Case Report

Cariprazine in an Adolescent with Tourette Syndrome with Comorbid ADHD and Depression: A Case Report

Jesjeet Singh Gill *

Posted Date: 14 August 2023

doi: 10.20944/preprints202308.1023.v1

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Cariprazine in an Adolescent with Tourette Syndrome with Comorbid Attention Deficit Hyperactive Disorder and Depression: A Case Report

Jesjeet Singh Gill

Department of Psychological Medicine, University Malaya, Kuala Lumpur, Malaysia; jesjeet@um.edu.my

Abstract: Tourette syndrome is a complex neuropsychiatric condition that manifests in childhood and is often associated with other psychiatric comorbidities. This case describes a young male with Tourette syndrome with major depressive disorder and attention deficit hyperactivity disorder (ADHD), who experienced troublesome side-effects due to his existing medications (escitalopram, risperidone and methylphenidate). In order to control his tics, ameliorate depressive symptoms, and eliminate side-effects of stiffness and sedation, risperidone was switched to cariprazine, a third-generation antipsychotic medication with D3-D2 partial agonism. In addition, the antidepressant dose was also increased. With the new combination, the patient reported good control of his tics, together with significant improvement in depressive symptoms and no side-effects. Based on this case and the reviewed literature, cariprazine might be a viable option for patients with Tourette syndrome with other comorbid illnesses, who are prone to side effects of medication.

Keywords: cariprazine; Tourette syndrome; major depressive disorder; ADHD; tics

1. Introduction

Tourette syndrome is a complex neuropsychiatric condition characterized by multiple tics i.e., sudden, repetitive, and stereotyped motor movements that affect discrete muscle groups. It is a unique neuropsychiatric condition as it sits at the interface of neurology (a movement disorder) and psychiatry (a behavioral disorder [1]. The 5th Edition of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM 5) states that there must be the presence of both motor and vocal tics, but not necessarily at the same time. The tics may wax and wane, but must persist at least for 1 year after the onset. It also states the onset must occur before the age of 18 years old [2]. It is estimated to affect about 1% of children and adolescents with a typical age of onset between the years of 4 to 6, usually following a stressful life-event, such as the start of school, being bullied or any psychosocial stressors [3,4]. The most severe symptoms are usually apparent between the ages of 10 to 12 years [4]. In most cases a marked reduction in severity and frequency of tics is expected over time regardless of medical treatment, but in some cases the symptoms may persist into adulthood [5]. The prevalence of Tourette syndrome in adults is low, only about 0.05% is affected [6] and it is more common in males than females (3).

Tourette syndrome is highly associated with other psychiatric conditions, such as Attention Deficit Hyperactivity Disorder, Obsessive Compulsive Disorder, affective disorders including Major Depressive Disorder and Anxiety disorders [2,7]. Indeed, affective symptoms can be present in up to 76% of Tourette syndrome patients with around 10% meeting the diagnostic criteria for Major Depressive Disorder [8]. A study by Chou et al. even found that the risk of developing Major Depressive Disorder is five times more likely in patients with Tourette syndrome as compared to the normal population [9]. In terms of Attention Deficit Hyperactivity Disorder, more than 50% of patients with Tourette syndrome can be affected [10] with it. Males with Tourette syndrome are more likely to have a comorbid Attention Deficit Hyperactivity Disorder as compared to females, and tend to have a poorer outcome. These many comorbidities are associated with greater functional, social, and academic impairment, therefore impacting the quality of life of patients negatively [11]. Tics typically have the greatest effect on a patient's self-esteem and relationships with family and friends

 doi:10.20944/preprints202308.1023.v1

around the ages of 7 to 12 years, especially during periods when forceful motor tics waxes, accompanied loud vocal tics that may persist non-stop for several hours [3].

The etiology of Tourette syndrome is most likely multifactorial, with many causes studied and proposed. Family and twin genetic studies have provided strong evidence that genetic factors are implicated in the transmission in families with a vulnerability to Tourette syndrome and related disorders. Other etiological causes that have been proposed include perinatal trauma, severe psychosocial trauma and drug abuse, particularly stimulants [3].

