

Psychosis resolves, but menses stop

Nicole Renee Graham, MD, Mustafa Pirzada, MD, Almari Ginory, DO, Laura Mayol-Sabatier, MD, and Mathew Nguyen, MD

Ms. S, age 30, says her classmates are ‘working against her.’ Paliperidone relieves her psychotic symptoms, but she misses 2 menstrual cycles while taking the drug. What is your next step?



How would you handle this case?

Answer the **challenge questions** throughout this article

CASE Paranoid and hallucinating

Ms. S, age 30, is an unmarried graduate student who has been given a diagnosis of schizophrenia, paranoid type, during inpatient hospitalization that was prompted by impairment in school functioning (difficulty turning in assignments, poor concentration, making careless mistakes on tests), paranoid delusions, and multisensory hallucinations. She says that her roommate and classmates are working together to make her leave school, and recalls seeing them “snare and smirk” as she passes by. Ms. S says that she feels her classmates are calling her names and talking badly about her as soon as she is out of sight.

Ms. S is antipsychotic-naïve and has a baseline body mass index of 17.8 kg/m², indicating that she is underweight. We believe that olanzapine, 20 mg/d, is a good initial treatment because of its propensity for weight gain; however, she experiences only marginal improvement. Ms. S does not have health insurance, and cannot afford a brand name medication; therefore, she is cross-tapered to perphenazine, 8 mg, and benztropine, 0.5 mg, both taken twice daily (olanzapine was not available as a generic at the time).

At discharge, Ms. S does not report any hallucinatory experiences, but is guarded, voices suspicions about the treatment team, and asks “What are they doing with all my blood?”—referring to blood draws for labora-

tory testing during hospitalization.

As an outpatient, Ms. S is continued on the same medications until she has to be switched because she cannot afford the out-of-pocket cost of the antipsychotic, perphenazine (\$80 a month). Clozapine is recommended, but Ms. S refuses because of the mandatory weekly blood monitoring. She briefly tries fluphenazine, 2.5 mg/d, but it is discontinued because of malaise and lightheadedness without extrapyramidal symptoms.

Clozapine is again recommended, but Ms. S remains suspicious of the necessary blood draws and refuses. After several trials of antipsychotics, Ms. S starts paliperidone using samples from the clinic, titrated to 6 mg at bedtime. Once tolerance and therapeutic improvement are observed, she is continued on this medication through the manufacturer’s patient assistance program.

Within 3 months, Ms. S and her family find that she has improved significantly. She no longer reports hallucinatory experiences, is less guarded during ses-

Dr. Graham is a Child and Adolescent Psychiatry Fellow, Dr. Pirzada is Chief Child and Adolescent Psychiatry Fellow, Dr. Ginory is Assistant Professor, Dr. Mayol-Sabatier is a Child and Adolescent Psychiatry Fellow, and Dr. Nguyen is Assistant Professor, Department of Psychiatry, University of Florida, Gainesville, Florida.

