

Severe Aripiprazole-Induced Extrapyrarnidal Parkinsonian Features In A Patient With Psychotic Depression On Sertraline: A Case Report

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Citation

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Abstract

Aripiprazole is a third generation antipsychotic with partial dopaminergic activity. In addition to its proven antipsychotic effects, it has become more widely accepted at the clinical level. It is FDA-approved as an adjunctive therapy for depression with or without psychotic features. This case report concerns the development of severe Parkinsonian features in a depressed psychotic patient following the addition of aripiprazole to his sertraline treatment.

BACKGROUND

Aripiprazole has a unique pharmacological profile that includes partial agonism at D2 receptors and at 5-HT1A receptors, as well as antagonism at 5-HT2 receptors. Aripiprazole was the first antipsychotic introduced whose mechanism of action deviates from those of both conventional and atypical antipsychotics. Its high affinity for the dopamine D2 receptor ($K_i = 0.34$ nmol) is similar to that of haloperidol ($K_i = 0.7$ nmol).¹ In vitro, aripiprazole acts as a partial D2 agonist, a property contrasting with the antagonism exhibited by all other conventional and atypical antipsychotic drugs^(1,2).

The efficacy of aripiprazole as an adjunct to antidepressant therapy in patients with major depressive disorder (MDD) has been replicated in several well-controlled studies⁽³⁻⁵⁾. Several controlled trials reported occurrence of aripiprazole-induced extrapyramidal side effects at rates similar to placebo; however, aripiprazole-induced akathisia was reported to occur at significantly higher rates (approximately 20%) in patients with schizophrenia or with bipolar mania. It has been suggested that partial agonism at D2 and 5-HT1A receptors accounts for the low incidence of extrapyramidal side effects seen with aripiprazole, but that akathisia may still occur^(6,7).

CASE HISTORY

The 35 year old single male patient worked as a butcher and lived with his family. Three months before we first

examined him, he began to experience nearly continual depression which was particularly accentuated during evening hours, reflecting a nocturnal rhythm of mood. The patient initially remained responsive to daily events with appropriate reactions, but he later became hypoactive with markedly diminished daily physical activities. Although his speech remained coherent, he began to speak very little and initiated few dialogues with others. He reported difficulty concentrating and also forgetfulness that was noticeable to colleagues at work.

Within the previous month, his ideas of people speaking negatively about him progressed to a strong belief, indicating the replacement of referential thought by delusions. He reported no hallucinations. The patient had great difficulty falling asleep and markedly interrupted sleep, reflecting an initial insomnia. Loss of appetite led to objective weight loss evidenced by loosening of his trousers. He also reported diminished libido. The patient had suicidal thoughts, stating a desire to end his life, but reported that his religious beliefs prevented him from ever attempting suicide or harm to himself or others. His condition progressed to severe impairment of personal care and social activities, including relationships with friends. His work became disrupted with frequent absenteeism.

His family brought him to a psychiatric outpatient service on April 18, 2010. Major depression was diagnosed, and a selective serotonin reuptake inhibitor (SSRI) was prescribed (sertraline, 50 mg/d, morning dose). The patient experienced

modest subjective improvement. By his family's account, the patient complied in taking his medication, but he did not return to the outpatient clinic for follow-up.

Three weeks later, we received him at our outpatient clinic because of his deteriorating condition, which included suicidal thoughts, delusional references, absenteeism from work, and nearly continual crying while withdrawn in his room. Major depression with mood-congruent psychotic features was diagnosed and discussed with the patient. A poor response to SSRI monotherapy for psychotic depression was hypothesized as an explanation of the negative outcome reported by the patient. We decided to add the antipsychotic aripiprazole to his treatment (10 mg/d, morning dose). The akathisia that the patient would likely experience was explained to him, and a follow-up appointment was scheduled for two weeks later. A thyroid profile was requested and the results obtained did not indicate any abnormalities.

Three days after the visit, the patient's mother telephoned to request an urgent appointment, stating that her son's condition had worsened, with near paralysis and drooling, and that swallowing had become difficult and slow. The patient was seen that evening. Clinical examination revealed severe hypertonia in all four limbs throughout the entire range of movement, suggesting extrapyramidal rigidity. Mild resting hand tremors and drooling were also noted, as well as walking with a shortened stride and a flexed posture. Aripiprazole was stopped, and injectable diphenhydramine (4 mg/d) was administered to alleviate drug-induced Parkinsonian features. When the patient was reevaluated three days later, he showed marked improvement on the extrapyramidal side effects. Olanzapine (5 mg/d) was initiated in combination with sertraline (50 mg/d), and regular follow-up visits were scheduled at two week intervals, with monthly monitoring of his weight and lipid profile. No extrapyramidal side effects were reported during his subsequent visits.

