Pramipexole in Rapid Cycling Bipolar Disorder: A Case Series

Matthew L. Prowler, MD, and Claudia F. Baldassano, MD

ABSTRACT

Pramipexole, a novel dopamine agonist, is approved for Parkinson’s disease and restless legs syndrome. Recent work has shown that pramipexole can provide a beneficial role in bipolar depression. To date, however, there has been no study of this compound for use in rapid cycling bipolar disorder. Cases of pramipexole augmentation in rapid cyclers with an active depressive episode are presented. A positive response with symptom reduction and without cycle induction or acceleration was observed. Possible mechanisms of this effect are considered. These findings suggest that pramipexole warrants more study in the treatment of affective disorders of varying illness courses.

INTRODUCTION

The phenomenology and validity of rapid cycling bipolar disorder remains a topic of debate in the literature. Rapid cycling has been conceptualized as a dimensional course specifier on a continuum of mood episodes (necessitating ≥4 episodes of mood disturbance in 1 year in a patient with a diagnosis of bipolar I or II). Whether or not rapid cycling represents a distinct etiologic variant of bipolar disorder remains unclear.1,2 While there are data to support the use of mood stabilizers and atypical antipsychotics for the treatment of rapid cycling, this effect has been predominantly observed in the manic phase of the disease course.3 However, rapid cyclers more often present in a depressed phase of illness and may also demonstrate increased depression severity when compared to non-rapid cycling bipolar patients.4,5

Pramipexole, a dopamine agonist with preferential affinity for the dopamine (D3) receptor, is approved for Parkinson’s disease and restless legs syndrome (RLS). Emerging evidence from two pilot studies6,7 shows that pramipexole can provide a beneficial role in bipolar depression. To date there has been no study of this compound for use in rapid cycling bipolar disorder. The authors present cases in which a positive response to pramipexole in rapid cyclers, with active depression phase predominance, has been observed.

These patients were evaluated and treated prospectively in the Hospital of the University of Pennsylvania Outpatient Bipolar Disorders Clinic. Diagnoses of bipolar disorder with rapid cycling were based on thorough initial evaluations and institution developed forms that follow the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition-Text Revision.8

CASE REPORTS

Case 1

Mr. C is a 46-year-old single white male with a 20-year history of bipolar I and rapid cycling, who presented
with a severe depressive episode of 6 month duration, and three previous and distinct, but less severe, depressive episodes within the past 12 months. His symptoms included depressed mood, decreased sleep with difficulty falling asleep, anhedonia, diminished energy, poor concentration, and decreased appetite resulting in a 7-pound weight loss. Suicidal ideation was not present. Mr. C’s medications included lithium 1,200 mg/day with a level of 1.1 mEq/l, carbamazepine with a level of 9.3 mg/l, and quetiapine 300 mg/day. This medication regimen had been helpful in reducing his cycling from 6–8 episodes to 3–4 episodes per year. For this current episode of depression, Mr. C had failed a therapeutic trial of lamotrigine up to 300 mg/day, aripiprazole augmentation up to 10 mg/day, olanzapine-fluoxetine combination up to 5/50 mg dose, and citalopram 60 mg/day. Pramipexole was added to his lithium/carbamazepine/quetiapine combination. The pramipexole was titrated slowly with an initial dose of .125 mg/day and increased every 3 days by .125 mg to a total dose of 2.5 mg/day. Mr. C responded rapidly to the pramipexole and began to feel significant improvement by day 12. By week 4, Mr. C reported improved mood with normal sleep, appetite, self-esteem, energy, and concentration. By week 12, Mr. C was in full remission of his depressive episode and his mood was considered euthymic. Side effects reported from pramipexole augmentation included mild nausea, which dissipated after 2 weeks of treatment, and sleepiness, which was mild and attenuated by taking at bedtime. After 1 year, Mr. C remains on pramipexole, lithium, and quetiapine. Carbamazepine was successfully tapered to discontinuation. His mood remains stable without evidence of rapid cycling.

