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CASE REPORT

Effectiveness of methylphenidate as augmentation therapy after failure of adjunctive neuromodulation for patients with treatment-refractory bipolar depression: a case report

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Abstract: Adjunctive use of methylphenidate, a central stimulant, has been considered as a potential therapeutic choice for patients with refractory unipolar, geriatric, or bipolar depression, and depression secondary to medical illness. We present a case of bipolar depression in which the patient responded significantly to augmentation with methylphenidate, without any side effects, after failure of adjunctive repetitive transcranial magnetic stimulation and electroconvulsive therapy. Mr U, a 56-year-old man with bipolar I disorder, had melancholic symptoms during his sixth episode of bipolar depression. After failure of repetitive transcranial magnetic stimulation and electroconvulsive therapy, he was treated with fluoxetine 80 mg/day, duloxetine 360 mg/day, mirtazapine 60 mg/day, and sodium valproate 1,000 mg/day, with no improvement. We added methylphenidate at a dose of 10 mg/day for one week, which resulted in mild clinical improvement, and then methylphenidate extended-release 20 mg/day for one week, with significant clinical improvement. He tolerated his medications well. His clinical recovery was stable over one year. The patient's antidepressants and methylphenidate were gradually tapered and finally discontinued after one year with no withdrawal syndrome. To date, he remains well on sodium valproate as monotherapy and is being followed up at our bipolar department. This case suggests that methylphenidate augmentation might be a therapeutic option when treating highly treatment-resistant patients with bipolar depression, even if they had not responded to adjunctive neuromodulation. In these clinical situations, physicians might be interested in prescribing methylphenidate because of its efficacy and safety.

Keywords: bipolar disorder, treatment-refractory, neuromodulation-refractory, depression, methylphenidate

Introduction

There is no definition of treatment-resistant bipolar depression in the literature. The International Society for Bipolar Disorders (ISBD) Task Force published their consensus definition of treatment response in bipolar depression[1] and proposed a nomenclature for relapse, remission, and recurrence, but did not define treatment resistance. Treatment response is defined as >50% improvement in the core DSM (Diagnostic and Statistical Manual of Mental Disorders) criteria for depression. Treatment-resistant bipolar patients remain symptomatic despite the best available care. Here, we propose that treatment resistance in bipolar depression be defined as failure of pharmacotherapy associated with failure of neuromodulation, such as electroconvulsive therapy and repetitive transcranial magnetic stimulation (rTMS).

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The antidepressant effects of psychostimulant drugs have been underappreciated because of conflicting data concerning efficacy, tolerance, and dependence. Orr and Taylor[2] reported that methylphenidate reduced tiredness and enhanced attention and arousal, and recommended its use for treating depressive episodes. Candy et al[3] reported that the main advantage of methylphenidate over antidepressants might be its rapid onset of action within one day, and highlighted that, unlike conventional antidepressants, methylphenidate reduces fatigue. Stoll et al[4] and Metz and Shader[5] showed that the combination of methylphenidate and a selective serotonin reuptake inhibitor antidepressant was effective. In a Cochrane meta-analysis,[3] Candy et al reported that psychostimulants (excluding modafinil) significantly reduced symptoms of depression in comparison with placebo.

Emphasizing the role of psychostimulants in increasing dopamine production, Stahl[6] and Nierenberg et al[7] support the view that psychostimulants are preferable for the more "biological" depressive disorders (melancholic and bipolar depression) but not for the wider spectrum of depressive conditions (especially nonmelancholic disorders). Reconsideration of the overall psychostimulant class is likely to be encouraged by the recent introduction of modafinil, a novel psychostimulant that has been studied in both unipolar and bipolar disorders.[8] Psychiatrists should always remember the potential usefulness of psychostimulants in the treatment of depression based on available evidence.

This paper reports the antidepressant effects of methylphenidate, suggesting that this agent might be highly effective and safe, even after neuromodulation had failed, with no withdrawal syndrome when stopped. Thus, methylphenidate might be of some considerable utility in managing patients with treatment-resistant depression.

We present a case of bipolar depression in which the patient responded significantly to methylphenidate augmentation, without any side effects, after failure of adjunctive rTMS and electroconvulsive therapy.

Case report

Mr U, a 56-year-old man with bipolar I disorder according to DSM-Fifth Edition criteria,[9] experienced his first melancholic depression in 1976, which was followed by five melancholic episodes and four manic episodes. He did not show any comorbid psychiatric condition and had no history of drug or alcohol abuse.

