

# Dose-dependent rapid-onset akathisia with aripiprazole in patients with schizoaffective disorder

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**Abstract:** A series of cases are reported in which patients on aripiprazole have developed akathisia, although the literature states that the rate is negligible.

**Keywords:** aripiprazole, akathisia

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## Introduction

Aripiprazole has been shown to have a favorable extrapyramidal symptom (EPS) risk profile in both short-term as well as long-term randomized double-blind clinical trials (Harrison and Perry 2004). The incidence of EPS and related adverse events is low when compared with both conventional and atypical antipsychotic agents (Lieberman 2002). In clinical trials with acutely psychotic patients, aripiprazole has similar efficacy to haloperidol and risperidone in the reduction of psychotic symptoms, although a considerably superior profile in the reduction of side-effects, namely extrapyramidal side-effects, akathisia, and dyskinetic movements (Potkin et al 2003). Prevalence of akathisia in short-term trials (up to 4–6 weeks) is 12% vs 5% in placebo for schizophrenia and 15% vs 4% (placebo) for bipolar mania (Marder et al 2003). Development of akathisia has also been reported in bipolar disorder (Cohen et al 2005).

Aripiprazole is a novel antipsychotic whose mechanism is unique in that it has a partial agonist activity at dopamine D2 receptors (Burriss et al 2002). It is also believed to have D2 antagonist activity under hyperdopaminergic conditions and D2 agonist activity under hypodopaminergic conditions. In addition, it is a partial agonist at serotonin 5HT1A receptors and an antagonist at 5HT2A receptors (Jordan et al 2002).

Initial studies showed no significant difference for akathisia for patients receiving placebo vs aripiprazole and no dose-response relationship was noted (Marder et al 2003). It was noted to be equally common in people allocated to aripiprazole, olanzapine, and risperidone (El Sayeh and Morganti 2005).

We report a case series about akathisia noted in patients treated with aripiprazole who were concurrently receiving selective serotonin receptor inhibitors (SSRI).

## Case reports

During the course of their psychiatric care in the outpatient clinic, four individuals developed akathisia when started on aripiprazole or when the dose of aripiprazole was titrated upwards. All the patients carried a diagnosis of schizoaffective disorder and an attempt was made to switch their antipsychotic medication to aripiprazole, as it is believed to have a better side-effect profile.

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## Case 1

Mrs CP is a 49-year-old African American woman who had a long history of schizoaffective disorder. After multiple medication trials she had been stabilized on citalopram 20 mg/day and quetiapine 100 mg at bedtime. However, the patient was unhappy with her weight gain and wanted to have her medication changed. She was started on aripiprazole 15 mg/day po and quetiapine was decreased by 25 mg every 2 weeks. The patient complained of akathisia (feeling restless in her legs) after being on aripiprazole for 2 weeks. At that time aripiprazole was decreased to 10 mg/day. She reported decreased “restlessness” of her legs the following week which decreased further with time and no further change in aripiprazole dose. She was stable on 10 mg/day of aripiprazole and 20 mg/day of citalopram.

## Case 2

Ms DC is a 32-year-old single white woman who worked as a secretary and lived with her boyfriend. She has a diagnosis of schizoaffective disorder with delusions of being watched and followed, in association with symptoms of mania and anxiety. Over the years the patient had been on various antipsychotics including risperidone (minimal response) and ziprasidone (developed palpitations). She had been free of psychotic symptoms and stable on olanzapine at 10 mg at bedtime; however, because a weight gain of about 18 kg had made her extremely unhappy, she started self-tapering the olanzapine. Additionally, she had been prescribed sodium valproate 1000 mg at bedtime, paroxetine 40 mg/day, topiramate 50 mg at bedtime, and lorazepam 1 mg as needed. As she stopped her olanzapine she was started on aripiprazole 15 mg/day. Within a week she complained of severe restlessness (unable to sit still at work) and increased anxiety. She refused to continue with aripiprazole. Subsequently, she became psychotic and was stabilized on molindone 50 mg at bedtime.