Case 2

Ms. H is a 24-year-old single white female college student with bipolar I, rapid cycling, who experienced her first depressive episode at 15 years of age. Ms. H had four hospitalizations for mania and had been refractory to, or intolerant of, the following medications: carbamazepine, divalproex, olanzapine, aripiprazole, risperidone, quetiapine, and most antidepressants including selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors. Ms. H had spent significantly more time manic than depressed since illness onset, and reported three to four hypomanic or manic episodes in the past year (prior to this presenting episode). Ms. H’s mania responded to a combination of ziprasidone 320 mg/day, lithium 900 mg/day, and clonazepam 3 mg/day. She remained stable for 6 months on this regimen; however, she developed a severe depressive episode, which included low mood, poor sleep with frequent mid-cycle awakenings, low energy, diminished concentration, and passive suicidal ideation. Given her history of poor response to multiple conventional agents, pramipexole was initiated at .125 mg/day and titrated by .125 mg every 4 days. Ms. H began to show improvement in her depressive symptoms by day 5, which continued to remission of her depressive symptoms by 1 month of treatment at pramipexole 2.75 mg/day. Three months post-remission, Ms. H reported sub-syndromal depressive symptoms. The pramipexole was gradually raised to 3.5 mg/day but Ms. H began to have elevated energy and racing thoughts. Due to concerns of emerging hypomania, pramipexole was reduced to 3 mg/day with subsequent resolution of hypomanic symptoms. Her mood remains stable on 3 mg/day without any significant side effects.

Case 3

Mr. L is a 48-year-old divorced white male with a 12-year history of bipolar I disorder, rapid cycling, who presented with 4 weeks of worsening depressive symptoms in the context of a refractory disease course. His first episode of depression at 35 years of age was treated with paroxetine. In the third week of the SSRI trial, at a dose 30 mg, Mr. L reported a sudden increase in energy, grandiosity, irritability, and impulsive behavior. Despite SSRI discontinuation, Mr. L reported a progression of mood episodes, -8–10 episodes/year, and depression “more than 50% of the time.” Mr. L had one hospitalization for bipolar depression associated with suicidal ideation, and was refractory to trials of carbamazepine, divalproex, olanzapine, risperidone, and quetiapine, as well as >16 sessions of bilateral electroconvulsive therapy. At the time of evaluation for the index episode of depression, Mr. L was taking lamotrigine 300 mg/day, lithium carbonate 900 mg/day, aripiprazole 20 mg/day, and lithium thionine sodium 50 mcg/day. He reported hopelessness, anhedonia, low energy, and poor sleep, and scored a 28 on the Beck Depression Inventory (BDI). No suicidality was present. Thyroid hormone was discontinued and pramipexole was initiated at a dose of .125 mg/day and titrated every 4 days by .125 mg to a total dose of 1.5 mg/day. At 3 months, Mr. L reported full remission of depressive symptoms, no cycling, and no side effects to the pramipexole. At 6 months, he reported stable mood with a BDI of 6.

Discussion

In these three cases, the introduction of pramipexole was temporally related to the reduction or remission of depressive symptoms in rapid cycling bipolar patients. Effective doses were 1.5–3.0 mg, which is comparable to therapeutic doses that have been utilized for the treatment of Parkinson’s disease. At a higher dose, there were signs of
emergent hypomania in one patient, which resolved with dose reduction. Pramipexole was otherwise well tolerated with side effects including mild nausea and fatigue. The positive effects from pramipexole augmentation appeared to be durable, lasting from 6 months to 1 year in these cases. While significant clinical improvement was observed in each case, ideally, it would have been beneficial to compare responses by means of standardized ratings. In each case, pramipexole was augmented to an existing regimen that included three psychoactive medications, perhaps reflecting the challenge of treating rapid cycling bipolar disorder as well as the refractory nature of these patients’ diseases. While polypharmacy may confound a clinical picture, it is notable that a positive response was appreciated with pramipexole introduction despite discrepant concomitant agents.

The role of dopamine agonists is evolving in the treatment of affective disorders. This practice is supported by a small, but promising, database (Table). While monoamine depletion studies have yielded inconsistent findings over the years, numerous reports using animal stress models have suggested that hypoactivity or decreased responsiveness of the mesolimbic dopamine pathway may be associated with, or mediate, concurrent depressed states. Further, potentiation of dopamine receptors has been forwarded as a final pathway mechanism of antidepressants. These findings were then clinically reinforced by two randomized controlled trials using pramipexole augmentation in depressed bipolar patients.

