Pramipexole in the Treatment of Refractory Depression in a Patient with Rapid Cycling Bipolar Disorder

Sir,

Bipolar depression offers significant treatment challenges since this condition is associated with treatment resistance as well as potential risk of “switching” to mania/hypomania with treatment.[1,2] The presence of rapid cycling-course offers added substantial therapeutic challenge with limited number of safe therapeutic options. Pramipexole, a dopaminergic agonist has been evaluated in treatment resistant depression[3] and it probably works with a distinct dopamine based neural mechanism.[4] However, its use in bipolar depression resistant to multiple therapeutic options in the context of rapid cycling disorder has not been reported.

Mr. S, a 37-year-old businessman with a 12-year history of bipolar II illness, in the initial 10 years of the course of the illness, had 13 episodes of depression and 7 episodes of hypomania. In the latter 2 years, he had multiple depressive episodes and 1 episode of hypomania. The depressive episodes would last between 2 weeks and 4 months while hypomaniac episodes would last between 1 week and 2 months. The most recent was an episode of severe depression along with catatonic symptoms (ICD-10) which continued for 7 months despite adequate treatment with lithium carbonate and lamotrigine, olanzapine and fluoxetine and 2 sequential adequate trials with antidepressants [sertraline (upto 150 mg) and escitalopram (20 mg) (both under the cover of lithium carbonate)]. He received lorazepam up to 6 mg per day for 2 weeks, for the catatonic symptoms without significant benefit. He also received 3 bitemporal Electro Convulsive Therapy (ECT) which was discontinued due to prolonged post-ictal confusion.

In addition to the existing treatment regimen consisting of lithium carbonate 900 mg/day (serum lithium level-0.8 meq/L), lamotrigine 150 mg/day and olanzapine 10 mg, pramipexole was introduced. The dosage was initially at 0.125 mg per day, hiked up to 0.5 mg per day in two divided doses over 2 weeks. Mr. S reported significant improvement in symptoms from the second week of initiation of pramipexole. His mood improved along with significant improvement in psychomotor activity and catatonic symptoms. The Hamilton Depression Rating Scale (HDRS) score improved from 22 to 7 by the end of 1 month of treatment. The Bush-Francis Catatonia Rating Scale (BFCRS) scores reduced from 8 to 0 during the same period. This clinical improvement was confirmed through independent assessment by two psychiatrists. The improvement persisted until the latest review 2 months after starting pramipexole and he has not reported any adverse effects with the drug.

DISCUSSION

There are small randomized-controlled trials and open-label studies,[3,5] supporting the efficacy of pramipexole in resistant bipolar depression. However, in majority of these studies, “resistance” indicates failure to respond to one or two medications. The improvement in depression “refractory” to multiple treatment options as shown in this case is note-worthy. Pramipexole did not cause adverse effects in the index patient, in particular, “switch” to hypomania, an important concern in the context of rapid cycling course. Considerable improvement was observed in many domains including catatonic symptoms. Hence, pramipexole augmentation appears to be a safe and effective treatment strategy in bipolar depression when conventional treatment options fail.

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REFERENCES

1. Vieta E, Valenti M. Pharmacological management of bipolar depression: Acute treatment, maintenance, and prophylaxis. CNS Drugs 2013;27:515-29.
2. Citrome L. Treatment of bipolar depression: Making sensible decisions. CNS Spectr 2014;19 Suppl 1:1-12.
3. Goldberg JF, Burdick KE, Endick CJ. Preliminary randomized, double-blind, placebo-controlled trial of pramipexole added to mood stabilizers for treatment-resistant bipolar depression. Am J Psychiatry 2004;161:564-6.
4. Mah L, Zarate CA Jr, Nugent AC, Singh JB, Manji HK, Drevets WC. Neural mechanisms of antidepressant efficacy of the dopamine receptor agonist pramipexole in treatment of bipolar depression. Int J Neuropsychopharmacol 2011;14:545-51.
5. Lattanzi L, Dell’Osso L, Cassano P, Pini S, Rucci P, Houck PR, et al. Pramipexole in treatment-resistant depression: A 16-week naturalistic study. Bipolar Disord 2002;4:307-14.

Mirtazapine Induced Akathisia: Understanding a Complex Mechanism

Sir,

Akathisia is a disabling extrapyramidal adverse effect which can occur with various psychotropic agents. Imbalance between dopaminergic and serotonergic/noradrenergic neurotransmitter systems is considered as a potential mechanism of akathisia. Mirtazapine is a noradrenergic and specific serotonergic antidepressant (NaSSA) which acts by blocking alpha 2 receptors in addition to antagonizing the 5HT2 and 5HT3 receptors selectively. Mirtazapine has been used to treat neuroleptic induced akathisia. Intriguingly, this medication has been associated with occurrence of akathisia as an adverse effect. Here we report the case of a patient with depressive illness who developed mirtazapine induced akathisia which was relieved by discontinuing the drug and by substituting it with another antidepressant.

A 42-year-old lady with past history of one depressive episode 2 years ago presented with 4 month history of pervasive low mood, marked social withdrawal, anhedonia, ideas of hopelessness, occasional expressing of death wishes, decreased sleep and appetite. Her physical examination was within normal limits. She had diabetes mellitus which was poorly controlled as she was not regular with her antidiabetic medication since the onset of depressive symptoms. She did not significantly improve with tablet fluoxetine up to a dose of 40 mg given for 5 weeks. Subsequently she was started on tablet mirtazapine 15 mg. After initiation of mirtazapine, family members noticed that she was not sleeping at night and was seen pacing restlessly inside the house. On clarifying, the patient reported feeling anxious and jittery. She felt a sense of uneasiness in her feet and felt like walking constantly. She was unable to sit peacefully for more than a few minutes. There were no signs of elevation of mood and hence a possibility of antidepressant induced switch to mania/hypomania was ruled out. A clinical inference of akathisia was made. The Naranjo probability scale suggested a possible relationship between mirtazapine and this adverse event (score 6). Mirtazapine was stopped and the akathisia improved immediately in a couple of days. Barnes Akathisia Rating Scale score dropped from 6 to 0 within 2 days of stopping mirtazapine. The patient was subsequently started on tablet escitalopram 5 mg and gradually increased to 10 mg under close supervision. She did not report of any recurrence of akathisia symptoms and the depressive episode responded to escitalopram 10 mg.

The patient mentioned in this report developed akathisia immediately after the initiation of mirtazapine 15 mg/day and it was relieved promptly after discontinuation of the drug, indicating that the adverse effect was indeed due to mirtazapine. The exact mechanisms for akathisia with mirtazapine is unclear. Mirtazapine has broad range of affinities for adrenergic, serotonergic and histaminergic receptors and this might contribute to its favorable effects in clinical and preclinical models. It has been found that α2 adrenoceptor blockade is a key feature in the mechanism of mirtazapine action. The α2 adrenoceptors are found in prefrontal cortex and striatum. Even though the affinity for mirtazapine in higher for the...