asleep during periods of inactivity be instructed not to drive because these patients do fall asleep without acute warning. Somnolence usually resolves with pramipexole dose reduction or discontinuation. Patients should also be alerted to pull over and stop driving immediately if they feel a wave of sleepiness coming on. They should be instructed that somnolence can begin after many months on a stable medication dose. Patient education and compliance are critical to maximize safety.

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