Aripiprazole for the Management of Antipsychotic-Induced Hyperprolactinemia

A Retrospective Case Series

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ABSTRACT

Objective: To demonstrate how effectively aripiprazole can be utilized to manage antipsychotic-induced hyperprolactinemia.

Methods: The files of 3 female patients with a history of psychotic illness and hyperprolactinemia who were treated at a state hospital between February 2018 and May 2019 were retrospectively analyzed. All were found to have elevated prolactin levels and underwent treatment with aripiprazole in addition to their concomitant medications.

Results: In general, the addition of aripiprazole to the treatment regimen of each of the patients corresponded to a decline in their serum prolactin levels.

Conclusions: Hyperprolactinemia is frequently observed in patients treated with antipsychotic medications. Low-dose treatment with aripiprazole may offer a relatively rapid relief from sustained hyperprolactinemia and associated adverse effects even after a long-acting injectable is discontinued.

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Hyperprolactinemia is a common, and often overlooked, adverse effect associated with antipsychotic drugs (APDs). Although this increase in prolactin is not gender specific, it is associated with a higher burden of more serious adverse outcomes in women than in men.[1] In normal prolactin physiology, dopamine acts as the predominant inhibitory factor for this hormone. One of the main primary mechanisms of most APDs is blockade of the dopamine-2 (D_2) receptors. When this blockade occurs in the tuberoinfundibular tract, the dopamine inhibition on prolactin secretion is removed, resulting in hyperprolactinemia.[2]

High levels of prolactin can result in a variety of symptoms, such as sexual dysfunction, menstrual abnormalities, and infertility. Hyperprolactinemia can also cause acne and hirsutism as well as changes in bone mineral density.[1,2] Because medication treatment for psychotic disorders in women is often started when the patient is in her late teens or 20s and continues for many years, these adverse effects can potentially have long-term consequences as well. It is vitally important to address elevated prolactin levels even in the absence of amenorrhea or galactorrhea given the long-term risk of osteoporosis and cardiovascular issues, as well as possible associations with endometrial and breast cancer.[3]

Hyperprolactinemia can be addressed by reducing the dose of APD or by adding a dopaminergic agonist or a prolactin-sparing APD[3]; however, these efforts carry the risk for a psychotic relapse. The biggest challenge is posed by antipsychotic long-acting injectables (LAIs), as it may take weeks to see any significant change in prolactin levels after decreasing the dose. However, a relatively newer group of APDs with partial agonism for D_2 receptors offers a novel approach to reduce prolactin levels in patients with antipsychotic-induced hyperprolactinemia[4–6] with no risk for worsening psychosis. Aripiprazole is a partial agonist APD with one of the strongest affinities for D_2 receptors. Thus, aripiprazole has the potential to displace some of the high-potency APDs (especially LAIs) with strong D_2 receptor antagonism, such as haloperidol or fluphenazine, to provide relief from hyperprolactinemia.[7,8] Here, we present a retrospective case series to illustrate the utility of aripiprazole treatment in the management of hyperprolactinemia in 3 female patients with psychosis being treated at a state psychiatric facility.

METHODS

In this retrospective case series, the files of 3 patients with a history of psychotic illness and hyperprolactinemia who were treated at the Oregon State Hospital between February 2018 and May 2019 were analyzed. The psychiatric diagnoses of these patients were

Clinical Points

- Hyperprolactinemia is frequently observed in patients treated with antipsychotic medications.
- Antipsychotic long-acting injectable–induced hyperprolactinemia takes a long time to normalize.
- Low-dose treatment with aripiprazole may offer relatively rapid relief from sustained hyperprolactinemia and associated adverse effects even after a long-acting injectable is discontinued.

reevaluated and confirmed by certified psychiatrists after hospital admission using *DSM-5* criteria.[9] The patients were women with a mean age of 36 (standard deviation of 8.6) years. All were found to have elevated prolactin levels and underwent treatment with aripiprazole in addition to their concomitant medications. Their diagnoses and treatment histories are presented in Table 1.

