Research Article

PRAMIPEXOLE IN TREATMENT-RESISTANT DEPRESSION: AN EXTENDED FOLLOW-UP

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We evaluated the long-term antidepressant safety and response of adjunctive pramipexole, a D2–D3 dopamine agonist, in the course of drug-resistant depression. Twenty-three patients with treatment-resistant major depressive episode (MDE) were followed up after a 16-week pramipexole add-on trial. Pramipexole was added to current treatment with TCA or SSRI, at increasing doses from 0.375–1.500 mg/day. The LIFE scale was administered at baseline of the acute trial, at Weeks 16, 32, and 48. Patients were analyzed for sustained remission (score = < 2 at LIFE for at least 8 weeks) and recurrence (after remission score > = 3 at LIFE for at least 2 weeks) of depression. Of 23 patients, 12 had major depression and 11 had bipolar depression (16 women; mean age = 52.8 years). Mean age of onset and median duration of current MDE were 35.1 years and 6 months, respectively; all subjects had at least two prior MDEs. Mean pramipexole dose was 0.990 mg/day. Median duration of follow-up was 28 weeks. Mean baseline MADRS and CGI-S scores were 33.7 ± 8.4 (sd) and 4.6 ± 0.8, respectively. Median time to sustained remission from baseline was 10 weeks and overall 60.9% (14/23) of subjects recovered within Week 22. Recurrence of depression occurred in 35.7% (5/14) of remitters after Week 24 and within Week 28 from remission. Although there were no sleep attacks, two cases of hypomania and one case of psychotic mania occurred at Weeks 22, 24, and 30, respectively. Pramipexole augmentation of antidepressant treatment was relatively safe and presumably effective in the long-term course of treatment resistant depression. Depression and Anxiety 20:131–138, 2004.

Key words: *mood disorders; dopamine agonists; treatment outcome; adverse effects; investigational therapies*

INTRODUCTION

Treatment resistant depression (TRD) is defined as a major depressive episode not responding to adequate antidepressant treatment [Nierenberg and De Cecco, 2001]. Multiple strategies of acute treatment for resistant depression have been investigated in clinical trials, typically averaging 8–16 weeks [Fava, 2001]. Data on the longer-term strategies of continuation and maintenance therapy in patients with TRD is much more sparse.

We reported previously a 68% response rate to pramipexole augmentation in patients with TRD treated for up to 16 weeks [Lattanzi et al., 2002]. In the present study, we report rates of sustained remission and depressive recurrence with pramipexole, in TRD patients treated up to 1 year.

Pramipexole is a non-ergot D2–D3 dopamine agonist, prescribed currently in Parkinson disease (PD) and proposed recently for the treatment of depressed patients. Pramipexole was found to be

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effective in major depressive disorder patients in an open study [Szegedi et al., 1997] and a double blind placebo-controlled study [Corrigan et al., 2000]. Two uncontrolled studies have shown a response to pramipexole augmentation in treatment-resistant depression [Lattanzi et al., 2002; Sporn et al., 2000]. In one retrospective study conducted on bipolar-II depressed patients the augmentation was also found effective but short-lasting [Perugi et al., 2001]. The efficacy of pramipexole in the treatment of bipolar depression was confirmed recently by a placebo-controlled study [Goldberg et al., 2004]. Pramipexole presented good tolerability overall in depressed patients, even in combination with antidepressants [Lattanzi et al., 2002].

PATIENTS AND METHODS

Our study is a prospective naturalistic follow-up of resistant depressed patients treated with pramipexole augmentation. The follow-up was conducted from August 1999 to May 2001 at the Department of Psychiatry of the University of Pisa in Italy, a tertiary care service recruiting patients nationwide.