His sixth melancholic depressive episode began in March 2008, just after a prison guard workmate had committed suicide. Mr U was admitted to our bipolar department on April 1, 2008. He showed a depressed and anxious mood, negative and obsessive thinking, loss of interest in activities, impairment in activities of daily living, psychomotor retardation, self-blaming behavior, guilty and suicidal thoughts, insomnia, reduced appetite, and a 5 kg loss of body weight. His laboratory examinations included a full blood count, blood biochemistry and urinalysis, electrocardiography, electroencephalography, and structural cerebral magnetic resonance imaging. His physical and laboratory examinations were normal. From April 1, 2008, blood pressure, pulse and temperature were monitored once daily by a nurse. His initial 21-item Hamilton Depression Rating Scale[10] score was 37 and his Clinical Global Impression-Severity[11] score was 6. From April 1, 2008 until June 10, 2010, he received various antidepressant (venlafaxine extended-release, clomipramine or duloxetine, combined with either paroxetine or mirtazapine) and mood stabilizer (olanzapine, aripiprazole, or sodium valproate) combinations with no significant clinical improvement. Each medication was prescribed at an optimum and stable dosage for the minimum recommended duration, with no significant clinical improvement. On February 6, 2009, we assessed the patient's whole-brain voxel-based regional cerebral blood flow with ^{99m}Tc-ethyl cysteinate dimer single photon emission computed tomography, and hypoperfusion was shown in the bilateral anterior cingulate cortices, the right inferior parietal cortex, and the left dorsolateral and bilateral orbital prefrontal cortices. rTMS was initiated on February 15, 2009. Twenty treatment sessions were administered over a 4-week period (five sessions per week). In mid March, after these sessions were completed, Mr U showed no significant clinical improvement. rTMS was initiated again, with 20 treatment sessions being administered over a 4-week period until April 15, 2009. After the last rTMS session, Mr U showed no significant clinical improvement. His physicians initiated electroconvulsive therapy three times a week on April 18, 2009 for 2 months until June 19, 2009. Mr U showed no significant clinical improvement after 24 sessions of electroconvulsive therapy. At that time, he was treated with a combination of fluoxetine 80 mg/day, duloxetine 360 mg/day, mirtazapine 60 mg/day, and sodium valproate 1,000 mg/day. On June 29, 2009, we added methylphenidate at a dose of 10 mg/day for one week. Two days after introduction of methylphenidate, Mr U reported some mood improvement after a single early morning dose. The second week after its initiation, the dose of methylphenidate was increased to 20 mg/day for one week using an extended-release tablet formulation, with significant improvement. Two weeks later, Mr U achieved significant and lasting clinical improvement, with Hamilton Depression Rating Scale and Clinical Global Impression-Severity scores of

8 and 3, respectively. He was in a stable condition one month after starting adjunctive treatment with methylphenidate. He tolerated his medications well and did not report any side effects. His antidepressants and methylphenidate were gradually tapered and finally discontinued after one year. He remains well on sodium valproate monotherapy and is regularly followed up at our bipolar department.

Discussion

This case report suggests that methylphenidate may be an effective and safe medication for treating treatment-resistant bipolar depression. Methylphenidate was well tolerated with no drug-related switching to hypomania or mania. During the treatment period, the patient did not abuse the prescribed stimulant or any other substance. Improvements in the Clinical Global Impression-Severity and Hamilton Depression Rating Scale scores indicated clinically significant improvement.

Our patient's melancholic depression was not improved satisfactorily by the combination of duloxetine, mirtazapine, clomipramine/fluoxetine, and olanzapine/valproate after adjunctive rTMS or electroconvulsive therapy. It was not until the patient received methylphenidate 20 mg/day that his severe depression improved substantially and durably, suggesting that adjunctive methylphenidate may have had an additional therapeutic effect in this difficult-to-treat patient. Unfortunately, whole-brain regional cerebral blood flow with single photon emission computed tomography was not performed at that time.

Theoretical use of methylphenidate has been discussed by Stahl,[12] who suggests that the dopamine-releasing stimulant properties of methylphenidate allow this agent to be used in combination with other antidepressants. Stahl suggests that methylphenidate may be particularly useful in patients with retarded or melancholic depression or those who require an antidepressant concomitantly with a mood stabilizer for bipolar depression. While a number of authors[2–4,6] have reported that methylphenidate is effective for treating treatment-resistant bipolar depression, Patkar et al[13] did not demonstrate any statistically significant benefit from augmentation with methylphenidate in treatment-resistant depression in a randomized, double-blind, placebo-controlled trial.

Theoretical and clinical use of methylphenydate is broadly consistent with our observations in our bipolar department over recent years, ie, that methylphenidate is useful (as monotherapy or augmentation) in patients with melancholic or bipolar depression, including many patients who do not respond to conventional antidepressant drugs or neuromodulation techniques.

Conclusion

Our case suggests that methylphenidate can be used as an adjunctive agent for some patients with treatment-resistant bipolar depression or melancholia who do not adequately respond to combination antidepressant therapy, a mood stabilizer, and rTMS or electroconvulsive therapy. Clearly, placebo-controlled studies are warranted within these diagnostic subgroups to test our clinical impressions. Such augmentation studies would be advanced by measuring serum levels of the relevant antidepressants to determine whether psychostimulants act by increasing these levels and/or if they have independent antidepressant activity.

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Disclosure

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