Guidance on the treatment of antipsychotic-induced hyperprolactinemia when switching the antipsychotic is not an option

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Purpose. This article aims to evaluate management options for antipsychotic-induced hyperprolactinemia and associated treatment considerations such as efficacy, tolerability, drug interactions, contraindications, and dosing regimens.

Summary. Hyperprolactinemia is a common adverse effect of antipsychotics. First-line management includes reducing the dose of the offending antipsychotic, discontinuing the antipsychotic, or switching to another antipsychotic associated with a lower risk of hyperprolactinemia. However, these options are not always practical and are associated with a risk of relapse of the psychiatric illness. Other management options include adjunctive aripiprazole, dopamine agonists (cabergoline and bromocriptine), metformin, and herbal supplements. A search of Embase, PubMed, and Google Scholar using key terms such as *hyperprolactinemia, prolactin, antipsychotic, treatment guidelines, aripiprazole, dopamine agonist, cabergoline, bromocriptine, metformin, herbals, supplements,* and *medications* was conducted for literature retrieval. Upon evaluation of the available literature we found the following: (1) aripiprazole is safe and effective in lowering prolactin levels within normal limits; (2) adjunctive cabergoline and bromocriptine decrease elevated prolactin levels, while cabergoline may be more effective in reducing prolactin but can also be associated with a more serious adverse effect of cardiac valvular abnormalities; (3) metformin causes a mild reduction of prolactin levels; and (4) there are limited data to support use of herbal medications (chamomile, Peony-Glycyrrhiza decoction, and shakuyaku-kanzo-to) in antipsychotic-induced hyperprolactinemia

Conclusion. There are treatments available for antipsychotic-induced hyperprolactinemia in patients who are unable to alter their current antipsychotic regimen. However, there remains a need for additional short- and long-term studies to determine the efficacy and safety of these treatment strategies, given that patients taking antipsychotics typically require chronic, life-long treatment for their illnesses.

Keywords: antipsychotic agents, adverse effects, aripiprazole, dopamine agonists, hyperprolactinemia, metformin, prolactin

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Antipsychotic medications play a key role in the management of psychiatric conditions such as schizophrenia, bipolar disorder, and depression. Unfortunately, these medications may cause hyperprolactinemia, leading to adverse effect, nonadherence, and worsening outcomes.[1] Antipsychotic-induced hyperprolactinemia occurs in up to 70% of patients, depending on the specific antipsychotic.[2] Antipsychotics are classified as being either typical (chlorpromazine, fluphenazine, haloperidol, loxapine, mesoridazine, molindone, perphenazine, thioridazine, thiothixene, and trifluoperazine) or atypical (aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine,

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iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone, and lumateperone). Haloperidol, paliperidone, and risperidone are associated with a higher risk of hyperprolactinemia.[1,3,4]

Hyperprolactinemia is an increase in prolactin secretion by the lactotroph cells in the anterior pituitary gland. Prolactin elevation can be caused by tumors, pregnancy, breastfeeding, stress, exercise, sleep, and medications and may cause amenorrhea, gynecomastia, galactorrhea, hypogonadism, and sexual dysfunction.[5,6] The long-term effects of antipsychotic-induced hyperprolactinemia are less understood than the short-term clinical consequences. The risk of osteopenia and/or osteoporosis may be increased by chronic hypogonadal states, but a strong cause-and-effect relationship to antipsychotic-induced hyperprolactinemia has not been established.[7-10] There may also be a small risk of breast or endometrial cancer associated with hyperprolactinemia, although a direct link to antipsychotic-induced hyperprolactinemia has not been established.[11-15]

Females generally have a higher normal value for serum prolactin concentration than males.[16] A normal prolactin level for nonpregnant females is <25 μg/L, while a normal value for males is <20 μg/L.[16,17] Dopamine acts as an inhibitory feedback cycle for prolactin on dopamine receptor D_2 on the lactotroph cell membrane.[18] Antipsychotics are antagonists of D_2 receptors and, as a result, they have the potential to interfere with dopamine's suppression of prolactin and increase prolactin secretion. An updated American Psychiatric Association treatment guideline for schizophrenia was released in December 2019. Based on this guideline, there is no recommendation for monitoring prolactin levels in all patients receiving antipsychotics. It is recommended that patients receiving antipsychotics known to increase prolactin be screened for symptoms of hyperprolactinemia at each visit until stable and then yearly thereafter. Female patients should be asked about changes in libido or menstrual cycle, and galactorrhea; males should be asked about gynecomastia, changes in libido and erectile or ejaculatory function. Obtaining a prolactin level is recommended if symptoms of hyperprolactinemia are present. There is no "threshold" for prolactin level elevation. If the patient is reporting symptoms of hyperprolactinemia and prolactin is elevated, then the clinician should initiate a treatment strategy to manage hyperprolactinemia.[19]