Disclosure

The authors report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

Figure 1

Pituitary gland and role in synthesis and ejection of milk

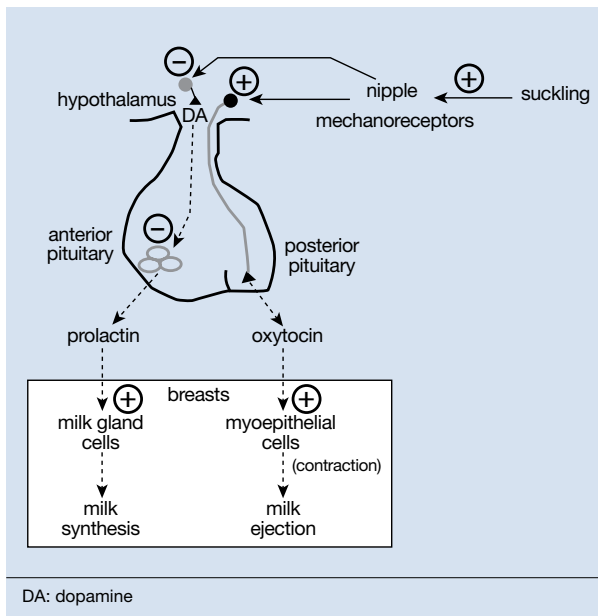
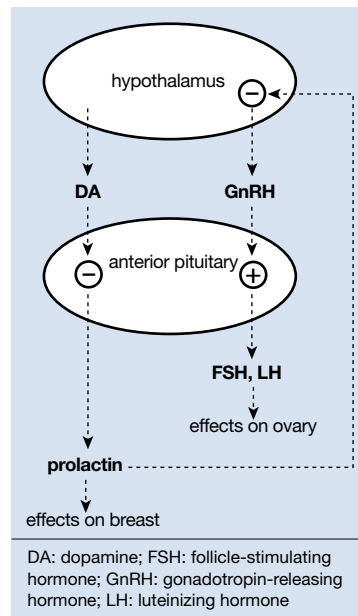


Figure 2

HPA axis and its effects on the ovaries and breasts



Clinical Point

A prolactin level of $>25 \mu\text{g/L}$ is considered abnormal; however, levels $>200 \mu\text{g/L}$ have been observed in patients taking an antipsychotic

sions, and has followed through with paid and volunteer job applications and interviews. She soon finds a job teaching entry-level classes at a community college and is looking forward to a summer trip abroad.

During a follow-up appointment, Ms. S reports that she had missed 2 consecutive menstrual cycles without galactorrhea or fractures. A urine pregnancy test is negative; the prolactin level is $72 \mu\text{g/L}$.

Hyperprolactinemia in women is defined as a plasma prolactin level of

- a) $>2.5 \mu\text{g/L}$
- b) $>5 \mu\text{g/L}$
- c) $>10 \mu\text{g/L}$
- d) $>20 \mu\text{g/L}$
- e) $>25 \mu\text{g/L}$

The authors' observations

A prolactin level $>25 \mu\text{g/L}$ is considered abnormal.¹ A level of $>250 \mu\text{g/L}$ may identify a prolactinoma; however, levels

$>200 \mu\text{g/L}$ have been observed in patients taking an antipsychotic.¹ Given Ms. S's clinically significant elevation of prolactin, she is referred to her primary care physician. We decide to augment her regimen with aripiprazole, 10 mg/d, because this drug has been noted to help in cases of hyperprolactinemia associated with other antipsychotics.^{2,3}

Prolactin serves several roles in the body, including but not limited to lactation, sexual gratification, proliferation of oligodendrocyte precursor cells, surfactant synthesis of fetal lungs at the end of pregnancy, and neurogenesis in maternal and fetal brains (Figure 1 and Figure 2). A 2004 review reported secondary amenorrhea, galactorrhea, and osteopenia as common symptoms of hyperprolactinemia.⁵ Hyperprolactinemia has been seen with most antipsychotics, both typical and atypical. Although several studies document prolactin elevation with risperidone, fewer have examined the active metabolite (9-hydroxyrisperidone) paliperidone.⁵⁻⁷



Discuss this article at www.facebook.com/CurrentPsychiatry

Table

Effects of hyperprolactinemia by organ system

Organ system	Effects
Bone	Decreased bone density mediated by relative or absolute deficiency of estrogen (women) or testosterone (men)
Reproductive	Infertility (women); reduced spermatogenesis, erectile dysfunction, ejaculatory dysfunction
Endocrine	Galactorrhea, menstrual abnormalities (women), gynecomastia (men), possible increased risk of cancer (breast, endometrial in women) needs to be further studied
Cardiovascular	Possible higher risk of cardiovascular disease
Mental health	Risk of depression

In women, a high prolactin level can cause

- menstrual disturbance
- galactorrhea
- breast engorgement
- sexual dysfunction
- all of the above

The authors' observations

Acutely, hyperprolactinemia can cause menstrual abnormalities, decreased libido, breast engorgement, galactorrhea, and sexual dysfunction in women.⁸ In men, the most common symptoms of hyperprolactinemia are loss of interest in sex, erectile dysfunction, infertility, and gynecomastia. Osteoporosis has been associated with chronic elevation of the prolactin level⁸ (Table).

