

Management of antipsychotic-induced hyperprolactinemia

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How to cite: Tewksbury A, Olander A. Management of antipsychotic-induced hyperprolactinemia. *Ment Health Clin* [Internet]. 2016;6(4):185-90. DOI: 10.9740/mhc.2016.07.185.

Abstract

Introduction: Antipsychotics represent a large portion of the psychotropics that may induce hyperprolactinemia. Clinical psychiatric pharmacists must be adept in stratifying the relative risk of hyperprolactinemia among psychotropics, identifying patient risk factors, recognizing differential diagnoses, and recommending therapeutic alternatives and treatment strategies. High-potency, typical antipsychotics are more likely to elevate prolactin although exceptions to the rule exist.

Methods: A literature search of PubMed and Google Scholar was performed to identify English language articles on the treatment of antipsychotic-induced hyperprolactinemia in humans. Methodological rigor is summarized for compiled studies in addition to feasibility and limitations of application to clinical practice.

Results: There is an absence of robust evidence for the management of antipsychotic-induced hyperprolactinemia. Among the pharmacological treatments studied, aripiprazole (switching or augmentation) possessed the strongest evidence. Pharmacological treatments with less evidence encompassed dose reduction, switching to lower potency antipsychotics, and adding dopamine agonists. To date, no head-to-head studies have been published on the above approaches.

Discussion: Atypical antipsychotics with low affinity for dopamine (D₂) receptors, such as olanzapine, are logical alternatives for the patient experiencing drug-induced hyperprolactinemia. When augmentation is clinically preferred to switching, a viable option is the addition of a full or partial dopamine agonist, such as bromocriptine or aripiprazole, respectively. Patient-specific risk of psychiatric decompensation and the severity of symptomatic hyperprolactinemia should be weighed when formulating treatment strategies.

Keywords: antipsychotic, amenorrhea, aripiprazole, dopamine agonists, hyperprolactinemia, galactorrhea, gynecomastia, neuroleptic, sexual dysfunction

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Disclosures: The authors have no conflicts of interest to disclose. No financial support was received for this article.

Overview/Background

Medications are the most common cause of nontumoral hyperprolactinemia. Antipsychotics are the primary psychotropics implicated in hyperprolactinemia, occurring in up to 70% of patients taking these agents.¹⁻³ Antipsychotics cause hyperprolactinemia through their primary

mechanism of dopamine (D₂) receptor antagonism. Dopamine exerts an inhibitory action on prolactin secretion; thus, dopaminergic inhibition increases prolactin release in the hypothalamic tuberoinfundibular tract. Prolactin elevation inhibits the release of luteinizing hormone and follicle-stimulating hormone from the pituitary gland. This results in low gonadal steroids and hypogonadism. For both sexes, this can cause sexual dysfunction, infertility, galactorrhea, decreased bone mineral density, osteoporosis, and fractures. Meanwhile, patients diagnosed with schizophrenia possess additional risk factors for osteoporosis, such as high alcohol consumption and cigarette smoking. Men may develop gynecomastia, and women may experience hirsutism,

acne, and menstrual abnormalities, including amenorrhea and oligomenorrhea.^{1,4} Such symptoms are not only embarrassing and distressing for patients, but represent serious long-term health consequences. Risk factors for antipsychotic-induced hyperprolactinemia include adolescence, high antipsychotic dose, specific dopamine D₂-receptor gene variants, and female sex, particularly those of reproductive age.^{1,3-5}

Although hyperprolactinemia occurs more frequently with high-potency, typical antipsychotics (40%–90%), several atypical antipsychotics have a high potential for prolactin elevation.^{1,3,4,6} Differential effects are largely attributed to more potent dopamine (D₂) receptor blockade of typical antipsychotics, but duration of receptor binding should be also considered as receptor occupancy is a dynamic process. Rapid D₂-receptor dissociation of atypicals results in wider variation of receptor occupancy over time. This is because periodic low D₂ occupancy permits endogenous dopaminergic transmission and physiological competition.^{4,7} Another contributing factor is blood-brain barrier penetration. Despite risperidone being an atypical antipsychotic, it has the highest prevalence of hyperprolactinemia (70%–100% in studies specifically monitoring for this effect).^{1,2,8} Due to poor blood-brain barrier penetration, risperidone has a greater presence at the pituitary gland.¹ On the other end of the spectrum, aripiprazole is considered prolactin-sparing and is actually used to treat hyperprolactinemia. Aripiprazole's partial D₂ receptor agonism provides sufficient dopaminergic tone to continue inhibition of prolactin release. Nonetheless, it still has a prevalence of 3.1% to 9.0% for hyperprolactinemia.²

