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## **MOVEMENT DISORDERS ASSOCIATED WITH ARIPIPRAZOLE USE: A CASE SERIES**

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Aripiprazole is an atypical antipsychotic that is a partial agonist at the D2 and 5HT<sub>1a</sub> receptors and an antagonist at 5HT<sub>2a</sub> receptors. Despite previous hypotheses that it would be less likely to cause movement disorders, recent reports suggest it actually may be more likely to cause movement disorders than other atypical antipsychotics. This case series illustrates the variety of movement disorders associated with aripiprazole use at three movement disorder clinics. It also suggests that aripiprazole be used with caution in patients with a prior history of dystonia, parkinsonism, or previous tardive dyskinesia.

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## BACKGROUND

Aripiprazole is a quinolinone antipsychotic and is FDA approved for the treatment of schizophrenia (Kane et al., 2002) and has been shown to be effective in the treatment of bipolar disorder (Keck et al., 2003). Aripiprazole has a high affinity for dopamine (D2 and D3) and serotonin receptors (Gupta & Masand, 2004). It is a partial agonist at D2 receptors, reducing dopamine synthesis and release at the dopamine autoreceptor (Taminiga & Carlsson, 2002). It is also an antagonist of the serotonin 5-HT<sub>2A</sub> receptor and partial agonist at the 5-HT<sub>1A</sub> receptor (Jordan et al., 2002). Due to its heterogeneous mechanism of action, it has been reported to have less risk of extrapyramidal syndromes than other antipsychotics. However, there have been increasing reports of worsening of PD (Fernandez, Trieschmann, & Friedman, 2004; Friedman et al., 2006; Wickremaratchi, Morris, & Ali, 2006), neuroleptic malignant syndrome (Chakraborty and Johnson 2004; Hammerman, Lam, & Caroff, 2006), tardive dyskinesia (Maytal, Ostacher, & Stern, 2006), and acute dystonic reactions (Desarkar, Thakur, & Sinha, 2006; Fountoulakis et al., 2006; Pinninti, Mago, & Adityanjee, 2006). This case series illustrates the variety of movement disorders temporally related to aripiprazole in patients who presented to three movement disorder clinics.

## METHODS

A retrospective review was conducted in three tertiary movement disorders clinics and patients with movement disorders secondary to aripiprazole were identified. All patients were referred for abnormal movement, although some patients were started on aripiprazole after care was established in the movement disorder clinic. A chart review was performed to obtain demographic information, medical history, and history of medications, dosages, and side effects. In addition, a neurological exam was performed and patients were evaluated by a movement disorders specialist.

## RESULTS

There were six patients identified, with a mean age of  $52 \pm 6.1$  years (all male). The six patients were on aripiprazole for a variety of movement disorders (Table 1). The dose of aripiprazole was 10–15 mg daily and patient exposure

**Table 1.** Summary of cases presenting with movement disorders on aripiprazole

Age/Gender	Underlying disorder	Dose	Duration of treatment	Resulting movement disorder
59M	Motor tics	10 mg	1 year	Akathesia, parkinsonism
62M	Motor tics	10 mg	2 weeks	Akathesia, chorea, orofacial dyskinesia
57M	Motor tics	15 mg	2 years	Akathesia, body rocking
46M	Bipolar disease	15 mg	3 weeks	Orobuccolingual dyskinesia
22M	Schizophrenia	10 mg	6 weeks	Severe acute torticollis
67F	Parkinson disease	10 mg	3 weeks	Orobuccolingual dyskinesia

ranged from two weeks to greater than two years. The following case reports illustrate the presentation and course of three of the patients.

### Case 1

A 20-year old man with a four-year history of schizophrenia and hand tremor presented with acute pulling of his head to the side. He reported symmetric tremor of his hands only when writing that had started four years prior. His family stated that it had worsened abruptly when he started risperidone and remained when he was switched to aripiprazole. His past medical history was remarkable for mental retardation from birth and attention deficit hyperactivity disorder. He had three family members with alcoholism, but there were no movement disorders in his relatives. Upon starting risperidone at the age of 18, he developed torticollis and was treated in the emergency department successfully with diphenhydramine. The medication was discontinued and aripiprazole was started at 10 mg daily. After four weeks, he woke up acutely with torticollis and was treated in the again in the emergency department with diphenhydramine. The torticollis resolved and he was started on quetiapine. On follow up two years later, he had a focal task-specific dystonia in the left hand only when writing and there was no evidence of torticollis.