Treatment guidelines for antipsychotic-induced hyperprolactinemia recommend discontinuing the antipsychotic, switching to an antipsychotic associated with a lower risk of hyperprolactinemia, or reducing the antipsychotic dose as first-line management. However, these options are not always feasible. Management options include the addition of aripiprazole, dopamine agonists, metformin, or herbal supplements to the antipsychotic regimen.[16,20-22] This article reviews management options for antipsychotic-induced hyperprolactinemia and associated treatment considerations such as efficacy, tolerability, drug interactions, contraindications, and dosing regimens. Searches of Embase, PubMed, and Google Scholar combining search terms such as *hyperprolactinemia, prolactin, antipsychotic, treatment guidelines, aripiprazole, dopamine agonist, cabergoline, bromocriptine, metformin, herbals, supplements,* and *medications* were conducted for literature retrieval.

KEY POINTS

- Treatment guidelines for antipsychotic-induced hyperprolactinemia recommend antipsychotic discontinuation, switching, or dose reduction as first-line management. However, these options are not always feasible.
- Other management options include adjunctive aripiprazole, dopamine agonists (cabergoline and bromocriptine), metformin, and herbal supplements.
- There is a need for additional short- and long-term studies in antipsychotic-induced hyperprolactinemia to determine the efficacy and safety of these treatment strategies, given that patients taking antipsychotics typically require chronic treatment for their illnesses.

Aripiprazole

Adding aripiprazole to current antipsychotic regimens can decrease prolactin to normal levels in patients with antipsychotic-induced hyperprolactinemia.[17,23-27] Aripiprazole is a dopamine partial agonist associated with prolactin-sparing effects.[28] Brexpiprazole and cariprazine are newer medications with dopamine partial agonism and can also decrease prolactin but have not been studied as treatments for antipsychotic-induced hyperprolactinemia.[29,30]

Efficacy. There are 2 published meta-analyses evaluating the use of adjunctive aripiprazole for antipsychotic-induced hyperprolactinemia.[31,32] The first meta-analysis (n = 639) included 5 randomized, single- or double-blinded, placebo-controlled trials of adjunctive aripiprazole therapy for the treatment of antipsychotic-induced hyperprolactinemia.[31] The primary outcome was prolactin normalization. The primary analysis included all doses of aripiprazole (5-30 mg/d) and a secondary analysis excluded doses greater than 5 mg/d. Baseline antipsychotics included risperidone, sulpiride, haloperidol, and quetiapine, with risperidone being the most commonly used agent. Hyperprolactinemia was defined as a serum prolactin concentration of ≥60 μg/L, while normal prolactin was variously defined as a concentration of <30 ng/mL for both female and male patients or concentrations of

<24 ng/mL for females and <20 ng/mL for male patients. Prolactin level normalization was greater with adjunctive aripiprazole vs placebo use (risk difference, 0.76; 95% confidence interval [CI], 0.67-0.85; I^2 = 43%, P < 0.00001). Normalization of prolactin levels remained significantly greater with adjunctive use of aripiprazole 5 mg/d vs placebo use (risk difference, 0.74; 95% CI, 0.62-0.87; I^2 = 59%, P < 0.0001). In regards to prolactin-related symptoms, one study found that 7 of 11 female patients regained menstruation and 1 of 2 patients no longer complained of galactorrhea in the aripiprazole group.[33] In another study, 27 of 28 patients regained menstruation and 16 of 16 patients no longer complained of galactorrhea.[34]