Other factors are worth consideration. Pramipexole, like antidepressants, has a suppressive effect on rapid eye movement (REM) sleep. In patients with RLS, pramipexole increased REM sleep latency (interval from sleep onset to first REM phase) and decreased total REM sleep time. Past work has found decreased REM latency in patients with depression. Thase and colleagues reported more frequent REM sleep abnormalities, including increased REM phase sleep, in patients with recurrent depression compared to a single episode. While findings from unipolar depression may not correlate to those of bipolar disorder, it is noteworthy that physiologic changes in sleep architecture, which pramipexole may affect therapeutically, are more pronounced in states of extreme affective cyclicity.

Furthermore, the D_3 receptor, for which pramipexole has a high affinity, is densely distributed in the mesolimbic system. This region has been implicated in the anhedonic and motoric symptoms of depression. Pramipexole is also thought to have neurotrophic effects, which are mediated by the anti-apoptotic protein, bcl-2. This is the same mechanism for proposed neuroprotection seen with lithium and valproic acid.

One concern in the use of dopamine agonists for bipolar disorder has been the risk of manic switch induction. The pramipexole trial by Zarate and colleagues found a hypomanic switch in one patient in the study group, which was fewer than those appreciated in the placebo group. A study by Leverich and colleagues examined manic switch rates in bipolar depression and augmentation with venlafaxine, sertraline, and bupropion versus placebo. Bupropion, the predominantly dopaminergic agent, conferred the lowest risk of switch to a hypomanic or manic state.

The risk of induction or acceleration of cycling is another consideration in the use of an agent such as pramipexole when treating depression in the context of rapid cycling.

### TABLE

<table>
<thead>
<tr>
<th>Study</th>
<th>Type (n)</th>
<th>Subjects/Intervention</th>
<th>Outcome</th>
<th>AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zarate CA et al</td>
<td>Double-blind, placebo-controlled (21)</td>
<td>Bipolar II depression; augmentation to lithium or valproate</td>
<td>Greater therapeutic response compared to placebo (MADRS)</td>
<td>One hypomanic switch in study group, two in placebo group</td>
</tr>
<tr>
<td>Goldberg JF et al</td>
<td>Randomized, double-blind, placebo-controlled (22)</td>
<td>Bipolar I and II, treatment-resistant depression; augmentation to mood stabilizer</td>
<td>Greater study completion and improvement compared to placebo (HAM-D, CGI)</td>
<td>One hypomanic switch in study group</td>
</tr>
<tr>
<td>Lattanzi L et al</td>
<td>Naturalistic, prospective (37)</td>
<td>Bipolar/unipolar depression; augmentation to antidepressant</td>
<td>Observed clinical response to augmentation (MADRS, CGI-S)</td>
<td>6 weeks, one D/C due to AEs</td>
</tr>
<tr>
<td>Sporn J et al</td>
<td>Chart review (32)</td>
<td>Bipolar/unipolar depression; augmentation to antidepressant or mood stabilizer</td>
<td>Observed clinical response to augmentation (CGI)</td>
<td>One case transient hypomania, eight D/C due to lack of efficacy, four D/C due to side effects</td>
</tr>
<tr>
<td>Gupta S et al</td>
<td>Case series (3)</td>
<td>Bipolar/unipolar depression; augmentation to atypical antipsychotic</td>
<td>Observed clinical response to augmentation (HAM-D)</td>
<td>None reported</td>
</tr>
</tbody>
</table>

MADRS=Montgomery Asberg Depression Rating Scale; HAM-D=Hamilton Rating Scale for Depression; CGI=Clinical Global Impression; D/C=discontinued; AEs=adverse events; CGI-S=Clinical Global Impression—Severity.
Previous studies have shown that antidepressants are risk factors for inducing cycling in bipolar patients with a history of rapid cycling. Since pramipexole is evincing antidepressant effects in two pilot studies as well as in the three cases presented in this article, one is prudent to raise a similar concern. For these patients that demonstrated a baseline rapid cycling pattern, pramipexole augmentation did not induce or accelerate cyclicity. This remains an important question that warrants study in a larger cohort.

This series builds on the findings of earlier studies to suggest that pramipexole is a promising pharmacologic agent that deserves more study in the treatment of affective disorders of varying illness courses.

REFERENCES