

Pramipexole in Psychiatry: A Systematic Review of the Literature

Chris B. Aiken, M.D.

Objective: To assess the risks and benefits of pramipexole in psychiatric populations.

Data Sources: A PubMed search was performed using the keywords *pramipexole* and *ropinirole*, which identified 500 articles.

Study Selection: All clinical studies in psychiatric populations were included in the primary review (24 articles). Studies involving other populations were then reviewed to evaluate potential risks and benefits not identified in the psychiatric studies.

Data Extraction: Effect sizes were calculated from controlled studies. Rates of intolerable side effects and manic switching were estimated by pooled analysis of controlled and uncontrolled studies.

Data Synthesis: Pramipexole has a large effect size (0.6–1.1) in the treatment of both bipolar and unipolar depression with a low short-term rate of manic switching in bipolar patients (1% mania, 5% hypomania). The pooled discontinuation rate for all reasons was 9%. Pramipexole is neuroprotective and exerts beneficial effects on sleep architecture. Pramipexole is associated with 3 rare but serious side effects: sleep attacks, which have only occurred in Parkinson's disease; compulsive behaviors and pathologic gambling, which have occurred in Parkinson's disease and restless legs syndrome; and psychosis, which has occurred in both psychiatric and neurologic populations.

Conclusions: Pramipexole is an important therapeutic option for treatment-resistant bipolar and unipolar depression; further studies are warranted to evaluate its safety in psychiatric patients.

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Dr. Aiken reports no financial affiliations or other relationships relevant to the subject of this article.

Corresponding author and reprints: Chris B. Aiken, M.D., 632 Holly Ave., Winston-Salem, NC 27101 (e-mail: christopher.aiken.med.99@aya.yale.edu).

Pramipexole, a dopamine agonist approved for the treatment of Parkinson's disease and restless legs syndrome, has unique properties that offer therapeutic potential in psychiatry. It possesses both dopaminergic and neuroprotective effects, making it a promising candidate for bipolar depression. Recent clinical studies have earned it a place as a stage-5 treatment in the Texas¹ and Canadian² algorithms for bipolar I depression. Concurrently, case reports from Parkinson's disease clinics have raised concerns about the potential for compulsive behaviors and sudden sleep attacks to arise during treatment with the drug. To investigate these promises and perils, the neurologic and psychiatric studies of pramipexole were systematically reviewed.

METHOD

A PubMed literature search was performed using the keywords *pramipexole* and *ropinirole*. Abstracts and titles from 500 articles were reviewed to identify all clinical studies in psychiatric populations. This yielded 24 studies, from which 3 randomized, placebo-controlled trials were identified and used to calculate Cohen effect sizes^{3,4} (using the Hamilton Rating Scale for Depression as the outcome measure).

To estimate short-term rates of intolerable side effects and psychosis, data from all treated subjects in prospective and retrospective studies of depression (253 subjects from 8 studies)^{5–12} were combined. Case reports and studies involving Parkinson's disease were excluded. To estimate the short-term rates of manic and hypomanic switching, data from all bipolar subjects in these studies were combined (85 subjects from 6 studies).^{5,7–10,12}

Lastly, to assess potential risks and benefits not identified in the psychiatric studies, a review of all clinical studies and case reports involving pramipexole and the related drug ropinirole was undertaken.

MECHANISM OF ACTION

Pramipexole is a presynaptic dopamine agonist with an 8-fold preference for the D₃ receptor and less affinity for D₁, D₂, and D₄.¹³ The D₃ receptor is densely distributed in the mesolimbic system and has been implicated in the motoric and anhedonic symptoms of depression.⁵ Potentiation of dopamine receptors within this system has

Table 1. Randomized Placebo-Controlled Trials of Pramipexole in Mood Disorders

Study	Condition	Daily Dose ^a	N	Duration, wk	Effect Size
Corrigan et al, 2000 ¹¹	Major depression, monotherapy	Fixed doses of 0.375, 1.0, and 5.0 mg	174	8	d = 0.6 ^b
Zarate et al, 2004 ⁵	Bipolar II depression, augmentation of mood stabilizer	1.7 mg	21	6	d = 1.1 ^c
Goldberg et al, 2004 ¹²	Bipolar I and II depression, augmentation of mood stabilizer	1.7 mg	22	6	d = 0.77 ^d

^aDaily dose is expressed as a mean except where noted.