A more recent meta-analysis evaluating the use of adjunctive aripiprazole for antipsychotic-induced hyperprolactinemia included 21 studies, of which the majority were conducted in China.[32] Eleven studies (n = 974) were used to determine the efficacy of adjunctive aripiprazole, defined as the proportion of subjects who recovered from hyperprolactinemia. Baseline antipsychotics included risperidone, haloperidol, sulpiride, chlorpromazine, perphenazine, and olanzapine, with risperidone being the most commonly used agent. The investigators' aim was to build upon the previously mentioned meta-analysis,[31] so we assume that the definitions of hyperprolactinemia and prolactin normalization were similar to those used in the earlier study. Compared to control groups, patients receiving adjunctive aripiprazole were significantly more likely to recover from hyperprolactinemia (relative risk for recovery, 8.81; 95% CI, 3.66-21.23; I^2 = 83%). After exclusion of 3 outlier studies, meta-analysis of 8 studies (n = 604) resulted in a higher likelihood of recovery from hyperprolactinemia with use of aripiprazole, with little between-study heterogeneity (RR, 19.17; 95% CI, 10.98-33.48; I^2 = 0%). Of the 8 studies, 4 were also included in the aforementioned earlier meta-analysis.[31] A secondary analysis was performed to evaluate high-dose (>5 mg/d) vs low-dose (≤5 mg/d) aripiprazole and its effect on hyperprolactinemia. Resolution of hyperprolactinemia was significantly more common among patients receiving either dose of adjunctive aripiprazole compared to patients in control groups (P < 0.001). Although a greater proportion of patients who received high- vs low-dose aripiprazole recovered from hyperprolactinemia (RR values were 30.0 [95% CI, 10.2-120.7] and 15.1 [95% CI, 8.1-28.1], respectively), the difference was not statistically significant (P = 0.23).

It can be concluded from these meta-analyses that aripiprazole is an effective adjunctive therapy for the treatment of antipsychotic-induced hyperprolactinemia. A multidisciplinary consensus paper (published in 2017) providing therapeutic recommendations for iatrogenic hyperprolactinemia secondary to antipsychotic use gave adjunctive aripiprazole a grade A recommendation, with the supporting evidence assigned the highest-level evidence rating.[21] The level of evidence and recommendation grade for adjunctive aripiprazole treatment for antipsychotic-induced hyperprolactinemia exceeded those for alternative strategies (decreasing the dose or substituting another agent for the prolactin-raising antipsychotic).

These analyses do not address the long-term efficacy or safety of adjunctive aripiprazole therapy, differences in efficacy based on which prolactin-raising antipsychotic is implicated in hyperprolactinemia, or differences in evaluated drug formulations. Another important question remaining pertains to optimal dosing of adjunctive aripiprazole for antipsychotic-induced hyperprolactinemia. The studies included in the 2 aforementioned meta-analyses evaluated aripiprazole doses of 5 to 30 mg/d and suggested that 5 mg/d is an effective dose. Aripiprazole doses less than 5 mg/d have not been evaluated. The later meta-analysis found that aripiprazole doses greater than 5 mg/d were associated with a greater likelihood of resolution of hyperprolactinemia than lower doses, but the finding did not reach statistical significance due to the wide CIs around the RR estimates. An 8-week, randomized, placebo-controlled, dose-response study of adjunctive aripiprazole therapy at doses of 5, 10, or 20 mg/d for risperidone-induced hyperprolactinemia found that prolactin levels were significantly lower in the 20-mg (effect size, 1.83 [P < 0.001]), 10-mg (effect size, 1.63 [P < 0.001]), and 5-mg groups (effect size, 0.89 [P < 0.001]) compared to the placebo group at the end of the study.[35] All 3 aripiprazole groups experienced a significant prolactin reduction by week 2, with no further significant reductions thereafter. All 3 aripiprazole groups experienced response rates significantly higher than response rates with placebo use; however, there was a significantly lower response rate in the 5-mg group compared to the 10-mg (P = 0.04) and 20-mg (P = 0.003) groups, with no significant difference between the 10-mg and 20-mg groups. After 8 weeks, 20% of patients in the 5-mg group, 51.7% of those in the 10-mg group, 66.7% of those in the 20-mg group had a normalized prolactin level, compared to just 3.3% of patients in the placebo group. Results of this study suggest that if a patient has not responded to 5 mg/d of adjunctive aripiprazole following 2 weeks of therapy, a dose increase to 10 mg/d would be appropriate. Further upward dosing adjustments could follow (as appropriate based on nonresponse and tolerability) to a maximum of 20–30 mg/d.