### Case 2

A 59-year-old man with motor tics for 47 years was seen for treatment. He was placed on 10 mg daily of aripiprazole for eight weeks and noted marked improvement in his tics. However, he developed akathesia in both

of his legs and the dose was decreased to 5mg daily. At his ten-month follow up in the movement disorder clinic after the dose reduction, he was noted to have parkinsonism, with hypomimia and bradykinesia. He also complained of continued restlessness in his legs. The aripiprazole was stopped and parkinsonism symptoms improved, with complete resolution at five-month follow up.

### Case 3

A 67-year-old man had a 13-year history of idiopathic Parkinson disease complicated by dyskinesia, motor fluctuations, and psychosis. His psychosis was initially treated with quetiapine 300 mg daily, with no worsening in motor symptoms. Because of incomplete resolution of hallucinations, olanzapine 5 mg was added for three months, but discontinued secondary to worsened parkinsonism and motor function subsequently improved without appearance of a tardive movement disorder. Several months later, aripiprazole 10 mg daily was added. Aripiprazole was discontinued after three years of treatment. One week after stopping aripiprazole, orobuccolingual dyskinesias emerged accompanied by involuntary, grunting vocalizations, consistent with tardive dyskinesia. The patient continued to have peak-dose dyskinesia associated with levodopa dosing, causing choreiform movements of trunk and extremities; however the orobuccolingual dyskinesias were not associated with levodopa dosing. These movements persisted for three months without resolution.

## DISCUSSION

This case series illustrates a variety of movement disorders related to aripiprazole use. As defined by the DSM-IV, tardive dyskinesias are involuntary choreiform, athetoid, or rhythmic movements (lasting for at least four weeks) of the tongue, jaw, or extremities that develop in association with at least three months of neuroleptic use (although the duration of use before symptom-onset may be shorter in the elderly) (DSMV). Patients in this series had both tardive syndromes and acute reactions.

The first acute dystonia from aripiprazole was reported in 2006 in an 18-year-old male with Tourette's syndrome who was given aripiprazole 10 mg orally daily, which produced a significant improvement in his tics (Fountoulakis et al, 2006). However, after three days of treatment, he experienced an acute episode of dystonia with facial muscle spasm, oculogyric crisis, and torticollis, which resolved after a single intramuscular injection of biperidine 5 mg. A

second patient was reported two months later: an 18-year-old male treated for a manic episode developed episodic torticollis three days after starting aripiprazole 15 mg daily and it resolved after the initiation of trihexyphenidyl (Desarkar et al., 2006). Similar symptoms were reported in a 19-year-old schizophrenic woman after being on aripiprazole for three days (Pinninti et al., 2006).

Tardive syndromes have been reported in a patient on aripiprazole 15 mg/day for 18 months for refractory depression (Maytal et al., 2006). Upon discontinuing the drug, tardive symptoms resolved within several weeks. Other movement disorders, including neuroleptic malignant syndrome and worsening of parkinsonism, have been related to aripiprazole and are similar to movement disorders associated typical antipsychotics.

There are several weaknesses with this study. First, these patients are a convenience sample and were recruited from a tertiary movement disorders center. This may suggest that these patients are biased to be more severe or refractory to standard treatment and not representative of movement disorder patient populations as a whole. Secondly, all of these patients had been exposed to other neuroleptics. Although the abnormal movement described in this case series temporally correlated with the aripiprazole, it is difficult to rule out lingering or confounding effects of the previous antipsychotics.

Aripiprazole has a novel mechanism of action and it has been associated in the literature with multiple movement disorders despite being on the market for only a few years. Reviews suggest that aripiprazole may be less likely to cause extrapyramidal syndromes than risperidone or haloperidol, but more likely than olanzapine or quetiapine (Gentile, 2007). This may mean that aripiprazole should be reserved for patients without underlying dystonia or parkinsonism or a history of acute or tardive reactions in the past. Future prospective studies will help to clarify the risk of associated movement disorders.

### **Declaration of interest**

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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