^bCalculated from HAM-D using the t test of the differences between the 2 groups: $d = t(n_1 + n_2) / [\sqrt{df} \times \sqrt{(n_1 \times n_2)}]$; see Cohen.⁴

^cCalculated from HAM-D using the difference of posttreatment means divided by the pooled standard deviation.³

^dCalculated from percent change in HAM-D using the difference of posttreatment means divided by the pooled standard deviation.³

Abbreviation: HAM-D = Hamilton Rating Scale for Depression.

been proposed as a final common pathway for antidepressants from diverse classes, including serotonin reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors and electroconvulsive therapy.¹⁴⁻¹⁷ The mesolimbic dopamine system has also been speculated to play a role in resilience to trauma by enhancing an individual's ability to recognize rewards and persist in their absence.¹⁸

Pramipexole also shares with antidepressants a suppressive effect on rapid eye movement (REM) sleep. In patients with restless legs syndrome, pramipexole increased REM sleep latency and decreased total REM sleep time.^{19,20}

The neurotrophic effects of pramipexole are mediated by the anti-apoptotic protein bcl-2, which is believed to be responsible for the neuroprotection seen with lithium and valproic acid. Preliminary data suggest that combining pramipexole with lithium or valproic acid yields a synergistic enhancement of bcl-2.⁵

CLINICAL STUDIES

Pramipexole's antidepressant effects were first observed in several animal models²¹⁻²³ and, later, in a series of uncontrolled clinical studies in which it was used as monotherapy⁶ or augmentation^{7-10,24} in bipolar and unipolar depression. Combined, these studies involved 156 patients treated for a mean of 30 weeks, with the longest follow-up recorded at 74 weeks. The weighted mean daily dose arrived at was 1.6 mg.

These observations have been supported by 3 randomized controlled trials of pramipexole, which found moderate to large effect sizes in unipolar and bipolar depression (Table 1).

The first trial compared 3 doses of pramipexole to fluoxetine and placebo in 174 subjects with unipolar major depression.¹¹ At 8 weeks, pramipexole performed comparably to fluoxetine and significantly better than placebo. A dose-dependent effect on depression was observed among the pramipexole groups (0.375, 1.0, and 5.0 mg daily), but dropout rates also increased with

each dose increment (25%, 34%, and 58%, respectively); dropout rates were comparably lower with fluoxetine (14%). The lowest dose of pramipexole (0.375 mg/day) did not separate from placebo. Outcomes were reported as completer analysis, which limits their interpretation, particularly in the pramipexole 5.0-mg group in which the high dropout rate precluded the calculation of p values.

The second trial involved bipolar II depression and is one of the few controlled trials to examine this population exclusively.⁵ Most of these subjects were considered treatment resistant and half were inpatients. After an initial 6-week phase of treatment with either divalproex sodium or lithium, those whose depression did not respond to the mood stabilizer were randomly assigned to receive augmentation with either placebo or pramipexole. Pramipexole began to separate from placebo at 3 weeks and brought about a significant reduction in depression by week 6 with a large effect size of 1.2 to 1.4. This study involved 21 subjects, had high completion rates (90% in both groups), and used intent-to-treat analysis.