It remains equivocal to what degree serotonin is implicated in the pathophysiology of drug-induced hyperprolactinemia. However, it is known that serotonergic projections to the hypothalamus regulate various prolactin-releasing factors and neuropeptides.⁹ Serotonin also plays an indirect role in tuberoinfundibular dopaminergic neuron inhibition. Serotonergic antidepressants, including selective serotonin reuptake inhibitors, pose a risk of hyperprolactinemia but to a much lesser degree than antipsychotics. One cross-sectional study found a prevalence of 10.9%.¹⁰ 5HT₂-receptor antagonism may confer some protection against this effect; this is demonstrated by the lower incidence of atypicals and minimal risk of the antidepressant mirtazapine. Additional nonpsychotropic medications that can cause hyperprolactinemia include histamine (H₂) receptor antagonists, estrogen, antiandrogens, opiates, protease inhibitors, antiemetics, and antihypertensives, specifically verapamil.¹

There are numerous physiological and pathological causes of hyperprolactinemia that should be considered for

differential diagnosis. This includes, but is not limited to, cirrhosis, polycystic ovarian syndrome, seizures, and stress. Discrepancies exist in the literature regarding the normal range for prolactin serum concentrations; however, recent reports utilize an upper limit of 18 ng/mL for men and 24 ng/mL for nonpregnant, non-nursing women.^{1,3,9,11} Prolactin levels can increase up to 200 ng/mL during pregnancy and up to 300 ng/mL while breastfeeding. Meanwhile, drug-induced hyperprolactinemia is typically associated with prolactin levels between 25 and 100 ng/mL. This may help distinguish it from other causes, such as pituitary tumors, that are typically associated with higher levels. Nonetheless, some agents, such as metoclopramide, risperidone, and phenothiazines, can result in prolactin levels exceeding 200 ng/mL.^{1,3,9} Routine monitoring of prolactin levels is not performed clinically as the Endocrine Society clinical practice guidelines recommend that clinicians do not treat asymptomatic hyperprolactinemia. In the presence of symptoms, fasting prolactin levels should be drawn in the absence of stress. The authors recommend discontinuing the suspected offending agent if levels are elevated. If discontinuation is not possible, a pituitary magnetic resonance imaging is recommended to rule out a pituitary or hypothalamic mass.⁸

Methods

A literature search of PubMed and Google Scholar was performed to identify studies on the treatment of antipsychotic-induced hyperprolactinemia. The search was restricted to human subjects and studies published in the English language without limitation to publication date. The following search terms were utilized: antipsychotic, amenorrhea, aripiprazole, dopamine (DA) agonist, hyperprolactinemia, galactorrhea, gynecomastia, neuroleptic, and sexual dysfunction. Citations from the collected articles were manually reviewed to identify articles not retrieved in the original search. Information on methodology, treatment modality, results, and limitations were extracted and presented in this review.

Treatment Strategies/Results

Antipsychotic Switching

Low-potency atypical antipsychotics present logical alternatives for the patient with antipsychotic-induced hyperprolactinemia. An open-label, randomized trial (N = 54) found that by week 4, patients that switched to olanzapine had significant improvements in mean prolactin level compared to patients that stayed on either risperidone or a conventional antipsychotic ($P < .05$).¹² Other open-label trials have shown improvements in prolactin levels after switching to quetiapine or aripiprazole.¹³⁻¹⁶

Casey et al¹⁷ studied the efficacy and safety of switching from risperidone or olanzapine to aripiprazole 30 mg/day utilizing 3 distinct switching strategies in a multicenter, open-label trial. Although not a primary outcome measure, the authors¹⁷ documented reductions in mean prolactin levels without exacerbation of psychotic symptoms. A post hoc analysis of the above study (N = 269) detected significant decreases in mean prolactin levels ($P < .001$) by week 1 with effects maintained at week 8. Most patients originally on olanzapine also had significant reductions despite lack of prolactin elevation at baseline.¹⁸

