

# Rapid onset Akathisia with low dose Aripiprazole- Two Case Reports

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## ABSTRACT

Akathisia is an extra pyramidal side effect with neuroleptic drugs which can be explained as a subjective desire to move or manifest restless movements like shuffling, tramping movements of legs/feet with objective evidence. Aripiprazole is a special category neuroleptic with a unique mechanism of action i.e., partial agonism to Dopamine D<sub>2</sub> and Serotonin 5-HT<sub>1A</sub> receptor in addition to antagonistic activity at 5-HT<sub>2A</sub> receptor. Long term and short term clinical trials have validated minimal extra pyramidal symptoms with Aripiprazole when compared to other conventional and atypical neuroleptics. Here we project two cases of rapid onset akathisia developed in a 17 year old male patient and 45 year old male patient who received Aripiprazole as an adjuvant in obsessive compulsive disorder. In both the cases there was a rapid onset of akathisia symptoms, in the first case within 15 days and in the second one he developed next day which turned more severe within 10 days. A global score of 4 was obtained on Global Barnes Akathisia Rating Scale in both cases. In both the cases after dechallenge (dose reduction in first case and withdrawal in second case) of the offending agent there was alleviation of symptoms without any further intervention and the patients have shown signs of recovery within a week.

**Key words:** Aripiprazole, Akathisia, Atypical antipsychotics, Extra pyramidal side effects, Dechallenge, Barnes Akathisia Rating Scale.

## INTRODUCTION

A typical antipsychotic, aripiprazole has a unique mechanism of action with partial agonistic activity to dopamine (D<sub>2</sub>) receptor and serotonin (5-HT<sub>1A</sub>) receptor. In addition to this, it also possesses an antagonistic profile at 5-HT<sub>2A</sub> receptor.<sup>1</sup> It has been exploited in various conditions like schizophrenia, bipolar disorder, depression and parkinsonism. The side effects associated with this are minor and has a very less tendency to cause extra pyramidal side effects (EPS).<sup>2</sup> EPS are generally expected to manifest at greater than 80% of D<sub>2</sub> receptor occupancy in the striatal area of basal ganglia.<sup>3</sup> Long term and short term clinical trials have validated a minimal EPS with aripiprazole when compared to other conventional and atypical neuroleptics like risperidone, clozapine, quetiapine, olanzapine, ziprasidone.<sup>3,4</sup> But there is incidence of EPS, akathisia and dyskinetic movements in short

term studies when it is used in the management of schizophrenia, bipolar disorder and bipolar mania.<sup>5-7</sup>

Akathisia is a side effect associated with antipsychotic drugs which is described as a subjective desire to move or manifest restless movements like shuffling, tramping movements of legs and feet. This is often confused with anxiety and makes it difficult to diagnose. The severity of akathisia is rated with Barnes Akathisia Rating Scale (BARS) which categorizes the severity to absent, questionable, mild, moderate and severe based on the scores obtained in objective, subjective and distress related to restlessness questionnaires thereby obtaining a global score.<sup>8</sup>

Probable mechanism underlying akathisia could be a dopamine inhibition induced by serotonin in mesocortico and mesolimbic

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area projecting from the ventral tegmental area (VTA) of the brain to the prefrontal cortex whereas dopamine deficiency in the nigrostriatal pathway explains other extrapyramidal symptoms.<sup>9</sup>

## CASE REPORTS

In a tertiary health care center in the psychiatric outpatient department we observed two cases of akathisia developed in the patients who were prescribed low tolerable dose of aripiprazole as an add on therapy in obsessive compulsive disorder.

### Case 1

A 17 year old male patient presented with irrational constellation of thoughts associated with anxiety and repetitive behaviors such as washing hands, chewing movements. He was clinically diagnosed to have obsessive compulsive disorder with poor insight. He was initially on monotherapy with fluoxetine 60 mg per day. After a few days and on follow up he developed psychotic symptoms and hence aripiprazole 10 mg was added for the management. On his next follow up, he complained of restlessness which was subjective as explained by the patient and objective associated with distress and inability to stand still. This exacerbation was seen within a short period of 15 days after initiation of aripiprazole. He neither had a personal nor family history of akathisia or psychiatric illness.

