

Aripiprazole Treatment in a Patient with Schizophrenia and Severe Antipsychotic-Induced Parkinsonism Following Long-Term use of Methylphenidate: A Case Report

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ABSTRACT:

Aripiprazole treatment in a patient with schizophrenia and severe antipsychotic-induced parkinsonism following long-term use of methylphenidate: a case report

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by various comorbid conditions including mood instability, personality problems, and addiction disorders, and ADHD-like features may also be an early vulnerability marker for schizophrenia. Because of these comorbidities, drug combination treatments and drug-drug interactions are becoming more important. Aripiprazole is an atypical antipsychotic medication with unique properties including dopamine D2 (D2) receptor partial agonism. The intrinsic activity of aripiprazole may serve as a basis for understanding why it can achieve a considerably higher degree of D2 receptor occupancy without causing the extrapyramidal side effects commonly seen with D2 receptor full antagonists and why clinicians may sometimes see aggravation of psychotic symptoms when they switch a patient from D2 full antagonists to aripiprazole. The present case report cautiously suggests the possible value of aripiprazole's stabilizing effects on the dopamine system in treating patients with schizophrenia who display severe antipsychotic-induced Parkinsonism after the cessation of methylphenidate used to treat attention deficit disorder.

Keywords: aripiprazole, schizophrenia, parkinsonism, methylphenidate, attention deficit disorder with hyperactivity

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INTRODUCTION

Symptoms of attention-deficit/hyperactivity disorder (ADHD) in children may persist in adulthood. Adult ADHD patients often exhibit several comorbid conditions¹. Children with ADHD are at heightened risk of developing schizophrenia as adults². There have been few scientific works about the comorbidity of ADHD with schizophrenia in adults³.

Methylphenidate is a psychostimulant that is commonly used to treat ADHD⁴. Methylphenidate acts on the brain's dopaminergic system, inhibiting synaptic dopamine reuptake by blocking the dopamine transporter, resulting in elevated

concentrations of dopamine at the synapses⁵. Several studies investigated the long-term use of methylphenidate reported down-regulation of the post-synaptic dopamine receptor and dopamine transporter in the striatal system^{6,7}.

Increasing dopaminergic signaling following repeated methylphenidate use has raised concerns about psychosis. All approved antipsychotics except for one are dopamine D2 (D2) receptor-antagonists. The only current exception is aripiprazole, which is a D2 partial agonist⁸. Antipsychotics and methylphenidate have opposite effects on the dopaminergic system⁹. Treatment with stimulants in childhood-onset schizophrenia with comorbid ADHD is safe once

psychosis has been stabilized, and it also has positive effects on cognition^{10,11}, but stimulants can induce psychotic symptoms¹².

Use of stimulants is an important issue when treating comorbidity of psychotic disorders and ADHD. Some case reports have described unexpected reactions such as dystonia with the abrupt cessation of stimulants in conjunction with atypical antipsychotics¹³⁻¹⁵. As the present case highlights, aripiprazole may be a possible modality to manage this condition.

CASE PRESENTATION

The patient was a 21-year-old Korean woman. She visited my outpatient clinic on August 1, 2013, because of difficulties in sustaining attention and organization, and she was also easily distracted. She was also forgetful during daily activities. She did not have a history of head trauma, seizure, medical diseases, or substance misuse, and there was no family history of neuropsychiatric disorders. After in-depth psychiatric interviews and psychological assessment, she was diagnosed with ADHD, Predominantly Inattentive Type in Partial Remission according to the Diagnostic and Statistical Manual of Mental disorders, Fourth Edition, Text Revision, (DSM-IV-TR) diagnostic criteria. Medication with methylphenidate Methylphenidate HCl Extended Release 10 mg was started on September 10, 2013. Drug dosage was titrated to 20 mg by October 29, 2013, and the dose was continued until October 2014. During this period, her inattentive symptoms and functioning at school significantly improved.