A third randomized controlled trial¹² compared flexible dosing of pramipexole (mean daily dose = 1.7 mg) to placebo as an augmentation strategy for outpatients with bipolar depression that was unresponsive to at least 2 antidepressant trials. All were taking mood stabilizers and none were taking antipsychotics. Twenty-two subjects were included; 32% had bipolar II disorder. Pramipexole brought about significantly greater improvements in depression than placebo on all measures except the primary outcome measure (response < 50% on Hamilton Rating Scale for Depression). Data were analyzed on an intent-to-treat basis, and 72% of subjects completed the trial. Dropout rates were higher in the placebo arm (40%) than in the pramipexole arm (17%).

Three of the randomized controlled trials of pramipexole in Parkinson's disease also evaluated depressive symptoms.²⁵⁻²⁷ The drug brought about significant benefits, particularly for anhedonia,^{25,26} and these benefits occurred independently of motoric relief.²⁷ In a randomized comparison trial, treatment with pramipexole

brought about significantly greater rates of remission from depression than did treatment with sertraline among patients with Parkinson's disease.²⁷

Supportive evidence for pramipexole's antidepressant properties also comes from studies of the related compound ropinirole. Ropinirole is also selective for D₃, but its affinity at this site is less than that of pramipexole.¹³ Ropinirole is neuroprotective,^{28,29} but unlike pramipexole is not known to mediate this effect through bcl-2. Ropinirole appears to lack the REM-suppressive effects of pramipexole.^{30,31}

The evidence for ropinirole as an antidepressant is limited to 2 uncontrolled studies. In a prospective case series of 10 patients with treatment-resistant depression (7 unipolar, 3 bipolar II), 40% responded to augmentation with ropinirole.⁸ In a retrospective review of 8 hospitalized patients with treatment-resistant bipolar II depression, 50% were considered responders to ropinirole augmentation.³²

OTHER POTENTIAL BENEFITS

Pramipexole is approved by the U.S. Food and Drug Administration (FDA) for moderate to severe primary restless legs syndrome, with 4 large randomized controlled trials supporting this indication.^{33,34} No significant safety problems emerged at 30 months in a separate, open-label follow-up study involving 195 patients who had started pramipexole for restless legs syndrome.³⁵

The evidence supporting pramipexole's use in other conditions encountered in psychiatric practice is limited to small or uncontrolled studies, which are described below.

Pramipexole produced improvements in subjective and objective measures of sleep quality, including suppression of REM sleep, in 2 placebo-controlled crossover trials involving a total of 21 patients with restless legs syndrome.^{19,20} Pramipexole also yielded sustained improvements of REM sleep behavior disorder in 2 open-label studies.^{36,37} This finding, if reproduced, will have particular relevance in Parkinson's disease, for REM sleep behavior disorder often heralds the onset of Parkinson's disease.³⁸ Lastly, a small pilot study of sleep-related eating disorder yielded negative results for pramipexole, but did confirm improvements in sleep quality with the drug.³⁹

For fibromyalgia, higher doses of pramipexole (4.5 mg given q.h.s.) reduced pain and improved functioning in 60 patients with significant illness (half were disabled or taking narcotic therapy) in a 14-week randomized placebo-controlled augmentation trial. These benefits occurred despite a lack of effect on depression. No significant safety concerns emerged and pramipexole was generally well tolerated.⁴⁰ Ropinirole, however, did not separate significantly from placebo in a pilot study of fibromyalgia conducted by the same investigator.⁴¹

An open-label study reported a reduction of negative symptoms in patients with schizophrenia taking pramipexole. Pramipexole was titrated to high doses (up to 10.25 mg/day) in 15 patients who were taking haloperidol. Although there was overall improvement in both positive and negative symptoms, 3 patients had to discontinue the drug due to worsening of their schizophrenia.⁴²

Pramipexole's effects on anxiety have not been assessed systematically. The case reports are mixed: 2 patients with treatment-resistant panic disorder had sustained remission with it,⁴³ and 1 patient with Parkinson's disease had new-onset panic attacks associated with the drug.⁴⁴

Pramipexole is known to reduce prolactin levels,⁴⁵ and there are reports of its successful use as an antidote to antipsychotic-induced hyperprolactinemia.⁴⁶

