

# The Role of Low-Dose Pramipexole in the Treatment of Treatment-Resistant Bipolar Depression: A Case Report

Fisun AKDENİZ, Ebru ALDEMİR, Simavi VAHİP

## Abstract

### *The Role of Low Dose Pramipexole in the Treatment of Treatment Resistant Bipolar Depression: Case Report*

*Despite a wide range of various drugs, a significant proportion of depressed bipolar patients fail to respond to the treatment strategies. Novel therapeutics for bipolar depression are needed. Preliminary studies suggest that pramipexole a dopaminergic agent that has been used in the treatment of Parkinson's disease and restless leg syndrome may have antidepressant properties in unipolar and bipolar depressed patients as well as neurotrophic properties. The optimal antidepressant daily dose of pramipexole is not known. It has been suggested to be used between 0.125 to 9.0 mg/day. In double blind placebo controlled bipolar depression treatment studies, the average daily dose of pramipexole was 1.7 mg. Manic switches have been reported with depressive subjects and with subjects without any mental disorders.*

*We report two cases of treatment resistant bipolar depression. Despite different treatment strategies and treatment adherence, the patients did not give optimal response to the treatments and continue to experience depressive relapses. They have been treated with low dose (0.5-0.75 mg/day) pramipexole augmentation successfully. The severity and the duration of the depressive episodes were decreased. No serious adverse event has been reported with pramipexole during the maintenance treatment.*

*Key Words: Pramipexole, bipolar disorder, depressive episode, treatment-resistant*

## INTRODUCTION

Although the primary goal of the treatment of acute bipolar depression is to maintain remission, clinicians should consider the longitudinal course of the illness when planning its treatment. The most important difficulties in the treatment of acute bipolar depression are managing manic/hypomanic switching and cycle acceleration. Despite effective treatment strategies, the course of bipolar disorder is dominated by depression and is related with poor functioning (Judd et al., 2005). Following a lack of response to  $\geq 2$  treatment strategies, novel empirical treatment alternatives should be used, including sleep deprivation, thyroid hormone repletion, psychostimulants, and dopamine agonists (Vahip, 2003).

Pramipexole, a dopamine agonist, is an empirical alternative for the treatment of bipolar depression. Pramipexole is structurally different than other ergo derivatives (bromocriptine and pergolide). Pramipexole, a synthetic aminothiazole derivative, has a full agonistic effect on dopamine receptors. In Turkey the approved daily dose for the treatment of Parkinson's disease is 1.5-4.5 mg/day. Pramipexole is widely used for the treatment of restless leg syndrome, with a recommended daily dose of 0.5-0.75 mg/day (Whisker and Taylor, 2004).

The literature contains 2 double blind, placebo-controlled studies of pramipexole for the treatment of bipolar depression (Goldberg et al., 2004; Zarate et al., 2004). Bipolar depressive outpatients that were unresponsive

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Fisun Akdeniz MD., e-mail: fisunakdeniz@yahoo.com

to at least 2 antidepressant trials were included in these studies. Pramipexole or a placebo was used in addition to mood stabilizers. At the sixth week the pramipexole arm showed more improvement in the depressive symptoms than the placebo arm; 72% of subjects completed the trial. Dropout rates were 17% and 40%, respectively, in the pramipexole and placebo arms (Goldberg et al., 2004). Most of the patients in the other trial were treatment-resistant and 50% were inpatients. Patients whose depression did not respond to an initial 6-week treatment with lithium or evaporate were randomly assigned to the pramipexole or placebo group. At the third week pramipexole was observed to be efficacious; at the sixth week the level of improvement observed in the pramipexole group was significantly better than in the placebo group. In all, 21 bipolar depressive patients were included in the trial and 90% of them completed it (Zarate et al., 2004). The daily dose of pramipexole was 1-3 mg/day.

In the light of these results pramipexole was added to the treatment of 2 treatment-resistant bipolar depressive patients. In this case report, 2 bipolar patients with recurrent long-term and severe depression that responded to low-dose pramipexole (< 1 mg/day) are presented, and the advantages of low-dose pramipexole for the treatment of bipolar depression is discussed.

### Case 1

Mr. A was a 46-year-old male patient, who was married and employed. At age 30 years he was diagnosed with bipolar disorder and at age 39 years he began prophylactic lithium treatment. After 3 years of lithium treatment his manic episodes remitted, but the patient experienced recurrent long-term and severe depression, with poor functioning. The patient had a family history of schizoaffective disorder–bipolar type in his younger brother. The patient reported no psychotic symptoms.