## Case 3

Ms DJ is a 39-year-old single white female, who has had psychiatric problems since 14 years of age. She has a diagnosis of schizoaffective disorder and has been hospitalized multiple times and has had multiple medication trials. Her psychotic symptoms consist of auditory hallucinations and paranoia in addition to depression and anxiety. She also exhibits self-injurious behavior. Over the years she has been on different antipsychotics with moderate improvement and also moderate side-effects (weight gain, sedation). The patient was on olanzapine but this was tapered

off and aripiprazole 15 mg/day started due to persistence of symptoms and weight gain. As her hallucinations continued, aripiprazole was increased to 30 mg/day. However, the patient became suicidal in response to auditory hallucinations and needed to be hospitalized. She was started on haloperidol, which was increased to 5 mg three times a day. However, her auditory hallucinations continued and aripiprazole was increased to 50 mg/day. At this point, the patient developed severe akathisia – she was unable to sit or stand still and felt she was going to jump out of her skin.

Haloperidol was decreased to 5 mg at bedtime, but the akathisia continued. Propranolol was added at 20 mg twice daily with minimal improvement. At this point aripiprazole was decreased to 30 mg/day and the restlessness (akathisia) decreased, and she was maintained at this dose. It should be noted that at the time the patient developed akathisia she was also on citalopram 60 mg/day, levothyroxine 50 µg/day, hydroxyzine 100 mg at bedtime, buspirone 7.5 mg twice daily, and triazolam 0.5 mg at bedtime, all of which were unchanged during the course of events.

## Case 4

Mr MW is a 29-year-old single white male, who became extremely paranoid about 2 years ago and was unable to trust his family members or leave his home. He was hospitalized briefly and discharged on risperidone 3 mg/day. During the patient’s outpatient treatment it was noted that he was unable to sit still in groups and constantly paced up and down. Although he did not complain he told his peers that he felt he was jumping out of his skin. In view of these side-effects his medications were switched to olanzapine, titrated to 10 mg at bedtime, which controlled his symptoms. Subsequently, the patient gained more than 23 kg (over one year) and continued exhibiting negative symptoms, some depression and some obsessive-compulsive symptoms. The patient’s family was worried about his physical health and it was decided to switch the patient to aripiprazole, which was started at 15 mg/day, and olanzapine was decreased to 7.5 mg/day. In addition the patient was also on paroxetine 40 mg/day and buspirone 7.5 mg twice daily, which remained unchanged. After a week the patient’s family noted that he was more alert, and exhibiting fewer negative symptoms; however, the patient complained of severe restlessness and agitation. Aripiprazole was continued with follow-up one week later. The patient returned, denying anxiety but complaining of his inability to sit or stand still. It was noted that he was constantly fidgeting a lot, which had never been noted earlier. The patient also stated that he

could not tolerate this symptom, he refused to continue with this medication, and stated that he wanted to return to olanzapine. Aripiprazole was therefore discontinued. Olanzapine was restarted at 7.5 mg at bedtime and the akathisia resolved.

## Discussion

The following factors may be related to the development of akathisia in the cases described in this report.

Akathisia secondary to conventional antipsychotic agents is frequently attributed to D2 receptor blockade in the mesocortical areas (Marsden and Jenner 1980). It is likely that this mechanism may also cause akathisia secondary to treatment with aripiprazole.

The hepatic microsomal enzymes CYP3A4 and CYP2D6 are primarily responsible for the metabolism of aripiprazole. CYP2D6 is inhibited by fluoxetine and paroxetine, which may in turn inhibit aripiprazole breakdown and thus increase its blood levels. SSRIs may also cause akathisia, perhaps a consequence of serotonergically mediated inhibition of the dopaminergic system (Lane 1998). All of the patients reported in this case series were on a SSRI. Furthermore, the risk of akathisia secondary to SSRI treatment may be heightened by the concomitant use of an antipsychotic medication (Gerber and Lynd 1998). Lastly, patients with affective symptoms have an increased risk of developing EPS and akathisia. All patients included in this report were diagnosed with schizoaffective disorder.

In summary it is noted that aripiprazole did cause symptoms of akathisia in patients who had not experienced their symptoms on their previous antipsychotic agents. These symptoms appeared to be dose-related. It appears that decreasing the dose in at least two cases caused a resolution of their symptoms. There was no correlation between the

onset, severity, or resolution of akathisia with clinical symptoms for the patients described in this report.

Three of these patients were started on aripiprazole at 15 mg/day and it has been our clinical experience that starting aripiprazole at lower doses, either 5 or 10 mg/day, minimizes the risk of akathisia and that starting at doses greater than 30 mg/day increases the risk. We feel that akathisia may be dose-related, particularly in cases in which there is an additional SSRI. Further investigation into the risk of akathisia secondary to aripiprazole treatment may be beneficial.

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