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FROM TIC TREATMENT TO TIC INDUCTION: A PARADOXICAL EFFECT OF ARIPIPRAZOLE IN SCHIZOPHRENIA

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ABSTRACT

Introduction: Aripiprazole, an atypical antipsychotic acting as a partial agonist at dopamine D2/D3 receptors, is generally recognized for its favorable extrapyramidal side-effect profile. However, cases of movement disorders induced by this medication, including tics, have been exceptionally reported in the literature.

Case Presentation: We report the case of a 30-year-old woman with schizophrenia who developed cervical motor tics after one year of treatment with aripiprazole monotherapy at a dose of 20 mg/day. She had no personal or family history of movement disorders. Switching treatment to olanzapine 10 mg/day resulted in partial improvement of the tics after one month of follow-up.

Discussion: This case illustrates a paradoxical adverse effect of aripiprazole that may be explained by its mechanism of partial dopaminergic agonism. Under certain pharmacodynamic conditions, aripiprazole may exert a net agonistic effect on the nigrostriatal pathway, thereby facilitating the emergence of tics.

Conclusion: Clinicians should be aware of this potential risk, particularly at higher doses and in patients with prolonged prior exposure to antipsychotic medications. Regular neurological monitoring during aripiprazole treatment is recommended.

KEYWORDS: Aripiprazole; Motor tics; Schizophrenia; Partial dopaminergic agonism; Adverse effects.

INTRODUCTION

Aripiprazole is a third-generation atypical antipsychotic whose mechanism of action is based on partial agonism at dopamine D2 and D3 receptors, partial agonism at serotonin 5-HT1A receptors, and antagonism at 5-HT2A receptors [1]. This unique pharmacological profile confers a "dopamine stabilizing" effect, allowing aripiprazole to function as a functional antagonist under hyperdopaminergic conditions and as a functional agonist under hypodopaminergic conditions [2]. It has been approved by major regulatory agencies for the treatment of schizophrenia, bipolar disorder, and certain autism spectrum disorders [3].

Compared with typical antipsychotics and several other atypical antipsychotics, aripiprazole generally exhibits a more favorable extrapyramidal side-effect (EPS) profile, with a relatively low incidence of severe akathisia, parkinsonism, and tardive dyskinesia [4]. Nevertheless, cases of aripiprazole-induced movement disorders have been reported in the literature, including parkinsonism, tardive dyskinesia, orofacial dyskinesia, and, more rarely, tics [5,6].

We report the case of a patient with schizophrenia who developed cervical motor tics during treatment with aripiprazole despite having no previous history of movement disorders. This case contributes to the growing body of evidence regarding this paradoxical adverse effect and provides insight into the potential underlying pharmacodynamic mechanisms.

Case Presentation

A 30-year-old woman with no personal or family history of movement disorders or neurological disease had been followed in psychiatric care for four years for schizophrenia. In 2022, she was admitted on an emergency basis for an acute psychotic episode characterized by severe psychomotor agitation, polymorphic delusions, hallucinations, heteroaggressive behavior, and insomnia. The diagnosis of schizophrenia was established according to DSM-5-TR criteria.

Because of refusal of oral medication, initial management consisted of injectable haloperidol and chlorpromazine. Shortly thereafter, the clinical course was complicated by a probable neuroleptic malignant syndrome (NMS), leading to the immediate discontinuation of first-generation antipsychotics. Following clinical and biological stabilization, treatment was switched to amisulpride 800 mg/day and quetiapine 100 mg/day.

Due to insufficient clinical improvement, aripiprazole 15 mg/day was added as an antipsychotic with a complementary mechanism of action, resulting in progressive improvement of psychotic symptoms. The patient was discharged after two and a half months of hospitalization on this triple therapy regimen.

During outpatient follow-up, hyperprolactinemia attributed to amisulpride was identified, leading to its discontinuation. The patient was subsequently maintained on aripiprazole monotherapy, with the dose increased to 20 mg/day, achieving satisfactory psychiatric stability.

One year after initiation of aripiprazole monotherapy, the patient gradually developed motor tics consisting of involuntary repetitive neck movements. No infectious trigger or recent medication changes were identified. Neurological examination revealed no additional extrapyramidal signs, including parkinsonism, akathisia, or dyskinesia. Investigation of personal and family history was negative for Tourette syndrome or tic disorders.

Given the suspected causal role of aripiprazole, treatment was switched to olanzapine 10 mg/day. After one month of follow-up, partial improvement of the motor tics was observed without recurrence of psychotic symptoms.

