Original Article

Add-on Aripiprazole for Atypical Antipsychotic-induced, Clinically Significant Hyperprolactinemia

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ABSTRACT

Background: Antipsychotic treatment-induced hyperprolactinemia is a highly distressing and disabling side effect for patients. The use of add-on aripiprazole has been identified as a possible treatment strategy in this situation. However, data on prolactin changes with add-on aripiprazole in a real-world naturalistic clinical setting from India are sparse. **Materials and Methods:** The retrospective chart review was conducted at the specialty metabolic clinic at the National Institute of Mental Health and Neurosciences, Bengaluru, India. Sixteen patients (female: male = 13:3) who were on a stable dose of antipsychotic medications, complaining of either sexual dysfunction or menstrual irregularities, were prescribed add-on aripiprazole. The serum prolactin values were obtained before the initiation of aripiprazole and during the follow-up. **Results:** Patients were on treatment with risperidone, amisulpride, and olanzapine and had a prolactin level of 87.1 ± 60.7 ng/ml. Add-on aripiprazole treatment was given with a mean dose of 13.8 ± 7.4 mg/day. Patients had a significant reduction in prolactin level (35.6 ± 29.1 ng/ml) following treatment with aripiprazole ($P = 0.004$). **Conclusions:** Add-on aripiprazole could be a clinically useful strategy in patients who develop antipsychotic-induced hyperprolactinemia.

Key words: *Antipsychotic, aripiprazole, hyperprolactinemia, prolactin*

INTRODUCTION

Hyperprolactinemia is a disabling adverse effect of antipsychotics with high incidence rates among both men and women.[1] The mechanism of antipsychotic-induced hyperprolactinemia is proposed to be due to dopamine 2 (D2) receptor antagonistic mechanism of antipsychotics, specifically on the tuberoinfundibular dopamine pathway. Blockage of D2 receptors in this pathway results in loss of inhibitory control of dopamine on prolactin secretion and results in hyperprolactinemia.[2,3] Hyperprolactinemia

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is associated with clinical symptoms and signs of hirsutism, acne, menstrual irregularities, poor libido, and galactorrhea in women, and in men, it leads to erectile dysfunction and gynecomastia. Long-term complications of hyperprolactinemia also include decrease in bone mineral density.[4]

In drug-induced hyperprolactinemia, prolactin levels typically range between 25 and 100 ng/mL. In suspected cases of psychotropic-induced hyperprolactinemia, the Endocrine Society guidelines suggest drug discontinuation for 3 days or substituting with an alternative drug and then remeasuring prolactin.[5] Lu *et al*. demonstrated that gradual switching over to aripiprazole reversed the hyperprolactinemia induced by either risperidone or sulpiride.[6] Other studies have also demonstrated that switchover to aripiprazole from the existing antipsychotic results in significant decrease in prolactin levels in addition to restoration of regular menstrual cycles.[6,7] However, this strategy carries a potential risk of relapse of the psychotic symptoms.[8]

Add-on aripiprazole to the preexisting antipsychotic has been proposed as a useful strategy in the management of antipsychotic-induced hyperprolactinemia. Aripiprazole is an antipsychotic with a unique mechanism of being a partial agonist of D2 receptors. A randomized placebo-controlled study demonstrated a significant reduction in prolactin levels and also PANSS scores with add-on aripiprazole.[9] A recent study with a randomized, open-label design using add-on aripiprazole also concluded that this strategy was associated with a significant reduction in serum prolactin levels in participants who were on stable dose of risperidone.[10] However, a meta-analysis on randomized trials with aripiprazole being used as an add-on in antipsychotic-induced hyperprolactinemia[11] found that, though aripiprazole addition (>5 mg/day) resulted in normalizing levels of serum prolactin, this difference was not statistically significant. While there are randomized controlled trials from the Western population, very few studies have examined the clinical utility of add-on aripiprazole in the real-world scenario from India. Hence, we examined the effect of add-on aripiprazole on prolactin levels in patients who had clinical symptoms of hyperprolactinemia due to atypical antipsychotics.

MATERIALS AND METHODS

This retrospective chart review was conducted at the specialty metabolic clinic at the National Institute of Mental Health and Neurosciences, Bengaluru, India. Case records of 16 patients (female: male = 13:3) who were on stable dose of antipsychotic medications, complaining of either sexual dysfunction or menstrual irregularities, were included. Thirteen patients had a diagnosis of nonaffective psychosis (schizophrenia/unspecified psychosis) while three patients had bipolar affective disorder (International Classification of Diseases 10). Patients were continued on the previous antipsychotic medication and add-on aripiprazole treatment was initiated. Serum prolactin values before initiating aripiprazole and during the follow-up were noted from the case records.