RESULTS

Reduction in prolactin levels after the addition of aripiprazole is summarized in Table 1. In general, the addition of aripiprazole to the treatment regimen in each of these patients corresponded to a decline in their serum prolactin levels.

Patient 1

Ms A is a 32-year-old woman who was diagnosed with developmental delay at a young age and later went on to develop schizoaffective disorder, bipolar type. She had a history of a suicide attempt that resulted in an anoxic brain injury and was subsequently committed for hospitalization at the state psychiatric facility. This was her fifth stay at the hospital. During her hospitalization in 2018, Ms A began refusing her medications and was subsequently switched to an LAI, paliperidone palmitate, to improve adherence. Shortly after beginning the loading dose process, she developed severe akathisia and was found to have a prolactin level of 138.9 ng/mL. These adverse effects were accompanied by increased agitation and aggression. A trial of 5 mg of aripiprazole was initiated in an attempt to address the adverse effects from the LAI, and her prolactin levels subsequently decreased. Eventually, given further decompensation and worsening symptoms, Ms A was switched to clozapine, which successfully decreased her psychosis and maintained her prolactin level within a normal range.[10]

Patient 2

Ms B is a 48-year-old woman with a psychiatric history significant for schizophrenia and medication nonadherence with psychotropic medications. Prior to her 4th inpatient admission to a state hospital facility, Ms B started refusing psychotropic medications and became increasingly paranoid. Initially, she was admitted to a community hospital and received paliperidone 12 mg/day and olanzapine 5 mg intramuscular as backup to improve medication adherence. Later, she was transferred to the state psychiatric facility to continue inpatient treatment, wherein she was first switched to paliperidone LAI and subsequently to risperidone LAI to improve compliance. However, this LAI had to be discontinued after Ms B was found to have a serum prolactin level of 275.4 ng/mL. In an effort to lower LAI-induced hyperprolactinemia, Ms B was started on a low-dose aripiprazole regimen (2 mg daily) before she was switched to aripiprazole LAI, which stabilized her psychotic symptoms and hyperprolactinemia.

Patient 3

Ms C is a 28-year-old woman with a history of schizoaffective disorder, bipolar type as well as substance abuse involving methamphetamines that followed a long history of psychotic and affective symptoms since the age of 12 years. She has had multiple involuntary admissions to mental health facilities due to psychosis and verbal and physical aggression toward others. Additionally, she suffers from a number of comorbid conditions including polycystic ovarian syndrome (PCOS). After admission to the state facility, Ms C was found to have a prolactin level of 166.1 ng/mL. She was started on an aripiprazole regimen of 10 mg daily, which was subsequently increased to 20 mg daily. During this time, her prolactin level decreased to 45.6 ng/mL.

DISCUSSION

Although the prolactin-lowering potential of aripiprazole was described earlier,[4] this case series documents relatively rapid reduction in sustained hyperprolactinemia after the discontinuation of LAIs in 3 patients with primary psychotic disorders. On preliminary report, the prolactin levels of patients 1 and 2 both returned to normal after the addition of aripiprazole (5 mg daily in patient 1 and 2 mg daily switched to LAI in patient 2). Patient 3's prolactin level decreased from 166.1 ng/mL to 45.6 ng/mL during our observation period, which is a value that is still above the reference range. This persistent increase in prolactin could be explained by this patient's having a number of comorbid conditions including PCOS and hypothyroidism. Although 1 retrospective case series found no association between PCOS and hyperprolactinemia,[11] 2 patients with PCOS were reported to have increased prolactin levels in a case report.[12] In addition, in patient 2, hypothyroidism (although managed with levothyroxine) may also have contributed to her hyperprolactinemia, as it has been shown to sometimes be a feature of subclinical hypothyroidism.[13] We therefore suspect that this patient's persistently elevated prolactin level is related to a combination of her antipsychotic medications and comorbid conditions. It is important to note that 1 of 3 patients in this case series did not respond to aripiprazole and had to be gradually switched to clozapine. This finding suggests that even in patients who do not respond, aripiprazole can be an effective short-term treatment for antipsychotic-induced hyperprolactinemia. It is important