Tolerability. Common adverse effects associated with aripiprazole are listed in Table 1. In addition, aripiprazole can less frequently cause prolactin-related adverse effects such as amenorrhea, gynecomastia, and sexual dysfunction.[28,36,53-57] It is plausible to be concerned about additive adverse effects associated with the use of 2 antipsychotics concomitantly (eg,

Table 1. Common Adverse Effects and Doses of Medications Used in Antipsychotic-Induced Hyperprolactinemia

Medication	Adverse Effects (>10% Incidence)	Oral Dose
Aripiprazole[36]	Increased serum glucose, weight gain, nausea, agitation, akathisia, anxiety, drowsiness, extrapyramidal symptoms, fatigue, insomnia, headache	5-30 mg/d
Cabergoline[37]	Nausea, headache, dizziness	0.25-0.5 mg weekly, titrate by 0.5 mg monthly until optimal response to maximum of 2 mg/wk
Bromocriptine[38]	Constipation, nausea, dizziness, headache, asthenia, rhinitis	1.25-2.5 mg/d, titrate by 2.5 mg weekly until optimal response
Metformin[39-41]	Diarrhea, nausea, vomiting, flatulence, infection	750-3,000 mg/d
Chamomile[42-44]	Anaphylaxis, dermatitis, gastrointestinal upset, lacrimation, sneezing, conjunctivitis	22.7 mg twice daily
Bambusa vulgaris[45,46]	Dermatitis	No standard dosage
Momordica charanthia[45,47]	Diarrhea, heartburn, gastrointestinal upset, anorexia, nausea, epigastric pain	2,000-4,000 mg/d for 10 wk
Rauwolfia vomitoria[45,48]	Extrapyramidal symptoms	No standard dosage
Ficus sur[45,49]	Photodermatitis (with topical use)	13 g/d
Clerodendrum capitatum[45]	None; well tolerated	No standard dosage
PGD[50,51]	None; well tolerated	No standard dosage
Shakuyaku-kanzo-to[52]	None; well tolerated	No standard dosage

Abbreviation: PGD, Peony-Glycyrrhiza decoction.

extrapyramidal symptoms, tardive dyskinesia, and metabolic adverse effects), but several studies[17,23,27,31,35] found no clinically significant increases in treatment-related adverse events with use of adjunctive aripiprazole; however, the second meta-analysis summarized above[32] found that somnolence (RR, 2.76; 95% CI, 1.34-5.69) and headache (RR, 2.31; 95% CI, 1.08-4.92) were more likely to be experienced by patients in the aripiprazole group relative to placebo recipients. It is important to remember these studies were of short duration. Tardive dyskinesia and metabolic adverse effects may not become apparent in short-term studies, so monitoring for movement disorders, weight gain, hyperglycemia, and hyperlipidemia remains important with chronic adjunctive aripiprazole use.

Drug interactions. Aripiprazole is a substrate of cytochrome P-450 (CYP) isozymes 2D6 and 3A4. Use of psychiatric medications that act as either inducers or inhibitors of these isozymes (which are frequently used in combination with aripiprazole) can result in adverse outcomes. Dosing adjustments may be required when using adjunctive aripiprazole. In addition, drug interactions between aripiprazole and antihypertensive agents and benzodiazepines can increase the risk of hypotension.[53]

Dopamine agonists

Several treatment recommendations support adjunctive use of dopamine agonists for the treatment of antipsychotic-induced hyperprolactinemia.[16,20-22,58] While several studies have shown that dopamine agonists lower serum prolactin, few studies have involved patients with antipsychotic-induced hyperprolactinemia. Bromocriptine and cabergoline are the most well-studied dopamine agonists in this context; however, treatment reviews suggest that amantadine and pramipexole also can be used, although evidence to support use of those agents is lacking.[20,22] Currently, there are no complete systematic reviews of dopamine agonists for the treatment of antipsychotic-induced hyperprolactinemia, but there is one drafted protocol.[59]

Efficacy. *Cabergoline.* There are 2 published studies evaluating the use of adjunctive cabergoline for antipsychotic-induced hyperprolactinemia.[60,61] One study involving 19 subjects with risperidone-induced hyperprolactinemia found that use of cabergoline 0.125 mg weekly normalized serum prolactin levels, reducing the mean (SD) concentration from 64.4 (31.7) µg/L to 8.6 (5.9) µg/L (P = 0.03) in 11 of the 19 patients at the end of 8 weeks.[60] The cabergoline dosage was increased to 0.125 mg twice weekly at the end of 4 weeks for nonresponders, resulting in a significant reduction in the mean prolactin level at the end of 8 weeks (from 116.9 [SD, 60.6] µg/L to 84.7 [SD, 44.7] µg/L, P = 0.036). The authors noted that

subjects were more likely to respond if the baseline prolactin concentration was below 86.5 µg/L. No adverse events or changes in psychopathology occurred during the study.