Adult patients with a Major Depressive Episode (MDE-DSM IV criteria) [American Psychiatric Association, 2000] resistant to antidepressants were recruited. Antidepressant resistance was defined as non-response to at least one trial (at least 4 weeks) with one antidepressant given at therapeutic dosage (e.g., paroxetine, 20 mg/day) [Thase and Rush, 1995]. For the purpose of classification, we considered the combination as one regimen/trial when different drugs were prescribed in combination. The adequacy of prior medication and compliance with prior medication were assessed by interviewing both patients and relatives. The latter was then confirmed by the secondary care psychiatrist. Patients with psychotic mood-incongruent features were excluded, as well as patients with substance use disorder and serious suicide risk. Exclusion criteria also comprised neurological and other general medical conditions that were not stabilized or controlled with adequate medication, as well as concurrent pharmacological treatments that could cause depression or potentially undermine treatment-response. Complete blood count, routine chemistries, and urinanalysis were carried out at baseline to exclude physical diseases that could be responsible for resistance (e.g., anemia, thyroid dysfunction, and neoplasias). Axis-I comorbidity was not an exclusion criterion. Thirty-one patients fulfilled these criteria and were consecutively enrolled in the acute phase trial with pramipexole. The latter has been described in detail elsewhere [Lattanzi et al., 2002].

For the purpose of the present study on the extended outcome of treatment-resistant depression the sample was then restricted to those patients with history of definitive non-response to antidepressants. For example, patients with low initial score (below 18) at the MADRS (Montgomery-Asberg Depression Rating Scale) [Montgomery, 1979] that were likely to present with at least a partial response to previous treatments were excluded. We also excluded those subjects who were resistant to therapeutical but low dosages of antidepressants (e.g., citalopram 20 mg/day). Selection criteria for the present sample were more restrictive for the definition of treatment resistance, as compared to the acute phase study. Patients had to be at least 18 years old and give written informed consent to be enrolled in the study.

All patients were admitted to our inpatient unit for treatment resistant depression (TRD) and were followed after discharge either in our outpatient unit or in secondary care. The treating clinicians, who prescribed treatment during the hospitalization or after discharge, were not directly involved in the study. During the acute phase of treatment, pramipexole was added to the current antidepressant regimen (SSRIs or TCAs) starting with 0.375 mg/day the first week, 0.75 mg/day the second week, and subsequently increased up to a maximal dose of 1.5 mg/day. Doses were then adjusted in individual cases. Severity of depression was assessed at baseline of pramipexole augmentation by the administration of the MADRS and CGI-S scales (Clinical Global Impression-Severity) [Guy, 1976]. The clinical course of depression including treatment, remission, relapse, as well as the occurrence of further depressive episodes (manic and hypomanic switches) were explored by patient interview at baseline (of the acute trial), Week 16, Week 32, and Week 48. Residents in psychiatry with at least 2 years of clinical experience carried out the interviews. In limited cases interviews were made by phone call. Relatives and treating clinicians were consulted and available clinical charts reviewed. Data were first recorded in the LIFE (Longitudinal Interval Follow-Up Evaluation) scale, which tracks the course of depressive and (hypo-)manic episodes as well as of other comorbid disorders. Severity of Axis-I disorders was scored from 1 to 6 overtime (the higher the score the greater the severity) by LIFE semi-structured interview [Keller et al., 1982]. Data were then entered in a data file. Although no inter-rater reliability was estimated for the LIFE, raters were trained to use the instrument by two senior psychiatrists (L.L.; S.P.) and supervised during several rating sessions. An additional form was used to record reasons of pramipexole discontinuation and to screen for the occurrence of sleep-attacks, defined as sudden and irresistible somnolence when performing specific tasks [Frucht et al., 1999]. Sustained remission was defined as at least 8 weeks of no depressive symptoms or just residual symptoms (LIFE score for depression ≤ 2). Relapse was considered a worsening of depressive symptomatology (LIFE score for depression ≥ 3 for at least 2 weeks) after short-lasting benefit of treatment (LIFE score ≤ 2 for < 8 weeks), according to the criteria for single depressive episode in the DSM-IV [American Psychiatric Association, 2000]

Recurrence was considered the occurrence of depressive symptomatology (life score for depression ≥ 3 for at least 2 weeks) after sustained remission had occurred (at least 8 weeks), and it was regarded as a new episode of depression. New episodes could be minor or major depressive episodes, according to DSM-IV criteria, and LIFE scores were respectively 3 in the first case and at least 4 in the second.

