Clinical Experience With High-Dosage Pramipexole in Patients With Treatment-Resistant Depressive Episodes in Unipolar and Bipolar Depression

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A trial of pramipexole is begun in a woman with long-term treatment-resistant depression

"Ms. A," a 42-year-old college professor, presented in a chronic major depressive episode, with severe anxiety and suicidal thoughts, that had lasted more than 5 years. Previous treatments, all of which had proved ineffective, included three selective serotonin reuptake inhibitors, venlafaxine, bupropion, nortriptyline, and a course of eight ECT treatments. Ms. A had been demoted in her job, adding financial and marital stresses.

Ms. A began pramipexole while continuing a regimen of venlafaxine, bupropion, and nortriptyline. Over 3–4 weeks, after her dosage reached 3.0 mg/day h.s., she responded and became more productive at work. Over several more weeks, her depression remitted. Venlafaxine was discontinued because of an inability to tolerate the side effects. The other antidepressants were tapered off, and the patient was maintained on pramipexole alone.

After being in remission on pramipexole for about 3 years, Ms. A suffered a cardiac event due to a genetically determined arrhythmia, requiring a cardiac pacemaker. Pramipexole was discontinued for fear of a negative effect on cardiac function. Within 10 days, her depression recurred, more severe than before pramipexole was initiated, so pramipexole was restarted. Within 2 weeks at 3.0 mg/day, her original therapeutic dosage, her depression remitted.

Except for this relapse after pramipexole discontinuation, Ms. A has remained in remission and has functioned at a high level in the 2.5 years since. She was recently offered her old job back.

Depressive disorders are common, costly, and often chronic or recurrent. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study revealed that more than 1 in 3 outpatients with major depressive disorder will not achieve symptomatic remission despite several attempts at monotherapy, augmentation, and/or combination treatment (1–3). The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study of over 2,000 outpatients with bipolar disorder found that adding antidepressants to mood stabilizers did not improve outcomes in patients with bipolar depression (4).

Most depressed patients initiate treatment in primary care settings. As primary care treatment improves, psychiatrists are likely to see more and more depressed patients with two, three, or more adequately delivered but failed treatment trials. Only a few treatments, such as atypical antipsychotic medications, olanzapine and fluoxetine combined, ECT, transcranial magnetic stimulation, lithium (5), and, most recently, pramipexole (6), have been studied in randomized controlled trials for treatment-resistant depression, which is usually defined as failure of one or two well-delivered antidepressant medications. Since these trials are often designed for regulatory approval, they selectively enroll treatment-resistant patients with few concurrent psychiatric or general medical conditions, and they cap the number of prior failed treatment trials at study entry. Consequently, despite the prevalence and the clinical, economic, and occupational impact of treatment-resistant depression (7–9), there is scant evidence from open case series or randomized trials to guide practitioners in treating patients with treatment-resistant depression.

Studies have long suggested that agents that enhance dopamine neurotransmission may be particularly useful in treatment-resistant depression (10–13). Results of clinical studies are consistent with the notion that the dopamine system plays a critical role in treatment-resistant depression. For example, monoamine oxidase inhibitors (MAOIs) (14) and stimulants appear to be effective augmenting agents in treatment-resistant depression (15, 16), and they both enhance dopamine function, albeit by different mechanisms. Furthermore, patients with treatment-resistant depression typically have profound deficits in interest, motivation, and

See related feature: **Clinical Guidance** *(Table of Contents)*

hedonic capacity (17). These symptoms are often associated with poor outcomes with antidepressants that selectively target the norepinephrine and serotonin systems. This same symptom constellation is thought to be most highly dependent on an intact dopamine system (18, 19). In addition, partial dopamine agonists, such as aripiprazole, are effective in augmenting various antidepressants in patients with treatment-resistant depression (20, 21).

Dopamine agonists, such as pramipexole—a relatively selective dopamine D_3 receptor agonist—are thus potential treatments for depression, especially anhedonic depression. D_3 receptors are found in the mesolimbic system, which in turn has been implicated in the motoric and hedonic deficits in depression (9, 10). Parkinson's disease (22, 23) is associated with dysfunction in the dopamine systems. In fact, among the 45% of Parkinson's patients who suffer from depression, anhedonia is a prominent symptom (24, 25). Both the depression and the anhedonia are frequently reduced with pramipexole (24–26).

Although preclinical studies suggested that pramipexole has antidepressant activity (24–26), Goldberg et al. (27) were the first to report on pramipexole's efficacy in unipolar and bipolar depression. The first randomized controlled trial in patients with non-treatment-resistant major depressive disorder, by Corrigan et al. (28), evaluated three dosages of pramipexole. The lowest dosage (0.375 mg/day) did not differentiate from placebo. The efficacy of the highest dosage (5.0 mg/day) was not evaluable, because of a 58% attrition rate. The third dosage (1.0 mg/day) was more effective than placebo.