TREATMENT Adjunctive aripiprazole

After 8 weeks of adjunctive aripiprazole, Ms. S's prolactin level decreases to 42 $\mu\text{g/L}$, but menses do not return. Because her family and primary care providers are eager to have the prolactin level return to normal, reducing her risk of complications, we decide to decrease paliperidone to 3 mg at bedtime.

Eight weeks later, Ms. S shows functional improvement. A repeat test of prolactin is 24 $\mu\text{g/L}$; she reports a 4-day period of spotting 1 week ago. One month later, the prolactin level

is 21 $\mu\text{g/L}$, and she reports having a normal menstrual period. She continues treatment with paliperidone, 3 mg/d, and aripiprazole, 10 mg/d, experiences regular menses, and continues teaching.

Pharmacotherapy of hyperprolactinemia includes

- haloperidol
- perphenazine
- bromocriptine
- olanzapine
- risperidone

The authors' observations

Our goal in treating Ms. S was to address her schizophrenia symptoms and improve her overall functioning. Often, finding an effective treatment can be challenging, and there is little evidence to support the efficacy of one antipsychotic over another.⁴ In Ms. S's case, our care was stymied by the cost of medication, challenges related to delusions intrinsic to the illness (she refused clozapine because of required blood draws), and adverse effects. When Ms. S developed amenorrhea while taking paliperidone—the only medication that showed significant improvement in her psychotic symptoms—our goal was to maintain her functional level without significant long-term adverse effects.

Clinical Point

In women, hyperprolactinemia can cause menstrual abnormalities, sexual dysfunction, breast engorgement, and galactorrhea

continued

Clinical Point

Aripiprazole is considered to be a prolactin-sparing agent; it has been shown to reduce an elevated prolactin level

Related Resources

- Peuskens J, Pani L, Detraux J, et al. The effects of novel and newly approved antipsychotics on serum prolactin levels: a comprehensive review [published online March 28, 2014]. *CNS Drugs*. doi: 10.1007/s40263-014-0157-3.
- Li X, Tang Y, Wang C. Adjunctive aripiprazole versus placebo for antipsychotic-induced hyperprolactinemia: meta-analysis of randomized controlled trials. *PLoS One*. 2013;8(8):e70179. doi: 10.1371/journal.pone.0070179.

Drug Brand Names

Aripiprazole • Abilify	Haloperidol • Haldol
Benzatropine • Cogentin	Olanzapine • Zyprexa
Bromocriptine • Parlodel	Paliperidone • Invega
Cabergoline • Dostinex	Perphenazine • Trilafon
Clozapine • Clozaril	Risperidone • Risperdal
Fluphenazine • Prolixin	

Managing hyperprolactinemia

Management of iatrogenic hyperprolactinemia includes decreasing the dosage of the offending agent, using a prolactin-sparing antipsychotic, or initiating a dopamine agonist, such as bromocriptine or cabergoline, in addition to an antipsychotic.^{1,4} Aripiprazole is considered to be a prolactin-sparing agent because of its propensity to increase the prolactin level to less of a degree than what is seen with other antipsychotics; in fact, it has been shown to reduce an elevated prolactin level.⁹⁻¹¹

Most typical and atypical antipsychotics are dopamine—specifically D2—receptor antagonists. These antipsychotics prevent dopamine from binding to the D2 receptor and from inhibiting prolactin release, therefore causing hyperprolactinemia. Aripiprazole differs from other antipsychotics: It is a partial D2 receptor agonist with high affinity, and therefore suppresses prolactin release.⁸ In a randomized controlled

trial, aripiprazole had a lower rate of prolactin elevation compared with placebo.¹²

Aripiprazole's ability to reduce an elevated prolactin level caused by other antipsychotics has been demonstrated in several studies with haloperidol,¹³ olanzapine,^{14,15} and risperidone.¹⁵⁻¹⁷ There has been 1 case report,¹⁸ but no controlled studies, of aripiprazole being used to decrease the prolactin level in patients treated with paliperidone.

