CASE REPORT

Aripiprazole (Abilify) and Tardive Dyskinesia

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ABSTRACT

Second-generation (atypical) antipsychotic agents are being used within their indications as well as widely off-label because of their lower risk of causing extrapyramidal symptoms and tardive dyskinesia (TD). The risk of metabolic disorders has taken over much of clinical practice and the current literature on adverse effects. In this brief article, we discuss a case of TD that developed after a patient used aripiprazole as off-label augmentation for treatment-resistant depression. We emphasize the fact that TD is an adverse effect that must still be monitored.

INTRODUCTION

Tardive dyskinesia (TD) is usually a late-developing, well-known neuromuscular adverse effect associated with the long-term use of first-generation (typical or conventional) antipsychotic agents, such as chlorpromazine (Thorazine, GlaxoSmithKline), haloperidol (Haldol, Ortho-McNeil), and fluphenazine (Prolixin, Apothecon). After months to years of therapy with dopamine-2 (D_2) receptor–blockers, patients often experience involuntary choreiform, athetotic, or ballismic dyskinetic movements. These movements most commonly involve the mouth, tongue, facial muscles, and upper extremities. Axial dyskinesias may also occur.[1]

With the advent of the second-generation (atypical) antipsychotic agents (SGAs), all of which utilize a serotonin-2 receptor (5-HT_2) blockade, the risk of TD has apparently decreased, thereby allowing clinicians to treat schizophrenia with less possibility of a side-effect burden. Given this fact and the potential of these agents to treat several targeted symptoms (i.e., cognition, dysphoria, mania, and agitation), pharmaceutical companies have proceeded with studies and have gained approvals from the Food and Drug Administration (FDA) for most SGAs in areas other than schizophrenia, such as bipolar mania and depression and, in the case of risperidone (Risperdal, Janssen), autism.[2,3] The off-label use of SGAs also continues to increase in the form of augmented therapies for resistant depression and anxiety.[4,5] In fact, the FDA recently approved aripiprazole as the first augmentation (add-on) strategy for the treatment of unipolar major depression.

This article presents the case of a patient with treatment-resistant depression who experienced TD during augmentation therapy with aripiprazole (Abilify, Bristol-Myers Squibb/ Otsuka). Aripiprazole may be considered an "atypical atypical" agent; it is a partial dopamine agonist, not a full antagonist. Its unique profile allows for subtle increases in tonic dopamine neuron firing rates in brain areas that are hypofunctioning and for dampening of dopaminergic activity in areas that are hyperfunctioning. This blockade of hyperdominergic regions in the brain is thought to alleviate psychosis.

RISK FACTORS FOR TARDIVE DYSKINESIA

Typical risk factors associated with the development of TD include older age, pre-existing movement or neurodegenerative disorders, female sex, the presence of affective illness, and neuroleptic exposure of more than six months.[6] The use of higher-potency, first-generation agents is also more likely to increase the risk of TD and extrapyramidal symptoms (EPS). There is little doubt that conventional antipsychotic agents, compared with SGAs, are more likely to cause TD. However, among the SGAs currently available, those with more transient D_2 receptor blockade and lower D_2 affinity, such as quetiapine (Seroquel, AstraZeneca), are associated with the smallest risk, at least for EPS and probably TD.

At a therapeutic dose, it is noteworthy that aripiprazole has one of the highest D_2 receptor affinities; however, because of its partial agonist properties, it has a lower risk of causing acute EPS and, probably, TD.[7–10] A timely study of exposure to antipsychotic drugs in nongeriatric adults suggests that the incidence of TD with SGAs is 0.8%, compared with 5.4% with haloperidol, a high-potency, first-generation antipsychotic agent.[11]

Case Study

Ms. A., a 46-year-old woman, initially reported a long history of mood lability; possible premenstrual dysphoric disorder; and recurrent–moderate major depressive disorder (MDD). At the time of presentation to our clinic, she reported an increased quantity of sleep, sad and irritable mood, poor concentration, low levels of interests and enjoyment, visual illusions, increased feelings of guilt, and passive suicidal ideation that had been present consistently for two years.

The patient had undergone an initial trial of fluoxetine (Prozac, Lilly) by another provider but otherwise had no previous psychiatric history. She was experiencing urinary incontinence, trigeminal neuralgia, and lumbar back pain. She used hydrocodone (Vicodin, Abbott) rarely, as needed, for trigeminal pain, and she was routinely using tolterodine (Detrol, Pfizer) for her bladder. Her family history was consistent with alcohol dependence and an anxiety disorder.

We initially prescribed and escalated the dose of duloxetine (Cymbalta, Lilly), up to 120 mg/day, an antidepressant that she had been taking for approximately two years. Although she was not experiencing any adverse effects, she had only a partial response to this medication.

Given the perceived clinical effectiveness and availability of some peer-reviewed literature, we discussed augmentation with a SGA.

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Accepted for publication November 6, 2007.

Disclosure: Dr. Schwartz has received financial support for research from Bristol-Myers Squibb during the past three years.

All of the SGAs possess serotonin-2 receptor antagonism, an effective antidepressant mechanism in the FDA-approved antidepressant nefazodone (Serzone, Bristol-Myers Squibb). With this rationale in mind, we attempted low-dose augmentation with ziprasidone (Geodon, Pfizer), 40 mg/day for two weeks, but akathisia and activation of adverse effects prompted the patient to discontinue taking this drug.