Recently, Cusin et al. (6) compared adjunctive pramipexole with placebo in an 8-week randomized double-blind trial with 60 outpatients with major depression for whom at least one adequate antidepressant medication trial (mean, two trials) had failed. Although a modest statistically significant benefit of pramipexole over placebo was detected, neither the response rates (40% compared with 33%) nor the remission rates (27% compared with 23%) differed significantly between groups. Dosages were modest (mean=1.35 mg/day; maximum=2.0 mg/day). The literature as a whole suggests a modest effect of pramipexole in non-treatment-resistant to mildly treatment-resistant depression.

Our findings in a consecutive case series of 42 patients with treatment-refractory depressive episodes treated with pramipexole suggest that higher dosages produce a more robust therapeutic effect in this patient population. In presenting the results below, we aim to address two questions in particular:

1. What outcomes might be expected with pramipexole used as an adjunctive medication in patients with treatment-refractory depression, with the dosage routinely increased to the highest tolerated level?
2. How are these patients, who are also taking concomitant antidepressant or mood stabilizing agents, best managed during adjunctive treatment with pramipexole?

This report includes all patients who were treated with pramipexole by the first author or by psychiatric residents he personally supervised between January 2009 and July 2014. Since these patients are from a treatment series, rather than a designed study, the diagnoses, clinical outcomes (e.g., symptomatic response, remission, nonresponse, intolerance), and side effects were assessed openly by the clinicians, and medication adjustments were based on these clinical assessments. Physicians informed their patients about potential risks and problems with pramipexole, based on the available literature. Patients were typically seen every other week during pramipexole titration. Because there was initially no plan to accumulate data or report on these patients for research purposes, neither institutional review board approval nor written informed consent to participate in this case series was obtained.

Results

Patient Sample. The sample included 42 outpatients (25–84 years old), 24 of them with major depressive disorder and 18 with bipolar depression; half of the group were women. (For basic demographic and clinical data on all patients, see Table S1 in the data supplement that accompanies the online edition of this article.) None of the patients had evidence of psychotic depression (hallucinations or delusions) at baseline. All patients had treatment-resistant depression, defined as having failed to respond to at least four adequate antidepressant medication trials; the mean number of failed trials was 6.0 (SD=1.45), and eight of the 42 patients had not responded to one or more courses of ECT. (For data on previous treatment trials for all patients, see Table S2 in the data supplement.)

Treatment. All patients began pramipexole while on other medications because it was not known whether adding pramipexole would be helpful. We initially selected patients with failed ECT trials who had exhausted many commonly used treatments. As we saw benefit and gained experience with pramipexole dosing and management, we began to use it in patients with treatment-resistant depression who had not received ECT.

All patients were directed to take pramipexole only at bedtime, with dosages ranging from 0.25 to 5.0 mg/day. For patients under age 45, dosing started at 0.25 mg/day and was raised every 3 days in 0.25-mg increments with an initial goal of 2.0 mg/day. Further dosage increases were undertaken if feasible and if remission had not been achieved after 2–3 weeks on 2.0 mg/day. For patients over age 45, given clinical observation and evidence of decreasing numbers of D_3 receptors with age (29, 30), dosing started at 0.5 mg/day and increased in 0.5-mg increments, but otherwise the same treatment plan was followed. For all patients, if intolerance was encountered with a dosage increase, the dosage was reduced to the prior level for 1–2 weeks and then raised again if remission was not achieved. The mean dosage of pramipexole for those who responded or remitted was 2.46 mg/day (SD=1.1).

In 5 years of using pramipexole, we have recognized tactics that may enhance the tolerability of pramipexole for patients. In dosing, there is a tension between the need to reach an individual's therapeutic level rapidly, before the patient becomes discouraged and discontinues the medication, and the need to avoid side effects that cause premature discontinuation. Some patients respond or remit with lower dosages of pramipexole, while others require higher dosages, so dosage escalation must be tailored to the individual patient. Table 1 summarizes our experience in managing patients receiving pramipexole.

TABLE 1. Practical Guidance in the Use of Pramipexole in Treatment-Resistant Depressive Episodes

Slower titration rate in younger patients
Starting dose not more than 0.125–0.50 mg/day h.s.
Dose only once a day at bedtime, unless patient has trouble with sleep (rare)
Therapeutic dose range, 1.0–5.0 mg/day
Common adverse events: nausea, sleepiness, dizziness, tremors, compulsive behaviors, sleep attacks
Depressive episodes that are associated with severe anhedonia, lack of motivation, inability to initiate behaviors, and unreactive mood are likely good candidates
Expected benefit, if it occurs, by 4 weeks at maximally tolerated dose
Avoid abrupt discontinuation because the risk of dopamine agonist withdrawal syndrome[a] may be as high as 1 in 7
When nausea is encountered, reduce the dosage, then try raising it again after 1–2 weeks

[a] Dopamine agonist withdrawal syndrome is characterized by autonomic instability, anxiety, insomnia, fatigue, and motor symptoms that can persist.