In Ms. S's case, adding aripiprazole, 10 mg/d, reduced her prolactin level by approximately 50%. Because several studies have shown that adjunctive aripiprazole with a D2 antagonist normalizes the prolactin level,¹⁹ it is reasonable to conclude that adding aripiprazole facilitated reduction of her prolactin level and might have continued to do so if given more time. Regrettably, because of patient and family concerns, paliperidone was reduced before this could be determined. It is unclear whether normalization of Ms. S's prolactin level and return of her menstrual cycle was caused by adding aripiprazole or by reducing the dosage of paliperidone.

Although additional randomized controlled trials should be conducted on the utility of this approach, it is reasonable to consider augmentation with aripiprazole when treating a patient who is stable on an antipsychotic, including paliperidone, but has developed hyperprolactinemia secondary to treatment.

References

1. Melmed S, Casanueva FF, Hoffman AR, et al. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2011;96(2):273-288.

Bottom Line

Hyperprolactinemia is a relatively common, underreported side effect of both typical and atypical antipsychotics. Paliperidone and risperidone have been shown to have the highest risk among the atypical antipsychotics; aripiprazole has the lowest risk. Treatment of an elevated prolactin level should include reduction or discontinuation of the offending agent and augmentation with aripiprazole.

- Madhusoodanan S, Parida S, Jimenez C. Hyperprolactinemia associated with psychotropics—a review. *Hum Psychopharmacol*. 2010;25(4):281-297.
- Hanssens L, L'Italien G, Loze JY, et al. The effect of antipsychotic medication on sexual function and serum prolactin levels in community-treated schizophrenic patients: results from the Schizophrenia Trial of Aripiprazole (STAR) study (NCT00237913). *BMC Psychiatry*. 2008;8:95. doi: 10.1186/1471-244X-8-95.
- Lieberman JA, Stroup TS, McEvoy JP, et al; Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005;353(12):1209-1223.
- Haddad PM, Wieck A. Antipsychotic-induced hyperprolactinaemia: mechanisms, clinical features and management. *Drugs*. 2004;64(20):2291-2314.
- Knegtering R, Baselmans P, Castelein S, et al. Predominant role of the 9-hydroxy metabolite of risperidone in elevating blood prolactin levels. *Am J Psychiatry*. 2005;162(5):1010-1012.
- Berwaerts J, Cleton A, Rossenu S, et al. A comparison of serum prolactin concentrations after administration of paliperidone extended-release and risperidone tablets in patients with schizophrenia. *J Psychopharmacol*. 2010;24(7):1011-1018.
- Holt RI, Peveler RC. Antipsychotics and hyperprolactinaemia: mechanisms, consequences and management. *Clin Endocrinol (Oxf)*. 2011;74(2):141-147.
- Friberg LE, Vermeulen AM, Petersson KJ, et al. An agonist-antagonist interaction model for prolactin release following risperidone and paliperidone treatment. *Clin Pharmacol Ther*. 2009;85(4):409-417.
- Skopek M, Manoj P. Hyperprolactinaemia during treatment with paliperidone. *Australas Psychiatry*. 2010;18(3):261-263.
- Aihara K, Shimada J, Miwa T, et al. The novel antipsychotic aripiprazole is a partial agonist at short and long isoforms of D2 receptors linked to the regulation of adenylate cyclase activity and prolactin release. *Brain Res*. 2004;1003(1-2):9-17.
- Bushe C, Shaw M, Peveler RC. A review of the association between antipsychotic use and hyperprolactinaemia. *J Psychopharmacol*. 2008;22(2 suppl):46-55.
- Yasui-Furukori N, Furukori H, Sugawara N, et al. Dose-dependent effects of adjunctive treatment with aripiprazole on hyperprolactinemia induced by risperidone in female patients with schizophrenia. *J Clin Psychopharmacol*. 2010;30(5):596-599.
- Lorenz RA, Weinstein B. Resolution of haloperidol-induced hyperprolactinemia with aripiprazole. *J Clin Psychopharmacol*. 2007;27(5):524-525.
- Aggarwal A, Jain M, Garg A, et al. Aripiprazole for olanzapine-induced symptomatic hyper prolactinemia. *Indian J Pharmacol*. 2010;42(1):58-59.
- Byerly MJ, Marcus RN, Tran QV, et al. Effects of aripiprazole on prolactin levels in subjects with schizophrenia during cross-titration with risperidone or olanzapine: analysis of a randomized, open-label study. *Schizophr Res*. 2009;107(2-3):218-222.
- Chen CK, Huang YS, Ree SC, et al. Differential add-on effects of aripiprazole in resolving hyperprolactinemia induced by risperidone in comparison to benzamide antipsychotics. *Prog Neuropsychopharmacol Biol Psychiatry*. 2010;34(8):1495-1499.
- Chen CY, Lin TY, Wang CC, et al. Improvement of serum prolactin and sexual function after switching to aripiprazole from risperidone in schizophrenia: a case series. *Psychiatry Clin Neurosci*. 2011;65(1):95-97.
- Rocha FL, Hara C, Ramos MG. Using aripiprazole to attenuate paliperidone-induced hyperprolactinemia. *Prog Neuropsychopharmacol Biol Psychiatry*. 2010;34(6):1153-1154.