Another study involving 84 subjects with antipsychotic-induced hyperprolactinemia found that use of cabergoline 0.25 to 3 mg weekly was associated with a return to normal prolactin levels in 95% of the subjects at a median of 14 weeks.[61] Three months after cabergoline discontinuation, prolactin levels remained normal in 71% of subjects. Prolactin normalization was associated with a reduction of prolactin-associated adverse effects such as menstrual disorders, galactorrhea, impaired sexual desire, and orgasmic dysfunction. Adverse effects of cabergoline were not mentioned; however, the rate of psychosis exacerbation was higher in the cabergoline group vs controls (37.5% vs 0%, $P < 0.001$).

Bromocriptine. Two studies have evaluated the use of adjunctive bromocriptine for treatment of antipsychotic-induced hyperprolactinemia.[50,62] One of the studies, which involved 60 subjects, was an 8-week randomized, single-blind, placebo-controlled trial of adjunctive bromocriptine 2.5, 5, or 10 mg/d[62]; there were significant reductions of serum prolactin by week 4 for all doses compared to placebo ($P = 0.007$, $P < 0.004$, and $P < 0.001$, respectively) but no significant difference between bromocriptine doses. Additionally, there were no significant reductions in prolactin after week 4 for any group. Baseline mean prolactin levels were different between groups ($F = 1.812$), which could have influenced the extent of prolactin reduction. It is important to acknowledge that mean prolactin levels at the end of the study were not within normal limits for any group. No severe adverse events were reported. Nausea and vomiting occurred more frequently in all bromocriptine groups as compared with the placebo group, while postural hypotension was more common in the bromocriptine 10 mg group vs the placebo group.

A randomized crossover study including 20 subjects evaluated bromocriptine 5 mg/d or Peony-Glycyrrhiza decoction (PGD) for the treatment of risperidone-induced hyperprolactinemia.[50] The initial treatment period of 4 weeks' duration was followed by a 4-week washout period before patients were transitioned to the alternative treatment. Both treatments significantly decreased serum prolactin levels; however, neither normalized prolactin levels. Types and rates of adverse events were similar in the study groups; however, one patient experienced an exacerbation of psychosis while taking bromocriptine.

Cabergoline vs bromocriptine. A meta-analysis of 4 randomized controlled trials comparing cabergoline and bromocriptine for idiopathic hyperprolactinemia and prolactinomas found that cabergoline was significantly more effective than bromocriptine for the normalization of prolactin (RR, 0.67; 95% CI, 0.57-0.80).[63] However, this analysis was not specifically focused on antipsychotic-induced hyperprolactinemia. Adverse effects were significantly more likely with use of bromocriptine vs cabergoline use (RR, 1.43; 95% CI, 1.03-1.98), specifically nausea and vomiting (RR values of 1.66 [95% CI, 1.33-2.06] and 2.02 [95% CI, 1.13-3.59], respectively).

It can be concluded from these studies that adjunctive cabergoline and adjunctive bromocriptine may decrease elevated prolactin levels induced by antipsychotics. Evidence suggests that cabergoline may be more effective in reducing prolactin but is also associated with more serious adverse events, such as cardiac valvular abnormalities, compared to bromocriptine. Risks vs benefits should be considered when choosing between dopamine agonists. Adjunctive dopamine agonist therapy for antipsychotic-induced hyperprolactinemia received a grade B recommendation and the second-highest rating for evidentiary support (below only the rating for adjunctive aripiprazole) in the previously summarized multidisciplinary consensus paper.[21] There is a need for more high-quality, short- and long-term studies to further support the efficacy and safety of adjunctive dopamine agonist therapy for the management of antipsychotic-induced hyperprolactinemia.