In animal models, pramipexole and other D₃ agonists reduced cocaine use without being reinforcing themselves.⁴⁷⁻⁴⁹ However, pramipexole was not effective for cocaine dependence when compared to placebo and venlafaxine in a small randomized controlled pilot study involving 60 patients.⁵⁰

SIDE EFFECT PROFILE

Among patients with mood disorders taking pramipexole, the pooled discontinuation rate for any reason was 9% (based on combined data from 253 subjects in 8 studies).⁵⁻¹² Nausea, headache, and somnolence were the most common limiting side effects and appeared to be dose related. Gradual titration is recommended to reduce most side effects. Anecdotal evidence from the fibromyalgia studies suggests that nausea can be minimized by concomitant use of a proton-pump inhibitor during dose titration.⁴⁰ Pramipexole can cause orthostatic hypotension and edema in susceptible individuals.³⁴

The medicine appears to be weight neutral and is not associated with significant laboratory abnormalities.³⁴ No significant safety problems emerged in a case series of 23 psychiatric patients followed for up to 48 weeks, although the complex treatment regimens, which included ECT in several cases, make conclusions difficult to draw.²⁴

The sedative effects of pramipexole give a hint that its actions are distinct from other dopaminergic medications such as stimulants. There is likewise no reason to think that pramipexole will have beneficial effects on cognition. Pramipexole has little affinity for the D₁ receptor, which is involved in working memory^{51,52} and the therapeutic mechanism of stimulants.⁵³ In Parkinson's disease, dopaminergic treatment is known to produce mixed effects on cognition,⁵⁴ which may explain the conflicting results of the studies examining pramipexole's effects on cognitive function.^{54,55} Cognitive effects were not reported in the studies of mood disorders.

RISK OF PSYCHOSIS

With pramipexole's antidepressant and dopaminergic properties comes a valid concern that it will induce mania or psychosis.

In the studies of Parkinson's disease, the rates of psychosis were consistently and significantly elevated in the pramipexole group compared with placebo (occurring at rates of 6%–21% for pramipexole, compared with 0%–6% for placebo). Visual hallucinations were the most common form of psychosis.^{26,56–60} The doses in these studies were higher (4.5 mg daily) than those used in depression, and in most cases the hallucinations resolved with dose reduction.

Reports also exist of psychosis associated with pramipexole in patients without Parkinson's disease. A patient with Holmes' tremor and a history of basilar-tip aneurysm had 2 episodes of delusional jealousy without mania after initiating pramipexole.⁶¹ The manufacturer reports that psychosis occurred in 1 patient with restless legs syndrome (of 889 patients treated in the premarketing trials).³⁴

Among the mood disorder studies, psychosis was reported in only 2 treated patients (overall rate of 0.8%): 1 with bipolar depression who developed psychotic mania¹² and another with unipolar depression who experienced hallucinations while taking an unusually large dose of 9 mg/day, which resolved with dose reduction.⁶

RISK OF MANIA

In the randomized controlled trials, patients taking pramipexole switched into mania or hypomania at rates comparable to or lower than those taking placebo, although none of these differences reached statistical significance. Combining data from all bipolar I and II patients who received pramipexole (N = 85; all were taking mood stabilizers) yields an estimated switch rate of 5% for hypomania and 1% for mania over the short-term (6–26 weeks; weighted mean of 14 weeks).^{5,7–10,12}

Although it is difficult to compare across studies, these rates are considerably smaller than those reported after 10 weeks of antidepressant treatment in 228 bipolar I and II patients taking mood stabilizers (11.4% hypomania, 7.9% mania).⁶² Caution should still be emphasized in the treatment of bipolar disorders with pramipexole, for the combined sample size of these studies is relatively small and the long-term risks of inducing mania and rapid cycling are unknown.