The patient presented 4 years earlier (2003) to Ege University, Psychiatry Affective Disorders Department, when he was suicidal. His treatment was lithium carbonate 1200 mg/day and risperidone 1 mg/day. The patient had extrapyramidal side effects (especially parkinsonism). Because he had no psychotic symptoms and was experiencing extrapyramidal side effects, risperidone was discontinued and the lithium daily dose was decreased to 900 mg/day because his serum lithium level was 1.35 mEq/l. Lamotrigine (gradual titration to 200 mg/day) and venlafaxine (titrated to 225 mg/day) was then added to lithium. The duration of the patient's depressive episodes became shorter (from 8 months to 1-2 months, with 2 weeks of remission between episodes), but the

severity of depressive episodes (suicide thoughts and ideation) did not change. Different treatment strategies (combination sertraline and venlafaxine, clomipramine, and combination sertraline and bupropion) were administered for 1 year. The treatment strategies were as follows: lithium (900 mg/day; serum level: 0.70-0.80 mEq/l), lamotrigine (200-300 mg/day), venlafaxine (225 mg/day), and sertraline 50 mg/day for 4 months. Then, venlafaxine and sertraline were discontinued and clomipramine (225 mg/day) was initiated for 4 months, then clomipramine was replaced with sertraline (100 mg/day) and bupropion (450 mg/day). There were no problems with the patient's treatment compliance or therapeutic alliance. Serum lithium levels were 0.56-0.85 mEq/l. No more than 15-20 days of remission were observed during the 4-year follow-up period. In November 2006, electroconvulsive treatment (ECT) was administered because of intense anxiety and severe suicidal plans. After 8 ECT treatments the patient experienced partial remission, and lithium 900 mg/day, venlafaxine 150 mg/day, and reboxetine 6 mg/day were initiated. At the fourth week the patient relapsed (anhedonia, psychomotor retardation, fatigue, and difficulty concentrating) and pramipexole was added to his treatment. Pramipexole was initiated at 0.125 mg tid and at the end of the second week it was increased to 0.75 mg/day. The patient complained about dysuria, spontaneous semen excretion, and defecation during urination. All of the side effects disappeared 2 days after the discontinuation of reboxetine. After the fourth week of pramipexole treatment the patient's depressive symptoms improved. The patient experienced the following adverse effects of pramipexole treatment: Reduced sleep duration (no more than 4-5 hours of sleep) and disruption of sleep continuity (3-4 awakenings per night). Zopiclon 7.5 mg/day was initiated and 7-8 hours of sleep were maintained. During 8 months of follow-up, at the fourth month 3 weeks of hypomania (euphoria, an increase in plans and projects, and increased sociability) were observed and venlafaxine was decreased from 150 mg/day to 75 mg/day. Seven days after reducing the venlafaxine dose the patient's hypomanic symptoms disappeared. The patient achieved his highest level of functioning in 5 years and was able to work and maintain social relationships.

### Case 2

Mrs. A was 39 years old, married, and retired. Her depressive symptoms appeared when she was 27 years old. Her younger brother was diagnosed with schizophrenia. She experienced hypomanic symptoms (euphoria, increased energy, and shopping, and reduced sleep

requirement) when she took sertraline. When she was 31 years old she was hospitalized at Ege University, Department of Psychiatry, Affective Disorders Inpatient Unit with a severe depressive episode. She was diagnosed with bipolar II disorder and lithium treatment was initiated. The patient experienced the recurrence of depression every fall during 8 years of follow-up (from September to January), despite sufficient serum lithium levels. Different treatment strategies were used and the patient was hospitalized 4 times due to long-term, recurrent, and severe depressive episodes. ECT, lithium in combination with antidepressant treatment (from 1999-2007, sertraline 200 mg/day, paroxetine 40 mg/day, venlafaxine 225-300 mg/day, amitriptyline 200 mg/day, and clomipramine up to 225 mg/day), lithium in combination with antidepressants and valproate (for 1 year [2003], 1000 mg/day), lithium in combination with antidepressants and lamotrigine (since 2004, 200-300 mg/day), and bright light therapy during the fall and winter (every late morning for 30 minutes) were administered. ECT was discontinued because the patient lived 6 hours from the hospital. When the patient was taking lithium 600 mg/day (serum lithium level 0.85 mEq/l), lamotrigine 300 mg/day, clomipramine 150 mg/day, and quetiapine 100 mg/day, she experienced depressive relapse, and then pramipexole 0.125 mg tid was initiated and tapered to 0.75 mg/day during the second week. At the fourth week of the treatment, she complained about nausea and vomiting; therefore, the dose was reduced to 0.50 mg/day. During this visit the patient's anhedonia, fatigue, and severe cognitive dysfunction were markedly improved, and her morning psychomotor retardation was mild. At the third month follow-up visit the quetiapine dose was decreased to 25 mg/day and clomipramine was reduced to 75 mg/day. At the sixth month pramipexole treatment follow-up visit she was in full remission. For the first time during 8 years of follow-up the patient experienced 6 months of remission.

## DISCUSSION

Two bipolar patients were presented in this article. With lithium treatment, manic/hypomanic episodes ceased; however there was a sufficient response to efficient treatment strategies for bipolar depressive episodes. In case 1 the duration of depressive episodes decreased; however, there was no change in the severity of the episodes or relapses. In case 2 there was no change in the duration and severity of the episodes with treatment; the patient continued to experience recurrent depression during the fall and residual depressive symptoms.