Tolerability. Common adverse effects associated with dopamine agonists are listed in Table 1. A serious adverse effect of dopamine agonists is the occurrence of restrictive cardiac valvular abnormalities. Cardiac valvular abnormalities are more often associated with cabergoline than with bromocriptine.[64,65] One meta-analysis found that patients treated with cabergoline for more than 1 year were more likely than nontreated patients to develop mild and moderate to severe tricuspid regurgitation (ORs of 1.91 [95% CI, 1.28-2.87; $P = 0.013$] and 3.74 [95% CI, 1.79-7.8; $P < 0.001$], respectively).[65] While cardiac valvular abnormalities are not a contraindication to use of bromocriptine, caution should be used.[38] All patients should undergo echocardiography before initiation of a dopamine agonist.[66] Echocardiography is recommended annually for patients taking cabergoline at a dosage of >2 mg weekly and every 5 years for those taking weekly doses of ≤2 mg, or as clinically indicated.[66,67] Both cabergoline and bromocriptine can diminish the effectiveness of antipsychotic medications and have the potential to exacerbate psychosis; psychosis needs to be closely monitored in patients initiated on dopamine agonists, especially those with a primary psychotic illness.[37,38,68,69]

Contraindications. The use of cabergoline is contraindicated in patients with a history of cardiac valvular disorders.[37] Both cabergoline and bromocriptine are contraindicated for use in patients with uncontrolled hypertension.[37,38]

Drug interactions. Bromocriptine is a substrate of CYP3A4. In addition, both bromocriptine and cabergoline can potentially interact with α- and β-agonists, metoclopramide, nefazodone, nitroglycerin, and serotonin receptor 1D agonists (triptans), which can respectively lead to increased

hypertensive effects, diminish the effect of cabergoline, cause serotonin syndrome, decrease vasodilatory effect, or enhance the vasoconstricting effect.[37,38]

Metformin

Metformin has been used for the treatment of metabolic abnormalities and has also been shown to reduce prolactin levels.[39,40] While the aforementioned 2017 multidisciplinary consensus paper on therapeutic recommendations for iatrogenic hyperprolactinemia secondary to antipsychotics[21] does not mention metformin, one treatment review suggests metformin as a therapeutic option.[22]

Efficacy. There is one published meta-analysis on metformin use (750-1,500 mg/d) for antipsychotic-induced hyperprolactinemia, which included 4 randomized placebo-controlled trials conducted in China (n = 509).[70] Two of the trials were double-blinded and the other 2 were open-label trials. The antipsychotics studied were quetiapine (1 study), risperidone (2 studies), risperidone, sulpiride, clozapine, and olanzapine (1 study each). The analysis found a significant decrease in prolactin in the metformin group compared to placebo (weighted mean difference, –6.87 µg/L; 95% CI, –13.24 to –0.51 µg/L; P = 0.03; I^2 = 80%). There were no significant differences in rates of adverse events or treatment discontinuation. Using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach, the quality of evidence for meta-analysis outcomes was rated as low, moderate, and high for 33.3%, 50.0%, and 16.7% of included studies, respectively. Due to between-study heterogeneity, further analyses could not be completed.

A systematic review on metformin use (750-1,500 mg/d) for the management of antipsychotic-induced hyperprolactinemia included 3 trials: 1 randomized, double-blind, placebo-controlled study and 2 observational studies (n = 235)[71]; one of the studies (n = 84) was also included in the above-mentioned meta-analysis.[70] A meta-analysis could not be performed due to heterogeneity; however, there was a mean reduction in serum prolactin of 54.6 µg/L across the 3 studies. Nausea, insomnia, and agitation were more frequent with use of metformin vs placebo.

Both of these analyses included a wide range of metformin doses; however, in 1 study reported prolactin reductions were greater with higher doses (1,000 and 1,500 mg/d).[71] Two studies found that metformin doses of 2.5 to 3 g/d reduced prolactin levels.[39,40] One of those studies found that metformin doses in that range were more effective at reducing prolactin levels after 6 months in patients with antipsychotic-induced hyperprolactinemia and type 2 diabetes compared to patients with antipsychotic-induced hyperprolactinemia and prediabetes receiving a lower dose (1.7 g) of metformin (23% reduction in prolactin levels vs 11% reduction).[39] Antipsychotics studied included phenothiazines, haloperidol, sulpiride, thioxanthenes, and risperidone. Lastly, a study found that metformin (2.5-3 g/d) plus bromocriptine significantly reduced prolactin levels in patients with hyperprolactinemia and impaired glucose tolerance (26%, P < 0.05 for comparison with baseline) compared to bromocriptine-treated patients with impaired glucose tolerance with normal prolactin levels and a control group with impaired glucose tolerance alone (P < 0.001 for both comparisons with baseline).[40]