Aripiprazole Augmentation

Several studies have investigated the effects of augmentation with aripiprazole.^{19–25} A recent meta-analysis of 21 randomized, controlled trials (RCTs), ranging from 4 to 26 weeks, was conducted comparing adjunctive aripiprazole to placebo in 1853 subjects. Six studies were classified as having high risk for bias for reasons including lack of blinding and selective reporting, but the overall risk of bias was deemed acceptable (kappa 0.62). Patients receiving adjunctive aripiprazole were more likely to have normal prolactin by study termination (pooled risk ratio 19.17, 95% confidence interval = 10.98–33.48) among the 8 studies (N = 604) reporting on this outcome measure. Three outlier studies were excluded for introducing substantial heterogeneity ($I^2 = 83\%$ vs 0%). Subgroup analysis by dose did not find statistically significant differences between low-dose (≤ 5 mg/day) and high-dose aripiprazole ($\chi^2 = 1.41$, $P = .23$). Somnolence and headache were more common in the treatment group. Significant differences were not detected between treatment groups with regards to psychiatric symptom improvement using the Positive and Negative Syndrome Scale (PANSS) or the Brief Psychiatric Rating Scale (BPRS; standard mean difference = -0.02 , 95% confidence interval = $-0.14 \sim 0.09$). Despite concerns for short follow-up time and incomplete methodological information provided by many included studies, the authors concluded that adjunctive aripiprazole is safe and effective in the treatment of antipsychotic-induced hyperprolactinemia.²⁵

Four of the above RCTs were included in a separate meta-analysis (N = 639), which also concluded that adjunctive aripiprazole was superior to placebo on the measure of prolactin level normalization ($P < .00001$). Original findings were replicated in a subgroup analysis of Chinese studies, all of which used an aripiprazole dose of 5 mg/day and defined hyperprolactinemia as a level >60 ng/mL.²⁴

Aripiprazole augmentation demonstrated success in patients with hyperprolactinemia induced by risperidone long-acting injectable in two small, open-label trials totaling 25 patients.^{22,23} These studies were performed in Spain²² and the Netherlands,²³ introducing diversity that bolsters generalizability, considering most RCTs included in the above meta-analyses were conducted in

Taiwanese and Chinese populations.²⁴ Both 5- and 10-mg daily doses achieved statistically significant decreases in prolactin levels by week 4.^{22,23} Another report by Boggs et al²⁶ described resolution of gynecomastia in 2 men, one of which received a lower aripiprazole dose of 2.5 mg daily adjunctive to risperidone long-acting injectable.

Despite these promising implications, a prospective, open-label study (N = 24) found that patients initially receiving benzamide antipsychotics (amisulpride or sulpiride) were less responsive to aripiprazole augmentation than patients taking risperidone. In the latter group, 93% achieved normal prolactin levels at study fulfillment compared to 10% of patients on benzamide antipsychotics.²¹ These findings are supported by a case study of amisulpride-induced hyperprolactinemia not reversed by adjunctive aripiprazole.²⁷

Dopamine Agonists

There is a deficiency in powered RCTs that investigate the efficacy and safety of using DA agonists for treatment of hyperprolactinemia. Evidence comes from 3 case reports, 4 case series, and 3 larger comparative studies, totaling 172 patients.^{28–37}

The sole RCT is a Korean study of schizophrenic females (N = 48) with hyperprolactinemia and amenorrhea. There were 3 treatment groups in which patients received bromocriptine 2.5, 5, or 10 mg daily. Mean prolactin levels significantly decreased in the bromocriptine groups compared to placebo from baseline to week 4 ($P = .001$) and no significant change between weeks 4 and 8 ($P = .07$). There were no significant differences between the bromocriptine treated groups ($P = .06$). In addition to lowered prolactin levels, 7 patients resumed menses.²⁸ One open-label trial (N = 19) also showed statistically significant decreases in mean prolactin level by week 8 following treatment with cabergoline 0.125 to 0.250 mg per week ($P < .05$). Remission of clinical symptoms was achieved in 11 of these patients.²⁹ Schizophrenic patients in a prospective parallel-group study (N = 83) received 3 cabergoline doses (0.25, 0.5, and 1 mg/day) based on prolactin levels (50, 50–99, or >100 ng/mL, respectively). The mean prolactin level decreased from 73.3 ng/mL to 42.0 ng/mL after 3 months and to 27.1 ng/mL after 6 months ($P < .001$). Thirty-one of 44 females ceased to have problems with their menstrual cycle.³⁰ No patients in these trials experienced worsening of psychotic symptoms per PANSS or BPRS scores.^{28–30}