For example, during titration, several patients experienced nausea severe enough for them to request discontinuation. We reduced the dosage to the last dosage at which nausea was not apparent, and then raised it again after 1–2 weeks. This second attempt was associated with less nausea, and we were thus able to raise the dosage. One patient (patient 16 in Tables S1 and S2 in the data supplement) initially could not tolerate even 0.5 mg/day and decided to discontinue the medication. We persuaded her to try again, this time titrating the dosage more slowly, and she achieved remission with 1.0 mg/day. An 84-year-old patient with bipolar disorder (patient 6) has remained well on 3.0–5.0 mg/day over 36 months, despite having undergone a necessary course of prednisone (up to 40 mg/day) for a lung infection.

Outcomes. Of these 42 patients, 20 remitted (47.6%), 12 responded (28.6%), two did not respond (4.8%), and eight could not tolerate the drug (19.0%). Intolerance was encountered early, often at a low dosage and usually due to nausea. Of the eight patients who had failed to benefit from ECT (two had bipolar disorder), four responded and four remitted with pramipexole (Table 2).

The 32 patients who responded or remitted have been followed for an average of 15.9 months (SD=14.2, range=3–60), accounting for 44.2 patient-years of pramipexole exposure. Two of these patients (patients 10 and 19 in Tables S1 and S2 in the data supplement) relapsed after being on pramipexole for 12 and 18 months, respectively.

Seven patients who responded or remitted with pramipexole (patients 9, 12, 15, 16, 19, 20, and 23) had to discontinue pramipexole for various reasons. In five of them (patients 9, 15, 16, 19, and 20), the depression returned within 1–2 weeks, and in the other two, the depression did not return. In four of the five patients who restarted pramipexole (patients 15, 16, 19, and 20), the prior response or remission returned within 1–2 weeks after the prior effective dosage was reestablished.

Adverse Events. Intolerance was the most frequent adverse event. Intolerance occurred early—within 3–10 days—and typically at low dosages (0.25–1.0 mg/day). Most early intolerance was due to nausea. The other acute adverse events included sleeplessness, sleepiness, increased anxiety, panic attacks (in one patient), early insomnia, and increased sexual arousal. In some patients, intolerance may be overcome by dosage reduction followed by repeat escalation.

Only one of the 42 patients had an activating response (irritability) to pramipexole after having a positive mood response. Two patients reported hypersexuality (patients 24 and 19 in Tables S1 and S2 in the data supplement), both of them men with bipolar II disorder. This was addressed by reducing the pramipexole dosage. No patient on pramipexole attempted suicide or reported increased suicidal ideation. No clinically apparent weight gain or loss was noted. One patient (patient 9) developed psychotic symptoms (delusions and visual hallucinations) after 12 months of response to pramipexole, during a period when she suffered high fever, chills, dehydration, and disorientation due to a renal infection; she has since been diagnosed with a genetic form of polycystic kidney disease. Pramipexole was discontinued as a precaution, but over 1–2 months, the patient suffered a recurrence of depression, which lifted when pramipexole was restarted at 1.0 mg/day, without a return of psychotic symptoms.

Discussion

To our knowledge, this is the first case series of adjunctive pramipexole in patients with treatment-resistant depression for whom at least four previous treatments in the current episode had failed. Overall, 76% of the patients showed a meaningful clinical response that persisted, while 24% were intolerant or nonresponsive to pramipexole. Effective pramipexole dosages ranged from 0.75 to 5.0 mg/day. The mean effective dosage of pramipexole in responders and remitters (N=32) was 2.46 mg/day (SD=1.1), which is a higher mean dosage than those reported in previous studies.

The beneficial effects of pramipexole that occurred among responders and remitters seemed largely to persist over the almost 16-month follow-up period. As of this writing, only two patients relapsed while continuing on pramipexole. This relapse rate is lower than that reported in the STAR*D study

TABLE 2. Outcomes by Mood Disorder Group in 42 Patients With Treatment-Resistant Depressive Episodes Treated With Pramipexole

Group	Remission	Response	Nonresponse	Intolerant
Bipolar disorder (N=18)	9	5	1	3
Unipolar depression (N=24)	11	7	1	5
Total	20	12	2	8

(40%−70%) (2), albeit in a naturalistic follow-up. In the STEP-BD study, the relapse rate was 50% over the 2-year follow-up (4).