It can be concluded from these studies that metformin decreases prolactin levels in antipsychotic-induced hyperprolactinemia. However, it should be noted that prolactin levels were not within normal limits at the end of the studies. Authors of one of the studies recommended that due to the moderate decrease of prolactin levels achieved, metformin should be paired with modification of antipsychotic therapy or use of other prolactin-reducing medications.[39] More quality trials of metformin are needed to determine the optimal dose, extent of prolactin-reducing effects, long-term tolerability as adjunctive treatment, and whether metformin has additive prolactin-lowering effects when paired with prolactin-sparing medications such as aripiprazole and dopamine agonists.

Tolerability. Common adverse effects of metformin are listed in Table 1. Antipsychotics can cause adverse effects such as hyperglycemia, dyslipidemia, and weight gain, which can be diminished by metformin due to its favorable metabolic profile; one meta-analysis found that use of antipsychotic medications plus metformin was superior to use of antipsychotics plus placebo in the reduction of glucose, weight, and lipids, while adverse effect rates were similar in the 2 groups.[72] If metformin proves to be an effective treatment for hyperprolactinemia in the future, this drug may address a wide range of antipsychotic adverse effects. However, metformin can decrease vitamin B_{12} absorption and cause lactic acidosis as serious adverse reactions.[41] It is recommended that vitamin B_{12} levels be monitored every 2 to 3 years during metformin use or if clinically indicated.[73]

Contraindications. Metformin is contraindicated for patients with severe renal dysfunction with an estimated glomerular filtration rate (eGFR) of <30 mL/min/1.73 m^2. Therapy should not be initiated in patients with an eGFR of 30 to 45 mL/min/1.73 m^2; if a patient is already taking metformin, the or dose should be decreased by 50% (to a maximum of 1 g/d).[41] It is recommended to obtain an eGFR measurement annually or more frequently in patients with impaired renal function while taking metformin.[73] In addition, metformin is contraindicated in patients with acidosis, including diabetic ketoacidosis.[41]

Drug interactions. Metformin interacts with alcohol and several medications that increase serum metformin, such as cimetidine, dolutegravir, iodinated contrast agents, ranolazine, and

tafenoquine. Metformin also interacts with patiromer which decreases serum metformin.[41]

Herbal preparations

Chamomile. Chamomile is a widely used medical plant. Components of chamomile have effects on osteoporosis prevention, as well as antioxidant, anticancer, and anti-inflammatory activities, which could play a role in treating idiopathic hyperprolactinemia. A 4-week randomized controlled trial compared the effects of chamomile and cabergoline in subjects with idiopathic hyperprolactinemia.[42] Fifty-six females received either chamomile syrup 5 mL (22.7 mg) twice daily or cabergoline 0.25 mg twice weekly. Mean (SD) prolactin levels decreased in both the chamomile and cabergoline groups (from 38.98 (12.95) μg/L to 22.99 (14.73) μg/L and from 40.12 (14.36) μg/L to 10.98 (12.2) μg/L, respectively). Mean prolactin levels were significantly lower in the cabergoline group than in the chamomile group ($P < 0.0001$). The prolactin normalization rate was higher in the cabergoline group than in the chamomile group (96% vs 72%, $P = 0.013$). No adverse effects were reported in the chamomile group.

Polyherbal mixture of *Bambusa vulgaris*, *Momordica charntia*, *Rauwolfia vomitoria*, *Ficus sur*, and *Clerodendrum capitatum*. A major cause of infertility in Nigeria is hyperprolactinemia, which is treated with herbal products, specifically a decoction of local plants including *Bambusa vulgaris, Momordica charntia, Rauwolfia vomitoria, Ficus sur*, and *Clerodendrum capitatum*.[45] Data from animal studies suggest that medium to high doses of this herbal preparation are effective for the treatment of haloperidol-induced hyperprolactinemia; it should be noted, however, that bromocriptine use resulted in lower prolactin levels than the herbal mixture.