These cases were considered treatment-resistant and the dopamine agonist pramipexole was added to their treatment regimens. The patients' depressive symptoms improved within the first month of pramipexole use. During long-term follow-up (8 and 6 months, respectively), relapse or recurrence was not observed. Because of the risk of manic shift, the daily dose of pramipexole was not increased to the reported recommended dose (1-3 mg/day), but was kept at a low dose (0.50-0.75 mg/day). Both of the patients improved, with ongoing remission.

Pramipexole's antidepressant effects rely on studies conducted with bipolar and treatment-resistant depressive patients. Only 1 study was conducted with unipolar depression patients, which included 174 non-psychotic unipolar depression patients in a randomized, double blind parallel design study. Three doses of pramipexole (0.375, 1.0, and 5.0 mg daily) were compared with fluoxetine (20 mg daily) and a placebo. At 8 weeks pramipexole 1.0 mg/day and fluoxetine were more effective than the placebo (Corrigan et al., 2000). In open design studies pramipexole was added to mood stabilizers or antidepressants in the treatment of treatment-resistant depressive patients and response rates of 40%-50% were reported (Goldberg et al., 1999; DeBattista et al., 2000; Sporn et al., 2000; Lattanzi et al., 2002; Gupta et al., 2006). Manic shift was reported in patients with or without depression during pramipexole treatment (Sporn et al., 2000; Perugi et al., 2001; Singh et al., 2005; Sharma et al., 2007); in these case reports the authors did not observe any relationship between the pramipexole dose and manic shift, although the daily pramipexole dose was > 1 mg daily.

The antidepressant dose of pramipexole is unknown; however, the recommended daily dose is 0.125 -9 mg (Whiskey and Taylor, 2004). The reported mean pramipexole daily dose is 1.7 mg in double blind, placebo controlled bipolar depression studies (Goldberg et al., 2004; Zarate et al., 2004). The effective dose of pramipexole in the treatment of Parkinson's disease is 1.5-6.0 mg/day. At doses > 6 mg the severity and frequency of adverse events increase (Bennett and Piercey, 1999). Corrigan et al. (2000) did not observe a dose-response relationship in the treatment of depressive patients. Patients taking pramipexole 5 mg/day had greater improvement compared to those that took 1 mg/day, but the dropout rate was higher among patients that took the higher dose. Common side effects of pramipexole are nausea, sleep disturbance, daytime sleep attacks, agitation, postural hypotension, headaches, and tremors (Whiskey and Taylor, 2004). Initiation with low dose pramipexole (0.375 mg/day) and gradual

titration is recommended to improve tolerability, followed by increasing the dose every 5-7 days.

Pramipexole is a full dopamine agonist with high selectivity for the dopamine D2 receptors. Pramipexole has greater affinity for the D3 receptor subtype than D2 and D4 receptor subtypes (Bennett and Piercey, 1999). Pramipexole is different than other ergot derivatives, such as bromocriptine and pergolide, because it does not have any affinity for D1 receptors, and its different than non-ergot derivatives such as ropinirole because it has greater affinity for D3 receptors (Hubble, 2000). In preclinical studies additional treatment properties of D3 receptors on motor and psychiatric symptoms of Parkinson's disease were reported (Piercey, 1998). The anatomical configuration of D3 receptors is high in the neuronal circuit related to depressive states (especially in limbic areas). Primate studies show that pramipexole produces statistically significant decreases in regional cerebral blood flow in the bilateral orbitofrontal cortex, thalamus, operculum, posterior and anterior cingulate cortex, and insula (Black et al., 2002). It is known that some of these areas are involved in the pathophysiology of mood disorders (Mayberg et al., 2000; Drevets, 2001).

It is proposed that pramipexole has neuroprotective

properties, other than symptomatic improvement, in the treatment of Parkinson's disease (Hubble, 2000). Pramipexole, like dopamine agonists, reduces dopamine synthesis and turnover in the brain via activation of dopamine autoreceptors. This may minimize dopamine catabolic oxidation and neurotoxic oxy radicals. In addition to the effects of pramipexole at the receptor level, it may produce neurotrophic effects by up-regulation of anti-apoptotic protein bcl-2 (Carvey et al., 2001; Le and Jankovic, 2001). The neuroprotective properties of lithium and valproate originate in their effect on bcl-2. Pilot studies showed that the addition of pramipexole to lithium or valproate produces a synergistic increase in the expression of bcl-2 (Zarate et al., 2004).

## CONCLUSION

The efficacy and safety of a new dopamine agonist, pramipexole, were reported in studies of Parkinson's disease. Because of its different pharmacodynamics and pharmacokinetics, pramipexole offers new hope for the treatment of treatment-resistant depression. Manic shift is a problem in bipolar patients treated with the recommended daily dose. The 2 bipolar depression patients present here showed improvement with a daily dose of 1 mg.

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