TITLE: The case for and against selective serotonin reuptake inhibitors in rapid cycling bipolar disorder

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ABSTRACT

Patients affected by the rapid cycling variant of bipolar disorder often experience significant functional difficulties. Physicians caring for affected patients face many challenges managing the turbulent course of this disorder, complicated at times by psychiatric comorbidities (including substance use disorders), polypharmacy, risk management (of suicidality and aggression), and difficulties with community functioning. There is some controversy about the use of selective serotonin receptor inhibitors (SSRIs) in managing bipolar depression, particularly in the rapid cycling variant. The potential benefit of SSRIs in reducing depressive symptoms must be balanced against the risks of mood phase switching and overall worsening of the rapid cycling course. This case report highlights challenges inherent in the application of SSRIs in a case of treatment-refractory rapid cycling bipolar disorder, and discusses the controversy of their use.

INTRODUCTION

Bipolar disorders (BD) are a group of major mood disorders that have a combined total lifetime prevalence of 2.4%.¹ They are characterized by episodes of mania, hypomania, and major depression.² Bipolar disorders are separated into two main subtypes, BDI and BDII.² Individuals with BDI experience at least one episode of mania, with or without depressive episodes, whereas BDII features hypomanic and depressive episodes, without full manias.²

In the DSM-5, a specifier exists to denote a “rapid cycling” variant of BD. The rapid cycling specifier is applied when an individual experiences at least four mood episodes (depressive, manic, or hypomanic) over a 12 month period.² Rapid cycling affects up to a third of patients with BD and is associated with a longer course of illness, earlier age of onset, more illicit substance use, and increased suicidality.³ Rapid cycling is often, but not always, a transient phenomenon, and most individuals convert to non-rapid cycling after around 12 months.⁴

Although the manic and hypomanic phases are critical to the diagnosis of BD, affected individuals typically spend substantially more time depressed than manic or hypomanic.⁵⁻⁶ Bipolar depression is often substantially impairing and difficult to treat. One treatment modality includes serotonin reuptake inhibitors (SSRIs), an antidepressant that increases synaptic serotonin and stimulation. However, there exists a risk of mood phase switching, where a patient converts from depression to mania or hypomania, associated with the use of most traditional antidepressants in BD treatment, such as (SSRIs) or the closely-related serotonin/noradrenalin reuptake inhibitors (SNRIs). These risks have to be weighed against their potential benefits. This report offers a reliably documented case of the use of SSRIs to assess the effectiveness in management of rapid-cycling bipolar disorder.

PATIENT PRESENTATION

JD (identifier modified) is a 66-year-old male residing in a forensic psychiatric hospital with treatment-refractory rapid cycling BDI. He has been detained in hospital since a finding of not criminally responsible (NCR) was made approximately 20 years ago. Prior to his NCR finding, he had numerous historical psychiatric hospitalizations beginning in his early 20s. Since his finding of NCR, several brief attempts at community placement were made; they were unsuccessful due to functional impairments associated with his severe mood episodes, medication nonadherence, and substance use. His history is otherwise notable for a cannabis use disorder (in sustained remission in a controlled environment), hypothyroidism, and mobility issues secondary to arthritis, sciatica, and probable antipsychotic-induced parkinsonism.

JD's depressive episodes are characterized by dysphoric mood, anergia, amotivation, and apathy. He experiences notable leaden paralysis. His physical function deteriorates to the point of being bed ridden for several consecutive weeks; he becomes incontinent of urine and feces, and requires enhanced nursing supports to eat and drink. During episodes of mania, JD presents with elevated energy, labile affect, impulsivity, and disinhibition; locked seclusion and physical restraints were often required historically to manage his risk of physical and/or sexual aggression. Although the intensity of his manic episodes has attenuated over the past year with the introduction of the atypical antipsychotic clozapine, his frequent and severe depressive episodes remain a barrier to community reintegration.

On chart review, in 2017-18 (approx. 14 months), JD had 7 mood disturbances: 4 depressive episodes and 3 hypomanic/manic episodes. JD was euthymic for less than one month combined. On average, JD's depressive phases lasted 6 weeks and his manic phases lasted 3.5 weeks. During this time period, his regimen included mood stabilizers (lithium and valproic

acid), antipsychotics (olanzapine, methotrimeprazine, zuclopenthixol decanoate), benztropine, and levothyroxine.

Treatment with an SSRI

Although JD had been on generally the same medication regimen for over a year, the treating team decided to trial an SSRI as he continued to experience ongoing mood episodes, including debilitating depression. In late 2018, JD was started on an SSRI (citalopram) to manage the depressed phases of his BD. Dosing ranged from 5-20 mg, and the medication was discontinued with taper when his mood became euthymic. After citalopram initiation, in 2018-2019 (16 months), JD had 10 mood disturbances: 6 depressive episodes and 4 hypomanic/manic episodes. He was euthymic for approximately 6 weeks. On average, his depressive phases lasted 4 weeks and his manic phases lasted 3.5 weeks.