The risk of affective switches is illustrated by a case report of a 41-year-old woman with bipolar II depression who developed a first-episode mania after responding to pramipexole augmentation of valproic acid. This mania, which had psychotic features, lasted 2 months and subsided within a week of pramipexole's discontinuation.⁶³

RISK OF COMPULSIVE BEHAVIOR

Reports of pathologic gambling with dopamine agonists have raised concerns about the behavioral effects of these drugs. In Parkinson's disease, pathologic gambling is related to a broader syndrome of dyscontrol known as hedonistic homeostatic dysregulation.⁶⁴ The full syndrome begins with overuse of dopamine agonists. This is followed by mood or anxiety symptoms and compulsive behaviors, which can include gambling, shopping, overeating,⁶⁵ hypersexuality,⁶⁶ and punding⁶⁷ (i.e., stereotyped, repetitive behaviors such as sorting or examining objects). These compulsive behaviors can also occur independently of the full syndrome. In most case reports, the hedonistic homeostatic dysregulation syndrome began within a few months of starting a dopamine agonist and resolved with discontinuation, dose reduction, or switching to a different dopamine agonist.⁶⁸

Compulsive problems have been reported with numerous dopamine agonists in Parkinson's disease, but the association is strongest with pramipexole. Both the case reports⁶⁸ and the FDA's database of adverse events⁶⁹ suggest a 4-fold higher risk with pramipexole compared to other dopamine agonists. The risk appears to be proportional to the agonist's affinity for D₃, underlining a causative role for hedonic drive.

Parkinson's disease may render patients uniquely vulnerable to pathologic compulsions, which are estimated to occur in 3% to 4% of patients in Parkinson's disease clinics.⁷⁰ Parkinson's disease patients are known to exhibit high rates of psychiatric and behavioral abnormalities in both medicated and unmedicated states, and dysregulation of their reward system is suggested by their poor performance on gambling tasks.⁷¹ Degeneration of the extrastriatal dopaminergic pathways may render them hypersensitive to the behavioral effects of dopamine stimulation. In contrast, patients with bipolar and unipolar depression do not have hypersensitive dopamine tracts.⁷²

Prior to 2007, case reports of compulsive behaviors in patients taking pramipexole were limited to Parkinson's disease. Since then, 4 cases of pathologic gambling have been reported during the treatment of restless legs syndrome. In all 4 cases, the problem began within 1 to 17 months of starting pramipexole treatment and resolved with discontinuation of the drug. Three of these patients were social gamblers before starting the drug, but only during pramipexole treatment did their gambling become pathologic, with losses of over \$100,000.^{73,74}

It is not known if psychiatric patients are also at risk for these problems. Although there were no reports of compulsive behaviors among the 253 patients treated in the short-term studies of mood disorders, there were also no such reports among the 889 patients in the premarketing studies of restless legs syndrome.³⁴

It may be that patients with obsessive-compulsive disorder, rather than mood disorders, are at risk for behavioral problems while taking pramipexole. Hedonistic dysregulation is distinct from mania, and may have more in common with obsessive-compulsive disorder in its biological origins.⁷⁵ A growing body of evidence supports a dopamine model of obsessive-compulsive disorder,⁷⁶ and stimulation of D₂ and D₃ receptors is central to this model.⁷⁷

Punding and hedonistic dysregulation bear a close resemblance to the impulsive side of the obsessive-compulsive spectrum, which includes pathologic gambling, compulsive shopping, kleptomania, binge eating, hypersexuality, Tourette's disorder, trichotillomania, self-injury, and intermittent explosive disorder.⁷⁸ The potential for adverse effects with pramipexole in these populations is illustrated by a case report from a long-term follow-up study. A 42-year-old woman with recurrent major depression, bulimia, and kleptomania developed worsening of kleptomania, verbal dyscontrol, and compulsive lying after 6 months of treatment with pramipexole (P. Cassano, M.D., written communication, 2006).