DISCUSSION

Although akathisia is not uncommon in patients receiving aripiprazole, other extrapyramidal side effects of this drug were equivalent to placebo in controlled trials^(8,9). Induction of adverse extrapyramidal reaction by aripiprazole within the therapeutic dose range was first reported in 2006. That report, describing a patient aged 56 years with no relevant medical comorbidities who developed extrapyramidal side effects 5 weeks after initiating aripiprazole, emphasized the

importance of slowly escalating the dose⁽¹⁰⁾. Two other reports of extrapyramidal manifestations in children with high dosage of aripiprazole have suggested the possibility of dose-dependent induction of extrapyramidal side effects^(11,12).

Although aripiprazole is known to have high affinity to D2 receptors in the striatum, this effect is partially agonistic, and clearly differs from the purely antagonistic effects of other conventional or atypical antipsychotics. This may account for its high margin of safety with regard to extrapyramidal side effects (other than akathisia) which have been comparable to placebo⁽¹³⁾. The occurrence of extrapyramidal side effects of aripiprazole in the case reported here is likely attributable to multiple drug interaction. This may be explained by hepatic cytochrome P450-dependent metabolism of aripiprazole, in particular the enzyme subtypes 2D6 and 3A4, both of which have been shown to be inhibited by sertraline⁽¹⁴⁾. Sertraline-inhibited metabolism of aripiprazole would cause serum aripiprazole levels to become elevated, resulting in greater occupancy of striatal D2 receptors and producing the observed extrapyramidal side effects.

CONCLUSION

Given the increasing use of aripiprazole to augment antidepressant therapy, we recommend slow titration of antidepressants known to suppress hepatic cytochrome P450 activity, in order to reduce the likelihood of extrapyramidal side effects arising through multiple drug interaction.

References

1. Burris KD, Molski TF, Xu C, Ryan E, Tottori K, Kikuchi T, Yocca FD, Molinoff PB: Aripiprazole, a novel antipsychotic, is a high affinity partial agonist at human dopamine D2 receptors. *J Pharmacol Exp Ther*; 2002; 302: 381–389.
2. Tadori Y, Miwa T, Tottori K, Burris KD, Stark A, Mori T, Kikuchi T: Aripiprazole's low intrinsic activities at human dopamine D2L and D2S receptors render it a unique antipsychotic. *Eur J Pharmacol*; 2005; 515: 10–19.
3. Pae CU, Patkar AA, Jun TY, Lee C, Masand PS, Paik IH: Aripiprazole augmentation for treatment of patients with inadequate antidepressant response. *Depress Anxiety*; 2007; 24: 522–526.
4. Berman RM, Fava M, Thase ME, Trivedi MH, Swanink R, McQuade RD, Carson WH, Adson D, Taylor L, Hazel J, Marcus RN: Aripiprazole augmentation in major depressive disorder: a double-blind, placebo-controlled study in patients with inadequate response to antidepressants. *CNS Spectr*; 2009; 14: 197–206.
5. Trivedi MH, Thase ME, Fava M, Nelson CJ, Yang H, Qi Y, Tran QV, Pikalov A, Carlson BX, Marcus RN, Berman RM: Adjunctive aripiprazole in major depressive disorder: analysis of efficacy and safety in patients with anxious and

atypical features. *J Clin Psychiatry*; 2008; 69: 1928-36.

6. Fleischhacker W: Aripiprazole. *Expert Opin Pharmacother*; 2005; 6: 2091-2101.

7. Kinghorn WA, McEvoy JP: Aripiprazole: pharmacology, efficacy, safety and tolerability. *Expert Rev Neurother*; 2005; 5: 297-307.

8. Marder SR, McQuade RD, Stock E, Kaplita S, Marcus R, Safferman AZ, Saha A, Ali M, Iwamoto T: Aripiprazole in the treatment of schizophrenia: safety and tolerability in short-term, placebo-controlled trials. *Schizophr Res*; 2003; 61: 123-136.

9. Cutler AJ, Marcus RN, Hardy SA, O'Donnell A, Carson WH, McQuade RD: The efficacy and safety of lower doses of aripiprazole for the treatment of patients with acute exacerbation of schizophrenia. *CNS Spectr*; 2006; 11: 691-702.

10. Salmoiraghi A, Odiyoor M: A case of Aripiprazole and extra pyramidal side effects. *Journal of Psychopharmacology*; 2006; 20: 592-593.

11. Lindsey RL, Kaplan D, Koliatsos V, Walters JK, Sandson NB: Aripiprazole and extrapyramidal symptoms. *J Am Acad Child Adolesc Psychiatry*; 2003; 42: 1268-1269.

12. Levine M, Traub S, Burns MJ: The pharmacology and toxicology of aripiprazole. *Internet J Med Toxicol*; 2004; 7: 5.

13. Mamo D, Graff A, Mizrahi R, Shammi CM, Romeyer F, Kapur S: Differential effects of aripiprazole on D2, 5-HT₂, and 5-HT_{1A} receptor occupancy in patients with schizophrenia: a triple tracer PET study. *Am J Psychiatry*; 2007; 164: 1411-1417.

14. de Leon J, Armstrong SC, Cozza KL: The dosing of atypical antipsychotics. *Psychosomatics*; 2005; 46: 262-273.

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