DISCUSSION

Use of SSRIs in Bipolar Depression Generally

According to the Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorder (ISBD) 2018 Bipolar Disorder treatment guidelines, SSRIs are not first line treatments in bipolar disorder depression due to the risks of mood phase switching to mania and rapid cycling.⁷ The guidelines make different recommendations for the use of SSRIs in BDI and BDII.

For BDI, SSRIs are recommended only when patients do not respond adequately to first line treatments (including lithium, lamotrigine, and select atypical antipsychotics), and are only appropriate when patients are on antimanic prophylaxis.⁷ The use of SSRIs in patients with a

history of antidepressant-induced mania or hypomania, predominant mixed features, and recent rapid cycling should be used cautiously or avoided.⁷ CANMAT/ISBD recommends that antidepressant monotherapy should not be used in patients with BD depression due to lack of efficacy and risk of mood phase switching.⁷ In patients with previous treatment response to antidepressants and no history of treatment-induced switch, adjunctive antidepressants may be appropriate.⁷

In contrast to BDI, the use of SSRIs in BDII is less likely to induce mania.⁷ The ISBD task force determined that the risk-benefit ratio of SSRIs was more favorable in BDII.⁷ However, SSRIs should still be used only in patients with pure depression, and avoided in patients with mixed symptoms or a history of antidepressant-induced hypomania.⁷ In patients with BDII with mainly pure non-mixed depression, SSRI monotherapy can be considered as second- or third-line treatment, depending on the drug.⁷

What About SSRIs in Rapid Cycling BD?

There is some controversy in the literature as to whether SSRIs and other antidepressants are appropriate to use in any rapid cycling BD, with some publications indicating their effectiveness,⁸⁻⁹ others showing benefit only in certain subpopulations,¹⁰ and still others underlining their deleterious effects.¹¹⁻¹⁴ For example, an analysis of the STEP-BD randomized control trial suggested SSRI treatment worsens rapid cycling.¹² The trial included 17 treated rapid-cycling subjects who had achieved clinical recovery from acute BD depression (includes BDI, BDII and BD not otherwise specified) with an antidepressant (primarily SSRIs and SNRIs) and a mood stabilizer. Rapid cycling patients who continued with the antidepressant therapy experienced more than twice the number of mood episodes per year compared to non-rapid

cycling patients.¹² No differences were seen between the rapid cycling and non-rapid cycling patients that discontinued antidepressant therapy.¹²

In contrast, an open label randomized trial of 83 patients with BDII found that that venlafaxine (an SNRI) monotherapy was more effective and had a similar mood conversion rate to lithium monotherapy for both rapid cycling and non-rapid cycling patients.¹⁵ Interestingly, in a separate study, the same authors found that fluoxetine (an SSRI) monotherapy was more effective in patients with rapid cycling BDII depression compared to those with non-rapid cycling depression.¹⁶ In a third study, the authors compared maintenance treatment of fluoxetine monotherapy and lithium monotherapy in rapid and non-rapid cycling BDII patients.¹⁷ They found that over a 12 week period, depressive relapse and treatment-emergent mood conversion episode rates were similar between the two treatments, and between rapid and non-rapid cycling patients.¹⁷

In this specific case with JD, it is unclear whether he benefited from the use of a SSRI. He had 7 mood disturbances without SSRI treatment and 10 with SSRI treatment over roughly equivalent timeframes, suggesting SSRI treatment may have worsened his rapid cycling course. However, the length of his depressive phases on SSRI treatment were shorter (on average 4 weeks vs 6 weeks), while his manic phases were approximately the same. He also spent more time euthymic during the SSRIs treatment period.

Given JD's long-term inpatient status, there is a high degree of confidence that his mood episodes were reliably documented during the time period in question. There are limitations to drawing conclusions from JD's course; the introduction of clozapine occurred during the reported period, the period represented a small sample of his historical illness, and there was an increased frequency of documented assessments of the latter time period, which could have

captured more mood disturbances. Despite an apparent improvement in the intensity and duration of depressive symptoms, the worsening of the overall course of his illness was consistent with other findings in the published literature, and stands as a cautionary tale against the use of SSRIs in this clinical population.

CONCLUSIONS

Clinicians should be aware that modern antidepressants, such as SSRIs, may be used to treat refractory rapid cycling bipolar disorder when there are no contraindications, such as a previous history of antidepressant induced mood switching. The available literature suggests the risk of worsening a rapid cycling course with SSRI treatment may be higher in BDI than in BDII. There is not enough evidence, including this report, to support a trial of SSRIs, with or without antimanic prophylaxis, in refractory cases of rapid cycling BDI. More research, including randomized controlled trials, would help clarify the appropriate role for SSRIs in bipolar depression.

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