Aripiprazole for the Treatment of Tourette's Disorder

Prasad R. Padala, M.D.; S. Faiz Qadri, M.D.; and Vishal Madaan, M.D.

Objective: Tourette's disorder is a neuropsychiatric syndrome that manifests with motor and vocal tics, including coprolalia. This article presents a report of successful treatment of these tics with aripiprazole in 2 consecutive patients with Tourette's disorder.

Method: After an informed consent was obtained from the subjects, approval for this retrospective case series was sought from the Institutional Review Board. A detailed history was obtained and physical and mental state examination was performed for each patient. Tic severity was assessed using the Yale Global Tic Severity Scale. Aripiprazole was started at a low dose (5 mg/day) and titrated. The severity of tics was monitored during follow-up.

Results: The 2 individuals presented in these case reports tolerated aripiprazole well and showed a clinically significant decrease in tic frequency and severity.

Conclusions: Aripiprazole, a newer atypical antipsychotic with a unique pharmacodynamic profile, appears to be efficacious in treatment of tics in Tourette's disorder, thus impressing upon the need for placebo-controlled trials in the management of this neuropsychiatric syndrome.

(Prim Care Companion J Clin Psychiatry 2005;7:296–299)

Received Sept. 14, 2005; accepted Sept. 26, 2005. *From Omaha Veterans Affairs Medical Center and the Department of Psychiatry, University of Nebraska Medical Center (Dr. Padala); the Department of Psychiatry, Creighton University (Drs. Qadri and Madaan); and the Department of Psychiatry, University of Nebraska (Drs. Qadri and Madaan), Omaha.*

Drs. Padala, Qadri, and Madaan report no financial or other relationship relevant to the subject of this article.

Corresponding author and reprints: Prasad R. Padala, M.D., 18802 Josephine Street, Omaha, NE 68136-1231 (e-mail: ppadala@unmc.edu).

Tourette's disorder is a neuropsychiatric disorder characterized by involuntary motor and vocal tics. Typically, the disorder is characterized by an early childhood onset and transient episodic motor and vocal tics. Although mainly episodic, the tics at times become persistent and may cause distress to the child and her or his family. On average, phonic tics begin 1 to 2 years after the onset of motor symptoms.

Although the etiology of Tourette's disorder is unknown, evidence suggests that pathophysiology of this disorder involves an abnormality in the central dopaminergic system. For this reason, a variety of psychotropic medications have been tried to treat tics. The U.S. Food and Drug Administration (FDA) has approved haloperidol and pimozide for the treatment of Tourette's disorder. Long-term use of these agents, however, has been less favorable, and the "reflexive" use of these agents should be avoided due to potential adverse effects.[1,2] Adverse effects of haloperidol and pimozide include sedation, cognitive dulling, extrapyramidal symptoms (including acute dystonic reaction, dyskinesia, and akathisia), and weight gain.[3,4] An additional concern for pimozide is the potential for QT prolongation, especially when combined with agents that inhibit the cytochrome P450 3A4 isoenzyme.[5]

More recently, atypical antipsychotics, including quetiapine,[6–8] ziprasidone,[9] olanzapine,[10,11] and risperidone,[12–16] have been successfully used to treat Tourette's disorder. Risperidone has been studied the most in this category with 2 double-blind placebo-controlled studies in small numbers of patients. Dion et al.[14] studied 46 subjects with Tourette's disorder and found that risperidone at a median dose of 2.5 mg/day was superior to placebo in the treatment of tics. Scahill et al.[16] found similar superiority of risperidone over placebo in a group of 34 patients. Two of these patients developed social phobia, and weight gain was also of concern. Furthermore, risperidone has been found to have efficacy equivalent to pimozide[13] and clonidine,[15] the other agents used in the treatment of Tourette's disorder. Sallee et al.[9] evaluated the efficacy and tolerability of ziprasidone in 28 children and adolescents with Tourette's disorder and chronic tic disorders. In this limited sample, ziprasidone (5–40 mg/day) appeared to be effective and well tolerated in the treatment of Tourette's disorder. Mukkades and Abali[6] investigated the short-term safety and effectiveness of quetiapine in the treatment of children and adolescents with Tourette's disorder in an 8-week, open-label trial that included 12 subjects. Clinical responses revealed a statistically significant reduction in tic scores ranging from 30% to 100%.

Atypical antipsychotics have more modest blocking effects on dopamine D_2 and also potent serotonin-2 ($5\text{-}HT_2$) blocking effects. Atypical antipsychotics are char-

acterized by lower rates of extrapyramidal symptoms as compared to conventional neuroleptics and thus are attractive alternatives for the treatment of tics in Tourette's disorder. However, recent data have shown that atypical antipsychotics are associated with few but significant side effects. It has been reported that olanzapine was associated with substantial weight gain and sedation,[11,17] while Margolese et al.[18] recently found a high incidence of depression and dysphoria in patients with Tourette's disorder treated with risperidone.