Aripiprazole was substituted, initially with a dose of 5 mg/day, which was gradually increased to 15 mg/day. The patient reported consistent and gradual improvement of her depressive symptoms throughout the next few visits, and she attained remission from depression several weeks later. There was no evidence of visual illusions or hallucinations. The patient did note a mild amount of weight gain of about 4 kg (about 9 pounds) as a primary side effect, but she clearly felt that the benefits of the medication in alleviating depression outweighed the side effects.

An evaluation for metabolic syndrome was negative; fasting blood glucose and lipid levels were determined, and blood pressure was normal. After 15 months of compliant and consistent treatment with duloxetine and aripiprazole, the patient continued to report remission from depression. However, she then began to have involuntary lateral jaw movements, primarily on her left side, at a rate of two to three movements every few minutes. She reported no dentition problems or pre-existing nervous or motor tics.

The patient underwent a series of voluntary movements so that we could test for the induction of or the natural occurrence of TD. The patient's score of 9 (range, 0–42), as observed in the Abnormal Involuntary Movement Scale (AIMS), confirmed new-onset TD.

The aripiprazole dose was tapered and discontinued. Eight weeks later, the patient's lateral movements completely resolved. Follow-up is ongoing.

DISCUSSION

Our case represents new-onset oromandibular TD arising during the use of the atypical neuroleptic agent aripiprazole when used at the time in an off-label manner to manage treatment-resistant depression. The Naranjo Scale is a series of questions that attempt to link the probability of an adverse effect being directly related to a specific drug exposure. Our patient's score was 5 (range, 0–12) on this scale.[12]

We then conducted a literature review of aripiprazole-induced TD. Maytal et al. had reported a similar case in which aripiprazole was used for depression and TD ensued. TD remitted several weeks after drug cessation.[13]

Zacher and Hatchett (2006) used aripiprazole 20 mg to treat bipolar illness. Pseudoparkinsonism occurred, and rabbit syndrome (characterized by rhythmic movements of the mouth) was considered to be a dystonic event but not necessarily TD.[14]

Another patient who was developmentally disabled with obsessive-compulsive disorder was treated with aripiprazole 10 mg. This patient experienced an acute dystonic face, tongue, and arm movements as well as upper limb athetosis. These acute dystonic events were alleviated with diphenhydramine (Benadryl, Pfizer).[15]

Sajbel and Evcimen and their colleagues[16,17] reported two cases of aripiprazole-induced TD in two patients with schizoaffective disorder. Both patients received 20 mg/day. After 10 days of discontinuing aripiprazole, one patient's abnormal tongue movements ceased. In other case reports, aripiprazole was used to treat and alleviate TD induced by other neuroleptic agents in patients with bipolar and schizoaffective illnesses. It is difficult to determine whether aripiprazole acted as a treatment or whether stopping the previous higher-potency neuroleptic agent allowed the remission of TD.[18–21]

Our own patient had an excellent response in terms of remission of depressive symptoms; she experienced a minimal amount of weight gain but ultimately developed lateral jaw movements, now considered to be TD. There was no evidence of dystonia, motor tics, nervous tics, or poor dentition to explain the involuntary movements. She was taking no other medication known for inducing dystonias or dyskinesias. AIMS testing revealed that the lateral jaw movements could be exacerbated during manipulation; her total score was 9, again suggestive of TD.

In this case, our patient had probable risk factors for the development of TD, including affective disorder, female sex, and exposure to antipsychotic agents for more than six months. Her dose was a moderate 15 mg/day, but duloxetine probably influenced a mild inhibition of liver enzyme cytochrome P450 (CYP 2D6), allowing elevated aripiprazole blood levels. (Aripiprazole is a substrate for this liver enzyme metabolic system.) There have also been isolated reports of serotonergic antidepressants causing movement disorders such as parkinsonism, which might be a complicating factor in the development of this patient's TD.

In theory, SGAs are safer than conventional agents in terms of causing TD and EPS. Statistically, SGAs are also safer, but our case report underlies the continued need for appropriate informed consent, patient monitoring, and patient care because of the ability of these agents to produce potentially permanent neuromuscular adverse effects.

We suggest that agents be used according to their FDA-approved indications when possible.[22] If off-label use is prescribed, clinicians should be aware of the evidence base for each SGA in terms of the psychiatric illness being treated. In off-label diagnostic prescribing, we propose that lower-potency SGAs (i.e., quetiapine, aripiprazole, or ziprasidone) be used, even though our case example showed that a lower-potency SGA caused TD.

We also encourage dosing for shorter periods of time, when feasible, and delineating the lowest effective dose on a case-by-case basis.

CONCLUSION

With their ability to reduce the risk of EPS, the atypical antipsychotic agents are the current drugs of choice for schizophrenia and bipolar illness as well as for many off-label applications. Almost all available SGAs have been linked to cases of TD, and a larger naturalistic evidence base is developing as patient exposures increase over time. Therefore, we need to continuously monitor individuals treated with antipsychotic medications regardless of their dose, diagnosis, or choice of SGAs over the conventional antipsychotic drugs.

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