DISCUSSION

1. A Documented Paradoxical Adverse Effect

Aripiprazole is generally considered a first-line pharmacological treatment for tics associated with Tourette syndrome (TS) and chronic tic disorders because of its demonstrated efficacy in several randomized controlled trials and meta-analyses [7,8]. In a randomized, double-blind, placebo-controlled trial conducted in children and adolescents with Tourette syndrome, He et al. reported that oral aripiprazole solution was significantly more effective than placebo in reducing motor and vocal tics as measured by the Yale Global Tic Severity Scale (YGTSS), with a response rate of 86.4% versus 56.6% in the placebo group [7]. A recent meta-analysis including participants aged 6 to 65 years further confirmed the efficacy of aripiprazole in improving both YGTSS-Total Tic Scores and Clinical Global Impression-Tourette Syndrome (CGI-TS) scores [8].

Paradoxically, several cases of tic induction or tic exacerbation associated with aripiprazole have been described in the literature. Lim et al. reported what was, to their knowledge, the first documented case of aripiprazole-associated tics in an adult patient with schizophrenia and suggested a possible dose-dependent relationship [6]. Additional reports have described aripiprazole-induced orofacial dyskinesia [5], oculogyric crises [9], and various other

movement disorders, highlighting the diversity of extrapyramidal adverse effects that may occur despite the drug's favorable safety profile [4].

2. Potential Pharmacodynamic Mechanisms

The mechanism by which aripiprazole may induce tics is likely related to its unique pharmacological profile as a partial dopamine receptor agonist [2,10]. Through partial agonism at D2 and D3 receptors, aripiprazole acts as a dopamine system stabilizer, exerting functional antagonism in hyperdopaminergic states while producing agonistic effects in hypodopaminergic conditions [2].

Several factors may explain the occurrence of tics in our patient. First, prolonged prior exposure to potent D2 receptor-blocking antipsychotics, such as haloperidol and amisulpride, may have induced striatal dopamine receptor supersensitivity. This phenomenon could render the nigrostriatal pathway particularly susceptible to the partial agonist activity of aripiprazole [11]. A similar mechanism has been proposed in withdrawal dyskinesia occurring after discontinuation or substitution of dopamine-blocking agents [12].

Second, the antagonistic action of aripiprazole at presynaptic 5-HT2A receptors may enhance dopamine release within the basal ganglia, thereby contributing to tic generation [6,10]. This serotonergic-dopaminergic interaction may further amplify the functional dopaminergic activity of aripiprazole in susceptible individuals.

The relatively high dose used in our patient (20 mg/day) may also have played a contributory role. Lim et al. observed that tic-like symptoms associated with aripiprazole appeared dose-dependent, worsening following dose escalation and improving after dose reduction [6]. This observation suggests that, at higher doses, the partial agonist properties of aripiprazole may exceed a critical threshold capable of triggering tics in predisposed patients.

3. Clinical Management and Therapeutic Implications

Several therapeutic strategies may be considered when motor tics emerge during aripiprazole treatment. Dose reduction should be the first option whenever clinically feasible, given the apparent dose-dependent nature of this adverse effect [6]. Alternatively, switching to another antipsychotic may be warranted, as was done in our case.

Olanzapine, which exhibits stronger D2 receptor antagonism combined with serotonergic activity, may help restore a more stable nigrostriatal dopaminergic tone, potentially explaining the partial improvement observed in our patient [13]. Symptomatic treatment with

alpha-2 adrenergic agonists, such as clonidine or guanfacine, may also be considered because of their demonstrated efficacy and favorable tolerability profile in tic disorders [8].

Interestingly, the combination of guanfacine and aripiprazole has been reported to be effective in managing refractory Tourette syndrome, emphasizing the complexity of the underlying neuropharmacological mechanisms [14]. In cases where tics persist despite treatment modification, referral for specialized neurological assessment is recommended to exclude an underlying tic disorder or previously unrecognized Tourette syndrome that may have been unmasked by pharmacological treatment.

CONCLUSION

This case illustrates the rare but clinically relevant occurrence of aripiprazole-induced motor tics in a patient with schizophrenia who had no previous personal or family history of tic disorders. The underlying mechanism is likely related to relative nigrostriatal dopaminergic hyperactivity resulting from the partial D2 receptor agonism of aripiprazole in a context of dopamine receptor sensitization induced by prior antipsychotic exposure.

This report highlights the importance of regular neurological monitoring in patients receiving aripiprazole, particularly following the discontinuation or substitution of potent D2 receptor antagonists and when high doses are prescribed. Early recognition of such adverse effects allows timely therapeutic adjustments while preserving both psychotic symptom control and the patient's quality of life.

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