The treatment of Tourette syndrome is complex. It is complicated by the variability of symptoms associated with this condition, as well as the different presentation among different individuals. Various studies have shown that there is no single pharmacological agent that has been identified that can reliably treat tics in all sufferers. To conclude whether a particular medication is efficacious in a particular child is complicated by the waxing and waning nature of the symptoms. A medication that appears to work in the beginning may turn out to be non-efficacious when the symptoms wax. A trial and error strategy is likely needed to determine the best medication, or treatment combinations in those with more complex symptoms, such as those with concurrent obsessive compulsive, attention deficit hyperactive or depressive symptoms. In these types of situations, especially involving children, there is a real concern regarding the use of these medications at a young age, together with the potential of drug interactions and contraindications [12].

Tics are usually treated with dopamine blockers i.e., antipsychotics, given the notion that the higher the potency of dopamine blockade is, the greater reduction in tics (80-90%) can be achieved [12]. Current antipsychotic medications approved by the US Food and Drug Administration (FDA) for the treatment of tics in Tourette syndrome are pimozide, haloperidol and aripiprazole [12–14]. Studies investigating the efficacy of risperidone have reported positive outcomes and therefore risperidone is also frequently prescribed for Tourette syndrome [12,15]. However, antipsychotics are usually associated with numerous troubling side effects. Risperidone can causes weight gain, sedation, extrapyramidal symptoms and prolactin elevation. Aripiprazole has been known to cause drowsiness, akathisia, restlessness, and sleep disturbance [16]. For cases with comorbid depression and anxiety, serotonin reuptake inhibitors (SSRIs) are often utilized, while stimulants such as methylphenidate are used for when symptoms of Attention Deficit Hyperactivity Disorder are present [11,17].

Besides antipsychotics, other drugs that may be useful include drugs that modulate GABA (e.g. benzodiazepines) noradrenaline (e.g. clonidine), and acetylcholine (e.g. nicotine). Behavioral approaches such as habit reversal training and exposure response prevention therapy have been found to have a role in treating Tourette syndrome, and may be used alone or in conjunction with pharmacological options. For the more severe resistant cases, surgical interventions such as deep brain stimulation (DBS) of the thalamus or globus pallidus can be considered. Electroconvulsive therapy (ECT) as well as repetitive trans cranial magnetic stimulation (rTMS) has also been utilized [12].

Cariprazine is a dopamine D_3-D_2 and $5HT_{1A}$ partial agonist and antagonist at the 5-HT_{2B} receptors with preferential binding to the D_3 receptors [18]. It is categorized as a third-generation antipsychotic medication and is currently approved by the Food and Drug Administration for the treatment of adult schizophrenia [19–22] and bipolar I disorder patients (manic, mixed, and depressed episodes) [23], as well as for the adjunctive treatment of Major Depressive Disorder [24,25]. Given its similar receptor profile to aripiprazole but with increased affinity for D_3 receptors, it might be a good treatment option for the treatment of Tourette syndrome with comorbid depression.

The aim of the present case report is to show the effectiveness of the novel antipsychotic medication, cariprazine, in reducing tics, ameliorating depressive symptoms and maintaining the reduction of tics without producing debilitating side-effects in a young male patient.

2. Case Presentation

This is an 18-year-old male student of Indian ethnicity, who presented to us with prior diagnoses of Tourette syndrome, Major Depressive Disorder, and Attention Deficit Hyperactivity Disorder

 doi:10.20944/preprints202308.1023.v1

while still experiencing low mood, impaired attention, tics as well as side effects (sedation and stiffness) due to his previously prescribed medication.