Beginning in October 2014, she refused to attend school or her part-time job, and she became indifferent concerning self-care and cleanliness. She experienced auditory hallucinations, displayed soliloquist behavior, and stood for hours in place with catatonic features. She also had persecutory delusions. She came to my outpatient clinic with her mother on November 22, 2014. After diagnosed with schizophrenia according to the DSM-IV-TR, she was admitted to the psychiatric ward on November 24, 2014. After her admission, her

methylphenidate was canceled. A single intramuscular injection of haloperidol (2.5 mg) was given on the first day of inpatient admission, and blonanserin (a relatively new atypical antipsychotic with potent D2 and 5-HT₂ antagonist properties) (4 mg/day) and lorazepam (1.5 mg/day) were given for two days. At that time, excessive eye blinking and grimacing developed, and signs of Parkinsonism including hand tremor, limb rigidity, and bradykinesia were observed. An extrapyramidal side effect scale (Simpson-Angus Rating Scale [SARS]) provided a score of 20, and her dyskinesia scale (Abnormal Involuntary Movement Scale [AIMS]) score was 3. With the identification of dyskinesia, blonanserin was changed to aripiprazole and titrated to a dosage of 15 mg/day. After the change in antipsychotics, her dyskinetic movement improved but extrapyramidal symptoms (EPS) of Parkinsonism parkinsonism persisted. She received vitamin E (1000 IU/day), lorazepam (3 mg/day), benztropine (1 mg/day), propranolol (80 mg/day), and aripiprazole (15 mg/day). There was no rapid improvement of EPS. These same medications and dosages were maintained for 26 days. Interestingly, since two weeks after changing antipsychotics, EPS started waxing and waning (SARS score ranged from 13 to 23) every 2 to 3 days but progressively improved (end point SARS score of 9). Psychotic symptoms also progressively improved. Her total score on the Positive and Negative Scale for Schizophrenia changed from 106 to 77. The patient was discharged on January 10, 2015, with improved psychotic symptoms and improved EPS.

DISCUSSION

This case highlights the possible value of aripiprazole in treating patients with schizophrenia who display severe antipsychotic-induced parkinsonism after long-term use of methylphenidate for treating ADHD.

In the present case, psychotic symptoms might have been induced by the long-term use of methylphenidate. Kraemer et al. described reported three cases of methylphenidate-induced

psychosis¹⁶. Two of the patients showed quick improvement of psychotic symptoms after stopping methylphenidate. Although the third patient in that study recovered over a 3-week period, my patient presented the psychotic symptoms for several months in the absence of methylphenidate. It cannot be excluded that her attention problems could have represented prodromal symptoms of schizophrenia. However, she did display improved functions and attention symptoms during her use of methylphenidate. Also, history taking and psychological assessment indicated that her attention problems had been present from a very early age.

The presence of antipsychotic-induced severe parkinsonism echoes other case reports^{13,14}. Meanwhile, Ekinçi et al. described psychosis associated with the switch from risperidone to aripiprazole with methylphenidate¹⁷. Aripiprazole has a higher affinity for dopamine receptors than does risperidone and low intrinsic D2 partial agonism to counter excessive D2 antagonism⁹. These different situations could be explained

by the intuitive formulation that aripiprazole would decrease dopamine transmission postsynaptically in areas that are hyperdopaminergic because its intrinsic activity is less than that of the natural agonist dopamine, and it increases transmission in areas that are hypodopaminergic^{18,19}. Hence, dopaminergic tone in the surrounding environment can be related to aripiprazole's mechanism of action.

Acute EPS usually responds to anticholinergics, beta blockers, and benzodiazepine²⁰. In the present case, drug-induced parkinsonism had not changed after medication for two weeks. An animal study revealed that dopamine D2 receptors are moderately elevated after a 7-day treatment with aripiprazole²¹, so the patient's improved psychotic symptoms and EPS could have been explained by aripiprazole's unique action mechanism on the dopamine system.

In conclusion, aripiprazole may be an option for treating schizophrenia with severe antipsychotic-induced parkinsonism after the long-term use of methylphenidate.

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