Clinical Point

It is unclear whether adding aripiprazole or reducing the paliperidone dosage caused normalization of Ms. S's prolactin level



GLOBAL MEDICAL
EDUCATION

Timely, unbiased, evidence-based medical education from the world's leading experts

Global Medical Education is an online medical education resource that addresses psychiatric topics from the commonplace to the most critical, through a **library of 700+ concise videos** available on-demand on all major digital devices.

The screenshot shows the Global Medical Education website interface. At the top, there is a search bar and navigation links for 'About GME', 'Videos', 'Faculty', 'Partners', 'Journal Watch', 'Resources', and 'Join/Renew GME'. The main content area displays a video titled 'BDNF and Schizophrenia' by Oliver Freudenreich, MD, Associate Professor of Psychiatry, (Harvard). The video player includes a rating system (5 stars), a 'No votes yet' message, and buttons for 'Add New Comment' and 'Take Quiz'. To the right of the video player is a sidebar with 'Show/Hide Thumbnails' and 'Previous Next' navigation. The sidebar contains a list of topics related to BDNF and Schizophrenia, including 'Brain-derived neurotrophic factor', 'Neurotrophin family', 'NGF, BDNF, NT-3, NT-4/5', 'Critical role in', 'Neuron survival (name)', 'Neuroplasticity', 'Synaptogenesis', 'Learning', 'Fear memory and extinction', 'Genetics: VAL66MET SNP', and 'Receptor: TrkB'. At the bottom of the page, there are links for 'About GME', 'Videos', 'Faculty', 'Join/Renew GME', and 'Resources'. A small copyright notice is visible at the very bottom: 'All material on this website is protected by copyright. Copyright © 2012 by GME, Inc. This website also contains material copyrighted by IM partners. GME does not provide medical advice. The website and articles are intended for informational purposes only. They are not a substitute for professional medical advice, diagnosis or treatment. Never ignore professional medical advice in seeking treatment because of something you have read on the GME Website. If you think you may have a medical emergency, immediately call your doctor or 911.'

To access our videos, go to
<http://gmeded.com/user/register>
 Use discount code: **quadrant**