The first signs of illness started when the patient was 13 years old, when he made the transition from primary to secondary school. He found immense difficulty in concentrating on schoolwork which made him feel stressed and eventually led to the development of motor tics. These initially manifested as intermittent puckering of his lips. Occasionally, he would also experience sudden neck jerky movements. Later, the patient started to experience vocal tics as well which manifested in sudden grunting sounds. This had caused him much embarrassment and led him to have low self-esteem as well. His classmates would frequently make fun of him and at times, avoid him all together. Despite all these, he could still cope with his studies. However at the age of 17 years old, he started to experience low mood and anxiety as well. This was associated with poor concentration, loss of interest, excessive eating, increased appetite and lethargy. This was when his studies started to deteriorate, and he started failing several exam papers. He felt guilty that he had let his mother down and had experienced some passive death wishes without any active plans.

Personal history revealed an adverse childhood period, where his father passed away suddenly when he was an infant; hence he grew up without a father figure. His mother was also seldom at home, as she had to take up several jobs to make ends meet. He was often taken care of by his elder sister, who was 5 years older than him. He also has a strong family history of psychiatric illness where both his elder sister and mother were diagnosed with Major Depressive Disorder. His mother also had several admissions to the psychiatric ward when he was younger. His maternal grandmother had committed suicide before he was born, but not much is known about the circumstances behind that..

As his mother was worried about about his progressively deteriorating grades, she mother brought him to consult a private physician. He was then diagnosed with Major Depressive Disorder, Attention Deficit Hyperactivity Disorder and underlying Tourette syndrome. To alleviate his symptoms, he was prescribed escitalopram (5 mg daily) to treat his depression, risperidone (0.5 mg daily) for his Tourette syndrome and methylphenidate (5 mg daily) for his Attention Deficit Hyperactivity Disorder. Over the next several weeks, escitalopram was titrated up to 10 mg daily and risperidone was titrated up to 2 mg daily, while methylphenidate was maintained at 5 mg daily. After six months, the patient was referred to us for continuation of care, as he could not afford the charges at the private physician's clinic.

During the first visit, the patient reported that initially his tics were fairly well-controlled, but he experienced sedation and stiffness with risperidone. Thus he stopped the risperidone a month back, causing a worsening of his tics. He was adherent though, to methylphenidate and escitalopram. He did report some improvement in his attention and concentration with methylphenidate, but not completely satisfactory. He also reported that his depressive symptoms were only about 60% better (according to his own evaluation). Though his mood had somewhat improved, he still had hypersomnia, lethargy and poor concentration in his studies. We decided not to restart the risperidone due to the bothersome side effects it had caused him before. Methylphenidate was maintained at a dose of 5 mg daily, but we decided to increase the dose of escitalopram to 15 mg a day, as he was still having significant depressive symptoms. Cariprazine was initiated at a dose of 1.5 mg a day, with the dual aim of controlling his tics due to his Tourette syndrome, as well as to augment the effect of the antidepressant.

Cariprazine was specifically chosen for several reasons. First of all, the patient responded to risperidone (a D_2 antagonist) previously, hence cariprazine's partial agonist activity at the dopamine receptors could confer the same benefit but with a decreased likelihood of side effects. Secondly, given the recent evidence regarding cariprazine's effectiveness as an adjunctive agent in depression, it could also provide additional help in ameliorating the patient's depression with its partial agonism at the 5-HT_{1A} receptors. Finally, cariprazine is also an antagonist at the serotonin 5-HT_{2B} receptor, which is considered to have an adjunctive effect in the presence of selective serotonin reuptake inhibitors.

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Throughout the subsequent visits over a 14-month period, the patient reported a gradual improvement in his mood alongside better control of tics. During his last visit, he felt that he had fully recovered from his depression. He also reported improvement in his attention and concentration, and subsequently improvement in his studies. More importantly, he did not complain about being sedated or stiff anymore and no additional side-effects emerged while being on the new medication regime.