The patient was observed while sitting, standing, when engaged in a neutral conversation and engaged in other activities each for two minutes and scores were elicited. Subjective phenomenon was rated by direct questioning. A global score of 4 was obtained on global BARS.

The dose of aripiprazole was tapered accordingly to 5 mg and there was alleviation of symptoms in the patient with an objective evidence, BARS global score was found to be 2. Tapering the dose of offending agent was found to be useful and did not require any further intervention. He was stabilized at this dose with questionable akathisia on later follow up. When a causality assessment was done a score of 7 was obtained for aripiprazole on Naranjo algorithm for causality assessment showing a "probable" relationship.

### Case 2

A 45 years old male patient presented with typical features of obsessive compulsive disorder with mild psychotic symptoms. He was prescribed fluoxetine 20 mg per day with risperidone 2 mg per day. He started complaining of severe sedation which was disabling and hence risperidone was withdrawn and aripiprazole 5 mg per day was started along with fluoxetine 20 mg per day.

The next day the patient started complaining of restlessness and fidgety. The patient was suggested to continue the medication for 15 days as the symptoms were mild. Within 5 days, the patient started complaining of inner restlessness and desire to move when standing and constant rocking movements with which the patient was uncomfortable. This patient was observed on sitting, standing, when engaged in a neutral conversation and engaged in other activities each for two minutes and scores were elicited. Subjective phenomenon was rated by direct questioning. A global score of 4 was obtained on global BARS. When a Causality assessment was done a score of 6 was obtained for aripiprazole on Naranjo algorithm for causality assessment showing a probable relationship.

The drug was withdrawn as the patient was not willing to take it and he was stabilized on fluoxetine. On later follow up, he has presented with mild fidgety movements and there was an improvement in the condition. He did not require any further intervention for the management of akathisia.

## DISCUSSION

Aripiprazole is documented as a safer drug with an established efficacy as an antipsychotic. There are a few reported cases that demonstrate a causal relation between use of aripiprazole and development of akathisia or other extra pyramidal side effects.<sup>5</sup> Anxiety and akathisia are two closely related clinical manifestations with subtle diagnostic factors. Patients cannot articulate the inner restlessness and agitation which makes the diagnosis more difficult.

In this case report we project two cases in which aripiprazole was prescribed as an adjuvant in obsessive compulsive disorder associated with anxiety like symptoms and psychosis and the patients developed akathisia in a short time giving a cue for more chances of development of akathisia in patients with anxiety like symptoms. Possible mechanisms could be a D<sub>2</sub> receptor blockade in the mesocortical area which is well accepted mechanism.<sup>10</sup> In both the cases the patients were taking fluoxetine concomitantly which is a hepatic microsomal enzyme CYP2D6 inhibitor, and is primarily responsible for aripiprazole metabolism in addition to other enzymes like CYP3A4. A probable inhibition of aripiprazole metabolism leading to the elevated drug levels in the blood is another mechanism. There is less possibility of selective serotonin reuptake inhibitors (SSRI) fluoxetine to cause akathisia mediated by dopaminergic inhibition controlled serotonergically as reduction of the dose of aripiprazole has resulted in the alleviation of the symptoms.

In both cases, there is a positive dechallenge and did not require any additional intervention implying an early identification and close monitoring is essential.

## CONCLUSION

To conclude, the akathisia associated with aripiprazole is implicated on a long term usage, but in patients with anxiety or anxiety like disorders, the chances of development of akathisia is rapid even at low dose and further investigation is warranted.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## ABBREVIATIONS

5 HT:	5 hydroxy tryptamine
BARS:	Barnes akathisia rating Scale
CYP:	Cytochrome P-450
D:	Dopamine receptor
EPS:	Extra-Pyridal side effects
NCC:	National Coordination Center
PvPI:	Pharmacovigilance Programme of India
SSRI:	Selective Serotonin Reuptake Inhibitor
VTA:	Ventral Tegmental Area