Psychosis resolves, but menses stop
Nicole Renee Graham, MD, Mustafa Pirzada, MD, Almari Ginory, DO, Laura Mayol-Sabatier, MD, and Mathew Nguyen, MD

**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 benzatropine, 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-

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**Disclosure**

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

**Clinical Point**

A prolactin level of >25 µg/L is considered abnormal; however, levels >200 µg/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 µg/L.

**Hyperprolactinemia in women is defined as a plasma prolactin level of**

- a) >2.5 µg/L
- b) >5 µg/L
- c) >10 µg/L
- d) >20 µg/L
- e) >25 µg/L

**The authors’ observations**

A prolactin level >25 µg/L is considered abnormal. A level of >250 µg/L may identify a prolactinoma; however, levels >200 µg/L have been observed in patients taking an antipsychotic. 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.

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. 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.
In women, a high prolactin level can cause
a) menstrual disturbance
b) galactorrhea
c) breast engorgement
d) sexual dysfunction
e) all of the above

The authors' observations
Acutely, hyperprolactinemia can cause menstrual abnormalities, decreased libido, breast engorgement, galactorrhea, and sexual dysfunction in women. 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 level (Table).

TREATMENT Adjunctive aripiprazole
After 8 weeks of adjunctive aripiprazole, Ms. S's prolactin level decreases to 42 µg/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 µg/L; she reports a 4-day period of spotting 1 week ago. One month later, the prolactin level is 21 µg/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
a) haloperidol
b) perphenazine
c) bromocriptine
d) olanzapine
e) 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. 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.

Table

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

Clinical Point
In women, hyperprolactinemia can cause menstrual abnormalities, sexual dysfunction, breast engorgement, and galactorrhea.
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. Aripiprazole is considered to be a prolactin-sparing agent because of its propensity to increase the prolactin level to a lesser degree than what is seen with other antipsychotics; in fact, it has been shown to reduce an elevated prolactin level.°-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


Clinical Point

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

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