Time to sustained remission and time to recurrence of depression from the outset of remission were estimated by a Kaplan Meier Survival Curve. Patients were censored when either loss to follow-up or pramipexole discontinuation occurred. Rates of remission and recurrence of depression were calculated on intent-to-treat basis at several time points. Similarly, we estimated rates of manic/hypomanic switches. We also wanted to explore a putative dose-related effect of pramipexole on early remission of depression. Because of the observational nature of the study, it is likely that clinicians increased pramipexole doses overtime in poor responders. Therefore, for the analysis, we decided to consider pramipexole dose at the end of the first week as the principal independent variable and also early (at Week 2) but sustained remission as the dependent variable. Early remission was chosen to minimize the occurrence of changes in concomitant treatments, which may affect the correlation. A logistic regression analysis was carried out including as covariates, baseline severity of depression, application of electro-convulsive therapy (within Week 2), and age of onset of the affective illness. Statistical tests were two-tailed and significance was set at an α level of .05. All analyses were performed using SPSS 1.0 software.

RESULTS

PATIENTS

Twenty-three patients entered the study (16 women; mean age 52.8 ± 12.5 (*sd*) years). The current episode of major depression had lasted in average 6 months (median) at the admission in our psychiatric ward, and the mean age of onset for the affective disorder was 35.1 years. The majority of patients had experienced numerous depressive episodes and half of them had more than five recurrences. Course of illness as assessed by first clinical interview was bipolar in 11 of 23 patients according to DSM-IV criteria. Of the 11 patients, the majority were bipolar-II ($n = 9$) and only a few ($n = 2$) bipolar-I. Severity of depression for current episode was shown by a mean total score of MADRS 33.7 ± 8.4 (*sd*) and a CGI-S score (Clinical Global Impression-Severity) 4.6 ± 0.8 (*sd*) (Table 1). In the current episode, four patients (17%) had already been prescribed an SSRI, four patients a TCA, and 12 patients (52%) had failed with both classes of antidepressants. Three patients failed to respond to venlafaxine, mirtazapine, and tranylcypromine, respectively. In terms of number of failed treatments during the current episode, most of subjects had one ($n = 12$), the remaining subjects either two ($n = 9$) or three ($n = 2$).

TABLE 1. Demographic, diagnostic and baseline characteristics of patients

Patient characteristic	
Gender	
Female	16 (69.6)
Male	7 (30.4)
Age (yr)	52.8 ± 12.5 (36–77)
Age of onset (yr)	35.1 ± 16.0 (14–76)
Previous MDEs	
n = 2	4 (17.4)
n = 3–5	7 (30.4)
n > 5	12 (52.2)
Diagnosis	
Major Depressive Disorder	12 (52.2)
Bipolar I Disorder	2 (8.7)
Bipolar II Disorder	9 (39.1)
DSM-IV axis-I disorders (lifetime)	
Panic Disorder	8 (34.8)
Obsessive–Compulsive Disorder	6 (26.1)
Social Anxiety Disorder	2 (8.7)
Eating Disorders	2 (8.7)
Overall (at least one disorder)	13 (56.5)
Duration of current MDE, months	15.3 ± 21.4 (2.5–72)
MADRS score	33.7 ± 8.4 (18–56)
CGI-S score	4.6 ± 0.78 (3–6)

MDE, major depressive episode; MADRS, Montgomery-Asberg Depression Rating Scale; CGI-S, Clinical Global Impression-Severity.