RISK OF SLEEP ATTACKS

Another serious side effect that has been associated with dopamine agonists in patients with Parkinson's disease is sleep attacks,⁷⁹ described as sudden and irresistible bouts of somnolence. The attacks usually resolved with dose reduction, and in no cases did the problem persist after pramipexole discontinuation.⁸⁰ No such attacks have been reported in patients without Parkinson's disease, and the rate in those with Parkinson's disease taking dopamine agonists is estimated at 4% to 7%.^{80,81} In Parkinson's disease, sleep attacks are more common when there is preexisting somnolence or advanced disease. Parkinson's disease patients may be uniquely predisposed to this reaction because of their elevated rates of sleep disturbances, including sleep apnea, and organic factors such as degeneration of neurons involved in the sleep-wake cycle.⁸²

DOSING, PHARMACOKINETICS, AND DRUG INTERACTIONS

Pramipexole is renally cleared and has no known metabolites or hepatic interactions. Its half-life is 8 to 12 hours, and peak concentrations are achieved within 2 hours. Dose reductions are recommended for individuals with impaired creatinine clearance (below 60 mL/min). Drug interactions appear limited to medications cleared by the cationic renal transport system (e.g., cimetidine, ranitidine, diltiazem, triamterene, verapamil, quinidine, and quinine), which can raise levels of pramipexole by about 20%.³⁴

Gradual titration is recommended to improve tolerability and reduce the risk of orthostatic hypotension. Pramipexole can be started at 0.25 mg daily and raised by 0.25 mg each week on the basis of individual response.³⁴ The weighted mean dose from studies of mood disorders was 1.6 mg, and there was some evidence for a dose-response relationship. Although it is recommended as a t.i.d. drug, it has been successfully given once at night in studies of fibromyalgia and restless legs syndrome, and this strategy may improve tolerability and adherence.⁴⁰ Higher doses were used in fibromyalgia (4.5 mg/day),⁴⁰ while lower doses (0.25–0.75 mg/day) were sufficient for restless legs.^{19,20,33,34}

Although pramipexole has no known withdrawal effects, discontinuation of other dopaminergic agonists in Parkinson's disease has been associated with rare cases of neuroleptic malignant syndrome,⁸³ and the manufacturer recommends withdrawing pramipexole gradually over 7 days.³⁴

CONCLUSIONS

Pramipexole brings novel benefits and risks to the psychiatric field. It is among a limited number of agents that have demonstrated efficacy for bipolar depression and is recognized as a stage-5 intervention for this condition in 2 recent treatment algorithms.^{1,2} It also has controlled data for the treatment of unipolar depression and depression associated with Parkinson's disease. Controlled trials support its use in restless legs syndrome and, more preliminarily, in fibromyalgia.

Although the evidence to date does not support an association of short-term pramipexole treatment with sleep attacks, compulsive behavior, or mania in psychiatric patients, it is possible that these problems are rare and would only come to attention after widespread use of the drug. The risk of psychosis appears small at the doses used in depression, but there is strong evidence of a dose-related risk of hallucinations when the drug is used in Parkinson's disease. Until there are more studies to confirm its safety, caution is warranted in patients with predispositions to fatigue, psychosis, or disorders of impulsivity and compulsivity.

While pramipexole's neuroprotective effects bear a resemblance to those of mood stabilizers, there is no evidence that its long-term use will prevent cycling, and the possibility remains that it may destabilize mood in some patients. The data presented here suggest that, at least in the short term, this risk may be less than that posed by antidepressants.

Drug names: cimetidine (Tagamet and others), divalproex sodium (Depakote), diltiazem (Cartia, Taztia, and others), fluoxetine (Prozac and others), lithium (Eskalith, Lithobid, and others), pramipexole (Mirapex), ranitidine (Zantac and others), ropinirole (Requip), sertraline (Zoloft and others), triamterene (Dyrenium), valproic

acid (Depakene and others), venlafaxine (Effexor and others), verapamil (Verelan, Isoptin, and others).

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