3. Discussion

To the best of our knowledge, this is the first case that describes the efficacy of cariprazine in ameliorating the symptoms of Tourette syndrome in an adolescent with comorbid Major Depressive Disorder and Attention Deficit Hyperactivity Disorder. Although currently there is no evidence regarding the efficacy of cariprazine in ameliorating tics, aripiprazole, which is also a dopamine partial agonist, has been shown to reduce tics with similar effect sizes as haloperidol and risperidone [26], providing a solid basis why cariprazine could also work in Tourette syndrome with comorbid Major Depressive Disorder and Attention Deficit Hyperactivity Disorder.

The efficacy of cariprazine in depressive symptoms was established in several Phase I clinical trials in patients with Bipolar I Disorder in the depressive phase [27,28]. In an 8-week randomized, double-blind, placebo-controlled, study in adult patients with bipolar I disorder experiencing a major depressive episode, cariprazine at dose of both 1.5 mg/day and 3 mg/day showed significantly greater improvement on Montgomery–Åsberg Depression Rating Scale total score change from baseline to week 6 as compared with placebo [27]. In another was a double-blind placebo-controlled Phase III trial, by Early et al. Cariprazine at doses of either 1.5 mg/daily and 3 mg/daily were both superior in reducing depressive symptoms in subjects with Bipolar I disorder experiencing a depressive episode [28].

Cariprazine has also been shown to be efficacious when used as adjunct in patients with Major Depressive Disorder who have inadequate response to standard antidepressant therapy, as shown in 2 studies. In the first study by Durgam et al., reduction in the Montgomery–Åsberg Depression Rating Scale total score at week 8 was significantly greater with adjunctive cariprazine at doses between 2 mg to 4.5 mg daily as compared to placebo [24]. The second study was a 19 week placebo controlled Phase II study that demonstrated cariprazine at doses of 1 - 2 mg a day, showed greater improvement in the Montgomery–Åsberg Depression Rating Scale when used as an adjunctive agent to antidepressants in subjects with treatment resistant depression [25]. Cariprazine efficacy in depressive symptoms is thought to be associated with both its dopamine and serotonin receptor activities. Its partial agonist activity at the D_3 is believd to reduce anhedonia and enhance cognition, where else its action on 5 HT_{1A} is thought to produce an antidepressant like effect. [29].

This positive effect on symptoms of Major Depressive Disorder was seen in this case, when he received cariprazine 1.5 mg/day together with escitalopram 15 mg/day. Compared to the previously achieved 60% improvement in mood symptoms with risperidone and escitalopram combination, the patient reported greater improvement in depressive symptoms when switched to this regime. In fact, just after slightly over 3 months on this combination of medication, he declared himself as having recovered from his depression. Being able to continue schoolwork, he did not mention any problems with his attention, a cognitive domain that might have also improved due to the D_3 activity of cariprazine [30].

When he was on the previous medication regime, the patient complained of being sedated and stiff which are frequently described side-effects of antipsychotic medications such as risperidone [31]. In contrast, cariprazine is considered an activating compound with insomnia being a more likely side-effect than sedation or somnolence [32]. This activating effect may also contribute to the reduction of depressive symptoms. Being a dopamine partial agonist, cariprazine is less likely to cause extrapyramidal side effects such as stiffness, which was experienced by the patient when he was on risperidone. Lacking anti-histaminergic actions also lessens the likelihood of causing sedation and weight gain In this patient, no side-effects were reported after the switch to cariprazine, which is important in treating young patients who are still studying.

4. Conclusions

In conclusion, we believe that cariprazine can be a valuable option for the treatment of Tourette syndrome, particularly among those who are suffering from comorbid conditions such as Major Depressive Disorder or Attention Deficit Hyperactivity Disorder, and are prone to the common side-effects of antipsychotics.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki. Case reports are exempt from ethical approval in our public medical institution.

Informed Consent Statement: Written informed consent was obtained from the patient for the publication of this case report.

Data Availability Statement: Research data are available, upon reasonable request, to the corresponding authors.

Acknowledgments: None.

Conflicts of Interest: The authors declare no conflict of interest.

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