Prior evidence exists for the efficacy of pramipexole in depressive episodes in major depressive disorder and bipolar disorder (13, 27, 28). Pramipexole seems to benefit patients who have major depression without evidence of treatment resistance (28) and patients in a treatment-resistant depressive episode in both unipolar depression (28) and bipolar disorder (6). The present case series suggests that an effective dosage for treatment-refractory depression is likely to be between 2.0 and 3.5 mg/day, but that some patients may respond or remit with lower dosages while others may need up to 5.0 mg/day. This estimate is consonant with suggestions in the literature (28).

Our clinical impression is that slower dosage escalation is called for in younger patients and that bedtime-only dosing is associated with a lower incidence and severity of side effects, especially nausea, compared with twice daily or thrice daily dosing. Generally, the dosage was increased in this sample until clinical response or remission was achieved or intolerable side effects developed. We are careful to tell patients never to discontinue pramipexole abruptly, since a withdrawal syndrome (dopamine agonist withdrawal syndrome) was reported in 19% of 26 Parkinson's disease patients whose treatment with a dopamine agonist was tapered off (31). The syndrome is characterized by increased anxiety, panic attacks, agoraphobia, depression, diaphoresis, fatigue, pain, and orthostatic hypotension.

Why might pramipexole, a D_3 agonist, be effective in treatment-resistant depression? Pramipexole has both neuroprotective and neurorestorative effects on dopamine function, especially in Parkinson's disease (32). Neuroprotection refers to preventing the death of dopamine neurons. Neurorestoration refers to the fact that despite substantial damage to dopamine neurons in the nigrostriatal pathways, one can reinstate the activity of surviving neurons enough to restore dopamine functional recovery (32). In studies of animals that received foot-shock to induce learned helplessness (a behavioral analogue of anhedonia and depression), those animals treated with pramipexole had an approximately 50% lower decrease in dopamine neuron population compared with controls (33).

The acute administration of pramipexole in mice shows a dose-dependent antidepressant effect in the forced swim test and the tail suspension test. The dose effect may be explained by the fact that at low doses pramipexole activates mostly D_3 presynaptic autoreceptors, and only a higher dose activates the postsynaptic receptors (34). It appears that both dose and duration of exposure of pramipexole to D_3 (mesolimbic) receptors affect dopaminergic function in the striatum. Therefore, low doses cannot work and higher doses may work but need time for desensitization of the presynaptic autoreceptors.

As noted earlier, clinical studies indicate that both MAOIs and stimulants enhance dopamine transmission and are effective in a meaningful proportion of patients with treatment-resistant depression who have not achieved remission with a range of agents that selectively target the norepinephrine and serotonin systems. As further evidence of the dopamine system's relevance in at least some patients with treatment-resistant depression, two double-blind studies found that aripiprazole, a partial dopamine D_2 and D_3 receptor agonist, is an effective augmentation agent in treatment-resistant depression (20, 21). Conway et al. (35) found increased indices of dopamine synthesis capacity in the striatum (using FDOPA positron emission scanning) in 11 of 14 patients who did not achieve response with selective serotonin reuptake inhibitors and then responded to 6 weeks of aripiprazole augmentation. It appears that pramipexole enhances dopamine firing tone by acting on D_3 autoreceptors, as opposed to the action of stimulants, which cause a surge of dopamine by reuptake blocking and release of dopamine. Enhancing D_3 receptor activity has been shown to promote reward activity (36).

This study has several limitations. There was no control group. Since this was not a planned study, patients were managed and evaluated clinically without rating scales or structured interviews. Clinical judgment was the basis for establishing the diagnoses and for gauging outcomes and side effects. When patients reported no remaining symptoms, their depression was considered to have remitted. When they reported significant improvement with some residual symptoms, they were considered to have responded. Outcomes were not blinded and indeed were used to adjust the medication dosage. No specific scale was used to document the degree of treatment resistance. Nevertheless, patients in the sample seem clearly to have treatment-resistant depression, as all 42 patients had failed to respond to multiple medication trials (a mean of six prior failed adequate antidepressant trials), and in some cases to ECT as well. The apparent effectiveness of pramipexole (when the dosage is pushed to the maximum tolerated) is about 75% of patients with this degree of treatment-refractory depression, which makes it seem unlikely that this observation is due to placebo response or spontaneous remission. Further evidence is provided by the five patients who relapsed after discontinuing pramipexole and the four who regained prior therapeutic benefit once pramipexole was restarted (albeit under open conditions).

Our results support the notion that pramipexole—and potentially other dopamine agonists—are of value for patients

in a treatment-resistant depressive episode. Appropriate precautions, careful patient monitoring, and gradual dosage escalation are advised. Pramipexole has not been approved by the U.S. Food and Drug Administration for the treatment of depression.

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