TREATMENT

All 23 patients received pramipexole in their acute phase of treatment as an augmentation therapy and all but three patients continued pramipexole up to and after discharge from the psychiatric ward. Mean maximal dose was 0.99 ± 0.3 (*sd*) mg/day (range = 0.75–1.5). Median survival on pramipexole was 28 weeks and overall 8 of 23 patients had at least 36 weeks of follow-up. At discharge, 11 of 20 patients received at least two antidepressants at therapeutical doses in addition to pramipexole. Five of twenty patients received anticonvulsant mood stabilizers. Lithium was administered to three patients, and thyroid hormone was administered to one patient. During the whole study, prescription patterns of mood stabilizers among bipolar subjects ($n = 11$) were as it follows: three patients received lithium (Patients 7, 11, 14; one of them in combination with Topiramate), two patients received carbamazepine (Patients 3, 6; one of them with Topiramate) and one patient was prescribed gabapentin monotherapy (Patient 23). Six of the study patients had electro-convulsive therapy (ECT) during pramipexole acute phase. During the follow-up, most patients continued and sometimes potentiated their concomitant antidepressant treatment. Few patients

reduced gradually the doses of their antidepressants remaining within therapeutical ranges. During follow-up, five patients experienced either dose increase of concomitant antidepressants or add/switch of new antidepressant drugs (Table 2).

OUTCOME

Overall, 14 of 23 patients (60.9%) encountered sustained remission of their major depressive episode during the follow-up with pramipexole (47.8% and 60.9% of subjects remitted within Week 13 and 22, respectively). The median time to sustained remission was 10 weeks. Electro-convulsive therapy, which is potentially the major confounding factor of our results, did not significantly affect rates of remission in our cohort (66.7% versus 58.8%; $\chi^2 = .115$; $df = 1$; $P = .735$). The median time of survival on remission was 28 weeks from the outset of the latter. Overall, 5 of 14 patients (35.7%) experienced the recurrence of either a major or minor depressive episode after Week 24 and within Week 28 from remission. Among bipolar subjects, two patients developed hypomania and psychotic mania at Weeks 24 and 30 of pramipexole treatment, respectively. One subject diagnosed with major depressive disorder encountered switching (hypomania) at Week 22 of pramipexole treatment. Nine patients (39.1%) never reached sustained remission and two of them experienced a transitory improvement of depression with persisting residual symptoms and subsequent relapse of their depressive episode. Five patients never attained the level of "residual symptoms" and some of these latter presented a chronic-like course. Two subjects were lost to follow-up within few weeks from pramipexole augmentation.

There was no correlation, using a multiple logistic regression model, between higher doses of pramipexole at Week 1 (≥ 0.75 mg/day) and early remission, occurring within Week 2 (data not shown).

DROPOUTS AND SAFETY

Of the 23 patients in the study, two were lost to follow-up within a few weeks from enrollment. Three and four additional patients discontinued the study because of lack of improvement and withdrawal of consent, respectively. Five adverse events required pramipexole discontinuation: psychomotor agitation, ataxia, hypomania, impulse dyscontrol, and vomiting (Table 3). Despite monitoring for sleep attacks, defined as sudden and irresistible somnolence when performing specific tasks, none of the subjects reported them.

DISCUSSION

This study on the outcome of resistant depression (TRD) treated with pramipexole presents rates of remission and recurrence that are consistent with existing literature on depression. The study is descriptive in nature and does not provide proof of the efficacy of extended pramipexole augmentation. The relative safety of pramipexole association to antidepressants and mood stabilizers is a relevant finding of the study.

In our cohort of TRD patients, rates of sustained remission seem to be consistent with those reported in previous follow-ups of subjects with major depressive episodes. Despite the resistance to antidepressants, our patients presented a 47.8% rate of sustained remission at Week 13, which is consistent with the range of 45–50% at Week 12 reported in naturalistic studies on depressed (but not treatment-resistant) patients [Keller et al., 1984; Ramana et al., 1995]. Interestingly, our data seem to suggest that prior resistance to antidepressants does not appreciably affect chances of remission. This similarity in the outcome may be due to several factors. Patients with treatment resistant depression in our cohort were typically prescribed antidepressants combinations in addition to pramipexole augmentation and 26% of them were also treated with electro-convulsive therapy. The complex and sometimes aggressive regimens may explain the aforementioned similarity in the outcome. This similarity could depend, at least in part, on response to pramipexole augmentation. Our clinical impression, that study patients had a relevantly better outcome as compared to resistant depressives treated as usual in our clinic, does favor the latter explanation. A third possible reason for the observed similarity in outcomes is inclusion of resistant patients in previous naturalistic studies reporting the outcome of major depressive episodes. Ultimately, the non-chronic nature of depression and the relatively limited number of failed previous trials in our study may explain the somehow benign treatment outcome of the TRD patients.