Peony-Glycyrrhiza decoction. PGD was introduced in China as a potential treatment for muscle spasms and can also be used for hyperprolactinemia symptoms. Two studies have evaluated PGD for antipsychotic-induced hyperprolactinemia.[50,51] The first study was a 16-week randomized, double-blind, placebo-controlled trial involving 100 females with antipsychotic-induced hyperprolactinemia.[51] Baseline antipsychotics included risperidone, paliperidone, sulpride, amisulpride, olanzapine, ziprasidone, and quetiapine. The primary endpoint was the change in total score on the Prolactin Related Adverse Event Questionnaire (PRAEQ) from baseline to weeks 8 and 16. The secondary endpoint was improvement of hyperprolactinemia symptoms. PRAEQ total score reduction was greater with PGD vs placebo use at both times points ($P < 0.05$). PGD use was correlated with a clinically significant improvement of hyperprolactinemia symptoms at week 8 ($P = 0.045$) but not week 16 ($P = 0.438$). There were no significant differences in serum prolactin levels between PGD and placebo recipients. In another study, PGD was shown to be as effective as bromocriptine in decreasing elevated serum prolactin levels induced by risperidone. (A description of this study was included in the discussion of dopamine agonists earlier in this article.) Additionally, approximately half of the patients receiving PGD showed improvement of hyperprolactinemia symptoms.[50]

Shakuyaku-kanzo-to. Shakuyaku-kanzo-to is a Japanese medication composed of 2 herbs (*Paeoniae radix* and *Glycyrrhizae radix*) that has been evaluated as a treatment for antipsychotic-induced hyperprolactinemia.[52,74] In one study, shakuyaku-kanzo-to 7.5 g/d was given to 20 males in an open-label study design.[52] The patients' average age was 57.1 years and all met DSM-IV (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*) criteria for schizophrenia and were being treated with neuroleptics. Prolactin levels had decreased significantly at week 4 of shakuyaku-kanzo-to use (from 26.6 [SD, 10.8] μg/L to 20.8 [SD, 11.2] μg/L, $P = 0.0009$). Prolactin levels at week 8 (4 weeks after discontinuation) were not significantly different from baseline levels. Five patients had an at least 50% reduction in prolactin levels. No adverse effects were noted.

There are limited data regarding the efficacy and safety of herbal products for antipsychotic-induced hyperprolactinemia. Herbal medication use is compromised by a lack of safety data and quality control, inadequate content labeling, and the absence of appropriate patient information. The 2017 multidisciplinary consensus paper[21] gave herbal medication, specifically PDG and shakuyaku-kanzo-to, a grade C recommendation due to lack of evidence supporting their use. More robust clinical trials are needed to support herbal medication use in antipsychotic-induced hyperprolactinemia. Herbal medication may be recommended in special situations where refusal, ineffectiveness, or tolerability issues prohibit use of aripiprazole, dopamine agonists, or metformin to treat antipsychotic-induced hyperprolactinemia, but the risks should be carefully reviewed and discussed with the patient and close monitoring of prolactin levels should occur.

Herbal medication tolerability and drug interactions. The previously reviewed studies of herbal medications were characterized by a lack of adverse effect reporting. Common adverse effects of herbal medications are listed in Table 1. Chamomile, PGD, *Rauwolfia vomitoria*, and shakuyaku-kanzo-to act as inducers and inhibitors of multiple CYP isozymes.[75-79] Also, the polyherbal mixture can interact with antithyroid, antidiabetic, and antihypertensive agents, as well as antipsychotics, digoxin, levodopa, monoamine oxidase inhibitors, propranolol, and stimulants.[80-84]

Other treatment approaches

In the 2017 multidisciplinary consensus paper providing therapeutic recommendations for iatrogenic hyperprolactinemia secondary to use of antipsychotics, the strategy of antipsychotic dose reduction was rated as a grade D recommendation, and the strategy of switching to a different

antipsychotic less associated with hyperprolactinemia (eg, aripiprazole, quetiapine, olanzapine, or ziprasidone) were assigned grade A, B, or C recommendations, depending on the specific agent.[20] Both of these treatment strategies are associated with a risk of relapse of psychiatric illness and cannot always be implemented in patients who are stable on their current antipsychotic regimen or have a history of treatment-refractory disease. Additionally, evidence suggests that hyperprolactinemia may occur with low doses of certain antipsychotics and may even be dose independent.

Conclusion

There are treatments available for antipsychotic-induced hyperprolactinemia in patients who are unable to alter their current antipsychotic regimen. However, there remains a need for additional short- and long-term studies to determine the efficacy and safety of these treatment strategies, given that patients taking antipsychotics typically require lifelong treatment for their illnesses.

Disclosures

The authors have declared no potential conflicts of interest.

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