Aripiprazole, a novel atypical antipsychotic agent approved by the FDA for schizophrenia and bipolar affective disorder, acts as an antagonist at D_2 receptors under hyperdopaminergic conditions and displays agonist properties under hypodopaminergic conditions.[19] A very few case reports indicate that aripiprazole is effective in the treatment of tics in Tourette's disorder and has an extremely favorable side effect profile.[20,21] Kastrup et al.[20] report that adults with a long-standing history of tic disorder responded well to aripiprazole. Dehning et al.[21] similarly report effective response to aripiprazole in a younger patient with multiple side effects to pimozide, sulpiride, and tiapride. Hounie et al.[22] suggest that a good response to aripiprazole might result partially from its inhibitory action on the $5\text{-}HT_{1A}$ receptors, thus resulting in a reduction of the excitatory pyramidal glutamatergic output.

In this retrospective case series, we report on 2 consecutive patients who presented with Tourette's disorder in whom motor and vocal tics improved with aripiprazole as evidenced by a significant improvement in scores on the Yale Global Tic Severity Scale (YGTSS) within 12 to 18 weeks.

CASE 1

Mr. A, a 55-year-old white man, was diagnosed with bipolar II disorder, current episode hypomania, with comorbid alcohol dependence in early full remission and Tourette's disorder, all according to DSM-IV-TR criteria.[23] The motor tics included repetitive eye blinking, shoulder shrugging, and hand and leg movements while the vocal tics comprised throat clearing, coughing, sniffing, and coprolalia. The patient had previously been treated for tics successfully with haloperidol and for bipolar disorder with lithium. Noncompliance with medications and comorbid alcohol dependence had resulted in multiple relapses. The patient had been abstinent from alcohol use for the past 6 months with the help of a substance use rehabilitation program but currently presented with significant distress from Tourette's disorder. He also reported initiating alcohol use to suppress the tics that caused impaired social and interpersonal functioning.

The severity of his motor and vocal tics was assessed at baseline using the YGTSS[24] before initiating treatment. His baseline tic severity as measured with the YGTSS revealed a total tic severity score of 34 and global severity score of 74. Lithium (900 mg/day in divided doses) was restarted for bipolar disorder symptoms, considering a previous good response to it. For the management of motor and vocal tics, the options of both typical and atypical antipsychotics, including the side effect profiles, were discussed with the patient. While haloperidol had previously helped the patient's tics, he refused initiating it again because of the associated side effects. He, however, preferred aripiprazole as an off-label agent due to a favorable side effect profile. He was initially prescribed aripiprazole at 5 mg/day, a dosage that was gradually titrated to 10 mg/day over a period of 4 weeks.

After 10 days, the patient was reassessed. Subjective report included a significant improvement in both his hypomanic symptoms and tics. This finding confirmed with collateral information. His global severity score on the YGTSS dropped to 48 (approximately 35% improvement), while the total tic severity score dropped to 28 (18% improvement). No side effects were reported or observed while on treatment with lithium and aripiprazole, and the patient was continued on the same dose of both medications with a second follow-up visit scheduled after 12 weeks.

At 12 weeks, Mr. A's symptoms of hypomania had resolved completely. Further improvement was noted in the tics using YGTSS: his global severity score was 36 (51% improvement from baseline), while his total tic severity score was 16 (53% improvement from baseline).

CASE 2

Ms. B, a 39-year-old white woman with diagnoses of major depressive disorder, panic disorder, and Tourette's disorder (all diagnoses made according to DSM-IV-TR criteria), presented with a 6-month history of poor treatment compliance. On examination, she had multiple motor and vocal tics, including eye blinking, facial grimacing, head jerks, abdominal tensing, mouth movements, writing tics, coprolalia, and stuttering. She reported having tics since childhood but that she had received treatment starting at age 23 years. Her depressive symptoms resurfaced a month before her presentation to the clinic, manifesting as sadness of mood, poor energy levels, anhedonia, poor concentration, insomnia, and increased appetite. She also complained of anxiety symptoms suggestive of panic attacks approximately once a week. She reported a 40-lb weight gain over the past 3 years, which in part had contributed to her poor treatment adherence. Her past medical history was significant for cluster headaches, chronic back pain, sciatica, and vertigo. She also had a family history of bipolar disorder, depression, and alcohol abuse in first-degree relatives.

Previous attempts at treating the Tourette's disorder symptoms included trials with haloperidol, pimozide, clonazepam, and carbamazepine. The patient believed that her tics responded best to carbamazepine but was reluctant to try again due to fear of weight gain.