As concerns recurrences of depression, we decided to take into account both major and minor depressive episodes because even the latter are associated with significant dysfunction and disability [Rapaport and Judd, 1998]. Chances of having a recurrence of depression were 35.7% of cases in between Weeks 24 and 28 from the outset of remission. Similar rates were encountered in the naturalistic follow-ups of major depressives by Week 40 from remission [Keller et al.,1984; Ramana et al., 1995]. Our data may suggest that recurrence in patients with resistance to antidepressants occurs earlier despite complex antidepressant treatment. Nevertheless, our finding could also be an overestimation, resulting from the inclusion of minor depression in the rate of recurrence.

Rates of recurrence in our follow-up are also remarkably higher than those reported in placebo-controlled trials with SSRIs. In fact, the latter typically present a percentage of recurrences ranging from 8–26% of remitters after 28–48 weeks of treatment from remission [Doogan and Caillard, 1992; Montgomery and Dunbar, 1993; Montgomery et al., 1988]. Differ-

TABLE 2. Pramipexole and concomitant psychopharmacological treatments

	Treatment at discharge from ward			First change of treatment			Second change of treatment		
Patient no.	Associations (drugs)	Dose (mg/day)	Period*	Association (drugs)	Dose (mg/day)	Period*	Association (drugs)	Dose (mg/day)	Period*
1	Pramipexole	0.75	3–48						
	Fluoxetine	40	3–48						
	Clomipramine	100	3–16	→	225	17–32	→	150	33–48
				Sertraline	50	28–33			
2	Pramipexole	0.75		Discontinuation before discharge (Week 6)					
	Clomipramine	50	7– NA						
	Trimipramine	75	7– NA						
3	Pramipexole	1.5	5–24						
	Sertraline	200	5–24						
	Imipramine	75	5–17	→	175	18–24			
	Carbamazepine	600	5–24						
4	Pramipexole	1.0	8–16	→	0.75	17–48			
	Clomipramine	75	8–36	→	50	37–48			
	Amitriptyline	150	8–16	→	50	17–48			
5	Pramipexole	1.5	7–48						
	Imipramine	75	7–48						
	Ect	no. 10	2–7						
6	Pramipexole	1.0	5–16	→	0.75	17–36			
	Mirtazapine	30	5–36						
	Thyroid hormone	50	5–31	→	100	32–36			
	Ect	no. 6	4–6	Carbamazepine	300	32–36			
				Topiramate	100	32–36			
7	Pramipexole	0.75	8–48						
	Clomipramine	225	8–48						
	Fluoxetine	60	8–39	→	40	40–48			
	Carbolithium	900	8–39	→	600	40–48			
	Topiramate	100	8–39	→	150	40–48			
8	Pramipexole	0.75	3–48						
	Fluvoxamine	300	3–10	Fluoxetine	40	11–48			
	Nortriptyline	150	3–23	Desipramine	150	24–48			
9	Pramipexole	0.75		Discontinuation before discharge (Week 5)					
	Nortriptiline	75	6– NA						
	Clomipramine	50	6– NA						
	Reboxetine	6	6– NA						
10	Pramipexole	1.0	4– NA	Lost to follow-up (Week 4)					
	Clomipramine	225	4– NA						
	Sertraline	150	4– NA						
	Ect	no. 6	2–4						
11	Pramipexole	0.75	4–10						
	Desipramine	50	4–10						
	Carbolithium	300	4–10						
12	Pramipexole	1.0	5–28						
	Clomipramine	100	5–28						
	Paroxetine	30	5–28						
	Ect	no. 6	2–4						
13	Pramipexole	0.75	2–4	Lost to follow-up (Week 4)					
	Nortriptyline	150	2–4						
	Clomipramine	50	2–4						
	Mirtazapine	30	2–4						
	Carbamazepine	400	2–4						
14	Pramipexole	0.75	1–32	→	0.50	33–48			
	Fluoxetine	40	1–48						
	Carbolithium	300	1–48						
15	Pramipexole	1.0	7–14						
	Nortriptyline	100	7–14						
16	Pramipexole	0.75	2–48						
	Nortriptyline	150	2–48						
	Sertraline	100	2–48						
	Amisulpride	50	2–13						