Statistical analysis

The follow-up prolactin values were not normatively distributed (Shapiro–Wilk, $P < 0.05$). Hence, baseline and follow-up prolactin levels were compared using Wilcoxon signed-rank test. In addition, Spearman's correlation was performed to examine the relationship of the percentage reduction in prolactin levels with the duration of aripiprazole treatment as well as the dose of add-on aripiprazole. The statistical threshold was set at $P < 0.05$.

RESULTS

The mean age of patients was 29.4 ± 5.6 years, and the mean age of onset of illness was 22.3 ± 4.8 years. Patients had a mean illness duration of 6.7 ± 5.2 years. Four of them had comorbid polycystic ovarian syndrome and three had hypothyroidism. While ten patients were treated with risperidone (4.9 ± 1.2 mg/day), two patients each were treated with amisulpride (350 ± 173.2 mg/day) and olanzapine (10 mg/day). The patients were started on add-on treatment with aripiprazole (mean dose = 13.8 ± 7.4 mg/day). Patients were treated with these medications for a mean duration of 24.31 ± 15.82 months (mean follow-up duration), and follow-up prolactin levels were assessed. There was a significant reduction in the follow-up prolactin level (35.6 ± 29.1 ng/ml) compared to baseline prolactin values (87.1 ± 60.7 ng/ml; $Z = 2.9$, $P = 0.004$). None of the patients reported worsening of psychotic symptoms or serious adverse effect. There was no significant correlation between reduction in prolactin level and clinical variables such as dose of aripiprazole or duration of aripiprazole or age of the patient.

DISCUSSION

This study demonstrates the clinical utility of add-on aripiprazole for the treatment of clinically significant antipsychotic-induced hyperprolactinemia. Importantly, aripiprazole resulted in significant decrease in prolactin levels in all patients except one. Hyperprolactinemia is an adverse effect associated with most of the typical antipsychotics and some atypical antipsychotics such as risperidone, paliperidone, and amisulpride. These side effects also carry the risk of poor patient compliance

with treatment regimen. Aripiprazole is an atypical antipsychotic with a distinct pharmacodynamic profile. It acts as a partial agonist at the D2 receptors, thereby reducing the prolactin levels. It has been reported to have a high D2 receptor affinity than many other antipsychotics.[12] Due to its unique mechanism, aripiprazole acts as a functional antagonist or functional agonist at D2 receptors, depending on the level of the dopamine in the immediate environment, that is it acts as an agonist in a hypodopaminergic state and antagonist in a hyperdopaminergic state.[13] It has also been reported that aripiprazole exhibited the highest affinity for the D2 receptors at 10 mg/day.[14] As it is not associated with risk of weight gain, dyslipidemia, or QTc prolongation,[15] it may be safely used in combination with other antipsychotic drugs. Switching of the drug to aripiprazole has been used as a strategy for patients with drug-induced hyperprolactinemia.[16] However, there might be a risk of worsening of psychotic symptoms in patients who are clinically stabilized on antipsychotics with this strategy.[8] Hence, add-on low dose of aripiprazole to the preexisting drug is useful in clinical settings.

We found no relationship between percentage reduction in prolactin and dose of aripiprazole used as well as the duration of treatment with aripiprazole. The dose of aripiprazole useful in reducing the prolactin levels has been found to be between 5 and 10 mg/day across studies. Patients in our study were on a relatively lower dose of aripiprazole, closer to the above-mentioned range. Previous studies have demonstrated a reduction in prolactin levels as early as 2 weeks with a sustained benefit over time with add-on aripiprazole.[10] This could explain the lack of significant correlation between percentage reduction in prolactin and the duration of treatment with aripiprazole in our study.

All the patients had clinical manifestations of hyperprolactinemia, and the aim of the study was to examine the effectiveness of aripiprazole in a naturalistic setting. Our study findings need to be interpreted in the background of limitations that duration between the baseline and follow-up prolactin assessment points was not uniform and the sample size of the present study is small.

CONCLUSION

In conclusion, findings of this naturalistic study from India suggest the effectiveness and clinical utility of add-on aripiprazole for the treatment of antipsychotic-induced hyperprolactinemia.

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Conflicts of interest
There are no conflicts of interest.

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