Table 1. Summary of Patient Demographics, Diagnoses, and Treatment History

Patient	Age/Sex	*DSM-5* Diagnosis	Comorbid Conditions	Day	Prolactin Level	Aripiprazole Dose	Concomitant Medications
1	32y/female	Schizoaffective disorder, bipolar type	Autism spectrum disorder Neurocognitive disorder due to anoxic brain injury Encephalopathy Esophageal stricture Asthma Crohn's disease	Baseline	138.9 (H)	0	Paliperidone LAI 234 mg[a] Paliperidone 3 mg QD Sertraline 50 mg QD Lorazepam 1 mg TID Guanfacine 1 mg BID
				Day 62	70.8 (H)	5 mg QD PO	Haloperidol 2 mg QD Mirtazapine 15 mg QD Trazodone 50 mg QD
				Day 83	95.5 (H)	5 mg QD PO	Haloperidol 2 mg BID Mirtazapine 15 mg QD Trazodone 50 mg QD
				Day 97	66.7 (H)	5 mg QD PO	Haloperidol 2 mg BID Mirtazapine 15 mg QD Trazodone 50 mg QD
				Day 139	21.3	0	Clozapine 100 mg QD Haloperidol 3 mg BID Mirtazapine 15 mg QD Trazodone 50 mg QD
				Day 363	12.2	0	Clozapine 100 mg QD Haloperidol 3 mg BID Mirtazapine 15 mg QD Trazodone 50 mg QD
2	48y/female	Schizophrenia	Hyperlipidemia	Baseline	275.4 (H)	0	Valproic acid 1,000 mg QD
				Day 12	59.9 (H)	2 mg QD PO	
				Day 28	39.6 (H)	LAI 441 mg monthly	
				Day 93	19.1	LAI 662 mg monthly	
3	28y/female	Schizoaffective disorder, bipolar type Substance use disorder (amphetamines)	Polycystic ovarian syndrome Hypothyroidism Diabetes mellitus 2 Hyperlipidemia Metabolic syndrome Obstructive sleep apnea Acute pancreatitis	Baseline	166.1 (H)	0	Gabapentin 300 mg BID Trazodone 150 mg QD
				Day 7	118.2 (H)	10 mg QD PO	Gabapentin 300 mg BID Trazodone 150 mg QD Clonazepam 2 mg BID Lithium 900 mg QD
				Day 49	45.6 (H)	20 mg QD PO	Haloperidol 10 mg BID, Gabapentin 300 mg BID Trazodone 150 mg QD Clonazepam 2 mg BID Lithium 900 mg QD

[a]Loading dose strategy was used: patient received paliperidone palmitate 234-mg injection on 1-25-18, 156 mg on 2-2-18, then 78 mg on 3-2-18; it was then discontinued.

Abbreviations: BID = twice daily, (H) = above the reference range for prolactin in females (4.79–23.30 ng/mL), LAI = long-acting injectable, PO = by mouth, QD = daily, TID = 3 times daily.

to note that the relatively rapid reduction in prolactin levels in our patients could not be due to discontinuation of LAIs, as it requires several weeks (ie, 5 to 6 apparent half-lives) to completely eliminate an LAI from plasma. However, the results from this case series should be interpreted with caution as they are based on a retrospective assessment of a small sample of patients in an uncontrolled environment.

CONCLUSION

Given its partial agonist mechanism of action and strong binding affinity to the D_2 receptors, aripiprazole may be a safe and effective add-on to help reduce hyperprolactinemia, especially in patients who are receiving long-acting injectables and in whom antipsychotic dose cannot be adjusted to address hyperprolactinemia.

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