TABLE 2. (Continued)

	Treatment at discharge from ward			First change of treatment			Second change of treatment		
Patient no.	Associations (drugs)	Dose (mg/day)	Period*	Association (drugs)	Dose (mg/day)	Period*	Association (drugs)	Dose (mg/day)	Period*
17	Pramipexole	1.5	4–16						
18	Pramipexole	0.75		Discontinuation before discharge (Week 3)					
	Paroxetine	60	8– NA						
	Nortriptyline	30	8– NA						
19	Pramipexole	0.75	8–24						
	Citalopram	40	8–24						
	Amantadine	300	8–16						
	Topiramate	250	8–16	→	300	17–24			
	Ect	no. 10	7–11						
20	Pramipexole	1.5	4–43						
	Sertraline	150	4–43						
	Citalopram	40	4–43						
	Nortriptyline	150	4–32						
21	Pramipexole	0.75	4–13						
	Carbolithium	750	4–13						
	Topiramate	50	4–13						
	Amitriptyline	225	4–8						
	Ect	no. 8	4–7						
22	Pramipexole	1.25	5–20						
	Sertraline	100	5–20						
	Clomipramine	75	5–13	→	50	14–20			
23	Pramipexole	0.75	4–48						
	Nortriptyline	30	4–13	→	75	14–41	→	30	42–48
				Gabapentin	400	29–41	→	600	42–48

*The Period given is from start week to stop week.
The first treatment is the combination of drugs at discharge; doses at pharmacological stabilization are reported along with the weeks of treatment. The week during the hospitalization when patients started pramipexole is considered as week zero.

TABLE 3. Dropouts for adverse events and miscellaneous reasons

Adverse event	*N*	Week
Psychomotor agitation	1	3
Ataxia	1	7
Hypomania	1	22
Impulse Dyscontrol	1	26
Vomiting	1	38
Lost of follow-up	2	4; 4
Lack of improvement	3	6; 14; 14
Refusal to continue	4	12; 18; 25; 28

ences are more likely to be due to the methodology used in clinical trials than to a poor prophylactic efficacy of pramipexole. The relatively favorable outcome of patients treated in the long-term clinical trials is probably associated with their strict entry criteria. Usually, remission should occur within few weeks of treatment (i.e., 8 weeks) and sometimes be sustained for up to 12–16 weeks before patients could be randomized to continuation/maintenance therapy [Terra and Montgomery, 1998].

Several methodological caveats prevent a straightforward conclusion concerning the extended response to pramipexole in TRD. First, the lack of a comparison group with either placebo or standard care and the observational/descriptive nature of the study prevent the possibility to control for all potential confounders, hence the assessment of a causal effect. Also, ECT and changes in the concomitant treatments during the acute phase of pramipexole could have influenced the improvement of depressive symptoms that we observed. However, both strategies of treatment seemed to have no relevant impact on acute response as reported elsewhere [Lattanzi et al., 2002]. After discharge from the inpatient unit, at any time during the follow-up, 36% of subjects either significantly increased antidepressant doses or changed their concomitant antidepressants. Nevertheless, these later changes are unlikely to have affected the chances of remission because median time to remission was as early as 10 weeks. The estimation of rates of sustained remission and of depressive recurrence on pramipexole is also potentially due to the limited statistical power of the present investigation (only 23 patients in our sample). Pramipexole dose at the early beginning of the trial was not associated with subsequent early remission

of depression. We should acknowledge that pramipexole doses were increased on the basis of clinical judgment instead of a fixed-dose design, therefore limiting the capability to assess a dose–effect relation. The use in our cohort of multiple antidepressant associations to prevent recurrence is consistent with a previous report by Berlanga and Ortega-Soto [1995] in treatment-resistant depressed patients.