Her baseline tic severity when measured with the YGTSS revealed a total tic severity score of 44 and a global severity score of 94. Aripiprazole was started at 5 mg once a day and was titrated to 20 mg/day over a course of 12 weeks. At 12 weeks, reassessment with YGTSS yielded a total tic severity score of 32 (27% improvement) and a global severity score of 62 (34% improvement). The patient reported dizziness for the first 2 days after initiation of aripiprazole that quickly subsided without any intervention. No other adverse reaction was reported. Aripiprazole was increased to 30 mg/day, and the patient was reassessed after 6 more weeks, at which time she had a total tic severity score of 25 (43% improvement) and a global severity score of 45 (52% improvement). Over the course of 18 weeks of treatment with aripiprazole, the patient reported a subjective sense of relief, a reduction in tic severity and frequency, and an ease in social gatherings that was corroborated by collateral information.

DISCUSSION

Tourette's disorder is a chronic neuropsychiatric condition characterized by recurrent, involuntary motor and vocal tics associated with comorbid difficulties in self-esteem, social acceptance, and school or job performance. The prevalence of Tourette's disorder has been estimated to be between 0.1% to 1% among children and adolescents, with most patients showing improvement in symptoms by late teens or early adulthood.[25] The tics are usually characterized by nonrhythmic, involuntary, rapid, repetitive movements or vocalizations. Tourette's disorder symptoms typically begin with motor tics at age 6 to 7 years, with the vocal tics presenting later. Coprolalia (uttering of obscene words) is believed to occur in about 10% of these patients.[26] Tics are believed to become exacerbated with an intense emotional upset or fatigue and decrease in intensity with sleep. Obsessional behaviors, attention-deficit/hyperactivity disorder, and autistic spectrum disorders are frequently comorbid with Tourette's disorder and might worsen the impact of the disorder.[27,28] Individuals with Tourette's disorder typically have normal intellectual functioning, although executive dysfunction, discrepancies between performance and verbal IQ, and a decrease in visual-motor skills have been associated with Tourette's disorder.[29] While the definitive pathophysiologic mechanism of Tourette's disorder has not been completely elicited, neuroimaging and neurophysiologic studies suggest the involvement of cortical-striatal-thalamocortical pathways, especially a prefrontal dopaminergic abnormality.[30,31] While a variety of neurotransmitter systems, including dopaminergic, glutamatergic, GABAergic, serotonergic, cholinergic, noradrenergic, and opioid systems, are possibly involved in these corticostriatal-thalamocortical circuits, the dopaminergic system has especially gained attention due to therapeutic response of Tourette's disorder to antipsychotics.[30]

With a better extrapyramidal side effect profile, atypical antipsychotics, including risperidone, olanzapine, and ziprasidone, have been recently preferred over the typical antipsychotics. Several case reports for the treatment of Tourette's disorder with these agents have been published: open-label studies are published for quetiapine,[6] olanzapine,[11] and ziprasidone,[9] whereas risperidone[13–16] and olanzapine[10] have been studied in double-blind controlled trials. The recent association of the metabolic syndrome with most of the atypical antipsychotics has brought out another dilemma regarding choice of the medication. Aripiprazole, the most recent addition to the atypical antipsychotic group, may provide a new avenue for symptomatic relief in Tourette's disorder.

Singer[25] has speculated that a tonic-phasic model of dopamine release might be responsible for the etiology of Tourette's disorder. He states that a reduction in tonic (basal) dopamine (resulting from an overactive dopamine transporter system) could result in a system with high concentrations of dopamine receptors and an increased phasic release of dopamine resulting in a hyperkinetic effect.[25] Interestingly, aripiprazole as a dopamine partial agonist acts as an antagonist at D_2 receptors under hyperdopaminergic conditions and displays agonist properties under hypodopaminergic conditions. It has been hypothesized that dopamine partial agonists may be capable of stabilizing the dopaminergic system without inducing a hypodopaminergic state, thereby reducing the risk of side effects associated with pure blockade of dopamine receptors.

Thus, aripiprazole may help resolve the dilemma of having to accept potentially serious side effects to relieve the associated social discomfort in Tourette's disorder. Placebo-controlled clinical trials are needed to establish the efficacy of aripiprazole in the treatment of Tourette's disorder. Another area of further study could involve the response to a combination of aripiprazole with nonpharmacologic strategies including biofeedback, conditioning techniques, and relaxation techniques. Further, most current case studies address Tourette's disorder in the adult population. It would be worthwhile to study response with aripiprazole in childhood.

CONCLUSIONS

Tourette's disorder is a neuropsychiatric disorder characterized by recurrent motor and vocal tics. Aripiprazole

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appears to be efficacious in management of the tics in Tourette's disorder. Double-blind, placebo-controlled studies are needed to further establish the treatment of tics with aripiprazole.

Drug names: aripiprazole (Abilify), carbamazepine (Carbatrol, Equetro, and others), clonazepam (Klonopin and others), clonidine (Catapres, Duraclon, and others), haloperidol (Haldol and others), lithium (Lithobid, Eskalith, and others), olanzapine (Zyprexa), pimozide (Orap), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

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