In case reports and series, bromocriptine, cabergoline, and pramipexole have decreased prolactin levels.^{31–36} Several patients also experienced resolution of symptoms, such as amenorrhea,^{33–35} galactorrhea,^{34,33,34} and sexual dysfunction.³² There have been a few reports on patients who had experienced an exacerbation of psychosis after initiation of a dopamine agonist. One female became acutely paranoid after 2 weeks of taking bromocriptine 2.5 mg daily.³⁷ Bliesener et al³³ performed a case series in which 2 of 5 patients taking amisulpride with bromocrip-

tine experienced an exacerbation of psychosis. In both cases, symptoms remitted after discontinuation of bromocriptine.^{33,37} Due to this risk of psychotic relapse and the dearth of large, well-designed trials, this strategy is generally not recommended.

Discussion/Recommendations

Current clinical guidelines recommend that if symptomatic, antipsychotic-induced hyperprolactinemia is suspected after performing differential diagnosis, the antipsychotic should be discontinued, and prolactin levels should return to normal within 3 days.⁸ If this is not clinically feasible or desirable, options include (1) reducing the dose, (2) switching to an alternative low-potency/prolactin-sparing antipsychotic, or (3) adding a full/partial dopamine agonist.

Over the past decade, an increasing number of studies on partial agonist aripiprazole augmentation have been published, and our review of the literature discovered the most robust data for this treatment option. In the absence of studies directly comparing aripiprazole switch and augmentation strategies, health care practitioners must weigh the risks of psychiatric decompensation with the long-term consequences of hyperprolactinemia when formulating treatment plans. If a patient is psychiatrically stable on his or her current antipsychotic and the risk of relapse is high, we recommend aripiprazole augmentation rather than switching. Conversely, if hyperprolactinemia is not the sole issue with the patient's current antipsychotic (eg, additional intolerable adverse effects, response or remission have not been achieved), switching makes sense to avoid polypharmacy. Preexisting antipsychotic(s) should also be taken into account; for instance, studies suggest that amisulpride-induced symptoms may not be as responsive to aripiprazole augmentation.²¹

Regarding aripiprazole augmentation, current evidence for dosing is conflicted. Some studies suggest that effects plateau at ~6 mg/day²⁰ whereas others have found higher response rates at 10 to 20 mg/day compared to lower doses.²⁸ Until studies with larger sample sizes further elucidate optimal dosing, we recommend starting with 5 mg orally once daily as this was the most commonly studied dose. Primary monitoring parameters include prolactin level, akathisia, sedation, activation, psychiatric symptoms, and resolution of hyperprolactinemia symptoms, such as normalization of menstrual cycle, reversal of gynecomastia or galactorrhea, and improved sexual function. Although it remains unclear how quickly aripiprazole exerts its prolactin-neutralizing effects, the shortest time frame during which statistically significant improvements were demonstrated was 4 weeks. Thus, if symptoms have not fully

resolved by week 4, we suggest increasing the dose by 5 mg/day as tolerated. Due to aripiprazole's long half-life, dosage adjustments should not be made more frequently than every 2 weeks.

Despite the reported success with adjunctive aripiprazole, case series of symptom exacerbation exist. This is likely due to aripiprazole's relatively strong binding affinity, which results in displacement of more potent antipsychotics from D2 binding sites, and acting as an agonist in the dopamine-deficient landscape. Thus, future studies should extend duration of follow-up.^{39,40}

One indirect patient care issue that arises in using adjunctive aripiprazole is the need to fulfill Hospital-Based Inpatient Psychiatric Services core performance measures. Psychiatric inpatients discharged on more than 1 scheduled antipsychotic must have appropriate justification documented in their medical chart. Appropriate justifications do not currently encompass management of adverse effects such as hyperprolactinemia.

In summary, evidence-based medicine and patient-specific parameters should be inextricably integrated when formulating treatment plans for antipsychotic-induced hyperprolactinemia. At this time, aripiprazole augmentation carries the strongest evidence.

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