With regard to tolerability, about 21.7% of patients discontinued pramipexole because of the occurrence of an adverse event. Because all patients received concomitant treatments together with pramipexole, we cannot establish a relation between the encountered adverse events and our augmentation. One case of psychotic mania and two of hypomania occurred during long-term treatment. Two of these patients were enrolled in the study with a diagnosis of bipolar disorder (2 of 11 bipolars, or 18%). In the worst case scenario (i.e., attributing such episodes to the experimental drug) there would be an increased risk of mania caused by pramipexole. The possibility of an augmented switch rate should not be discounted. Interestingly, in our cohort of depressed patients no sleep-attacks occurred. Sleep-attacks were reported in patients with PD undergoing D2–D3-dopamine agonists augmentation of standard treatment. Typically, patients experiencing this side effect presented sudden and irresistible somnolence when performing specific tasks as phone calls or car driving [Frucht et al., 1999]. Our data do not suggest a risk for this potentially life-threatening adverse event in depressed patients treated with pramipexole. Because in our cohort pramipexole dose was on average nearly four-fold lower than in parkinsonians, we cannot exclude that in depressed patients sleep attacks will appear with higher doses [Pogarell et al., 2002]. Alternatively, the relatively high risk of sleep attacks in parkinsonians could be explained by different doses of pramipexole or the co-occurrence of sleep disorders with Parkinson disease [Chaudhuri et al., 2002; Homann et al., 2002]. Future studies on D2–D3 dopamine agents in depressed patients should include not just tracking forms for sleep attacks, but also specific rating scales on sleepiness and sleep-related falls.

Exploratory analyses testing for predictors of outcome, including diagnosis of major depressive disorder versus bipolar disorder, yielded negative results (data not shown). The latter do not suggest a differential use of pramipexole augmentation based on lifetime diagnosis of mood disorders. In conclusion, our data provide a longer follow-up evaluation than previous reports on the response to pramipexole augmentation in patients with resistant depression. They also suggest the relative safety of pramipexole add-on in patients treated for depression over time.

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REFERENCES

American Psychiatric Association. 2000. Diagnostic and statistical manual of mental disorders: DSM-IV-TR. Washington DC: APA.

Berlanga C, Ortega-Soto HA. 1995. A 3-year follow-up of a group of treatment-resistant depressed patients with a MAOI/tricyclic combination. J Affect Disord 34:187–192.

Chaudhuri KR, Pal S, Brefel-Courbon C. 2002. 'Sleep attacks' or 'unintended sleep episodes' occur with dopamine agonists: Is this a class effect? Drug Safety 25:473–483.

Corrigan MH, Denahan AQ, Wright CE, Ragual RJ, Evans DL. 2000. Comparison of pramipexole, fluoxetine, and placebo in patients with major depression. Depress Anxiety 11:58–65.

Doogan DP, Caillard V. 1992. Sertraline in the prevention of depression. Br J Psychiatry 160:217–222.

Fava M. 2001. Augmentation and combination strategies in treatment-resistant depression. J Clin Psychiatry 62:4–11.

Frucht S, Rogers JD, Greene PE, Gordon MF, Fahn S. 1999. Falling asleep at the wheel: Motor vehicle mishaps in persons taking pramipexole and ropinirole. Neurology 52:1908–1910.

Goldberg JF, Burdick KE, Endick CJ. 2004. Preliminary randomized, double-blind, placebo-controlled trial of pramipexole added to mood stabilizers for treatment-resistant bipolar depression. Am J Psychiatry 161:564–566.

Guy W. 1976. Clinical Global Impression. ECDEU Assessment Manual for Psychopharmacology (Revised). Rockville, MD: US Dept. Health, Education, and Welfare Publication (ADM), National Institute of Mental Health.

Homann CN, Wenzel K, Suppan K, Ivanic G, Kriechbaum N, Crevenna R, Ott E. 2002. Sleep attacks in patients taking dopamine agonists: Review. Br Med J 324:1483–1487.

Keller MB, Shapiro RW, Lavori PW, Wolfe N. 1982. Recovery in major depressive disorder: Analysis with the life table and regression models. Arch Gen Psychiatry 39:905–910.

Keller MB, Klerman GL, Lavori PW, Coryell W, Endicott J, Taylor J. 1984. Long-term outcome of episodes of major depression. Clinical and public health significance. JAMA 252:788–792.

Lattanzi L, Dell'Osso L, Cassano P, Pini S, Rucci P, Houck P, Gemignani A, Battistini G, Bassi A, Abelli M, Cassano GB. 2002. Pramipexole in treatment-resistant depression: A 16-week naturalistic study. Bipolar Disord 4:307–314.

Montgomery SA, Dunbar G. 1993. Paroxetine is better than placebo in relapse prevention and the prophylaxis of recurrent depression. Int Clin Psychopharmacol 8:189–195.

Montgomery SA, Dufour H, Brion S, Gailledreau J, Laqueille X, Ferrey G, Moron P, Parant-Lucena N, Singer L, Danion JM, et al. 1988. The prophylactic efficacy of fluoxetine in unipolar depression. Br J Psychiatry Sep:69–76.

Montgomery SM. 1979. Depressive symptoms in acute schizophrenia. Prog Neuropsychopharmacol 3:429–433.

Nierenberg AA, DeCecco LM. 2001. Definitions of antidepressant treatment response, remission, nonresponse, partial response, and other relevant outcomes: A focus on treatment-resistant depression. J Clin Psychiatry 62:5–9.

Perugi G, Toni C, Ruffolo G, Frare F, Akiskal H. 2001. Adjunctive dopamine agonists in treatment-resistant bipolar II depression: An open case series. Pharmacopsychiatry 34:137–141.

Pogarell O, Gasser T, Van Hilten JJ, Spieker S, Pollentier S, Meier D, Oertel WH. 2002. Pramipexole in patients with Parkinson's disease and marked drug resistant tremor: A randomised, double blind,

placebo controlled multicentre study. J Neurol Neurosurg Psychiatry 72:713–720.

Ramana R, Paykel ES, Cooper Z, Hayhurst H, Saxty M, Surtees PG. 1995. Remission and relapse in major depression: A two-year prospective follow-up study. Psychol Med 25:1161–1170.

Rapaport MH, Judd LL. 1998. Minor depressive disorder and subsyndromal depressive symptoms: Functional impairment and response to treatment. J Affect Disord 48:227–232.

Sporn J, Ghaemi SN, Sambur MR, Rankin MA, Recht J, Sachs GS, Rosenbaum JF, Fava M. 2000. Pramipexole augmentation in the treatment of unipolar and bipolar depression: A retrospective chart review. Ann Clin Psychiatry 12:137–140.

Szegedi A, Hilibert A, Wetzel H, Klieser E, Gaebel W, Benkert O. 1997. Pramipexole, a dopamine agonist, in major depression: Antidepressant effects and tolerability in an open-label study with multiple doses. Clin Neuropharmacol 20:S36–S45.

Terra JL, Montgomery SA. 1998. Fluvoxamine prevents recurrence of depression: Results of a long-term, double-blind, placebo-controlled study. Int Clin Psychopharmacol 13:55–62.

Thase ME, Rush AJ. 1995. Treatment-resistant depression. In: Bloom FE, Kupfer DJ, editors. Psychopharmacology: The Fourth Generation of Progress. 4th ed. Philadelphia: Lippincott-Raven Healthcare. p 1081–1097.