

# Strategies for managing medication-induced hyperprolactinemia

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Ms. E, age 23, presents to your office for a routine visit for management of bipolar I disorder and posttraumatic stress disorder with comorbid type 2 diabetes mellitus. She currently is taking risperidone, 3 mg/d, lamotrigine, 200 mg/d, metformin, 2,000 mg/d, medroxyprogesterone, 150 mg every 3 months, and prazosin, 8 mg/d. Her mood has been stabilized for the last 3 years with this medication regimen.

Ms. E has a history of self-discontinuing medication when adverse events occur. She has been hospitalized twice for psychosis and suicide attempts. Past psychotropic medications that have been discontinued due to adverse effects include ziprasidone (mild abnormal lip movement), olanzapine (ineffective and drowsy), valproic acid (tremor and abdominal discomfort), lithium (rash), and aripiprazole (increased fasting blood sugar and labile mood).

At her appointment today, Ms. E says she is concerned because she has been experiencing galactorrhea for the past 4 weeks. Her prolactin level is 14.4 ng/mL; a normal level for a woman who is not pregnant is <25 ng/mL. However, a repeat prolactin level is obtained, and is found to be elevated at 38 ng/mL.

Prolactin, a polypeptide hormone that is secreted from the pituitary gland, has many

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functions, including involvement in the synthesis and maintenance of breast milk production, in reproductive behavior, and in luteal function.<sup>1,2</sup> Hyperprolactinemia—an elevated prolactin level—is a common endocrinologic disorder of the hypothalamic–pituitary–axis.<sup>3</sup> Children, adolescents, premenopausal women, and women in the perinatal period are more vulnerable to medication-induced hyperprolactinemia.<sup>4</sup> If not asymptomatic, patients with hyperprolactinemia may experience amenorrhea, galactorrhea, hypogonadism, sexual dysfunction, or infertility.<sup>1,4</sup> Chronic hyperprolactinemia may increase the risk for long-term complications, such as decreased bone mineral density and osteoporosis, although available evidence has conflicting findings.<sup>1</sup>

Hyperprolactinemia is diagnosed by a prolactin concentration above the upper

#### Practice Points

- In the absence of a tumor, **medications are frequently identified as the cause of hyperprolactinemia.** Medication-induced elevated prolactin levels typically range from 25 to 100 ng/mL.
- **Antipsychotics, antidepressants, hormonal preparations, antihypertensives, and gastrointestinal agents** have been associated with hyperprolactinemia.
- **Antipsychotic-induced hyperprolactinemia management strategies** may include watching and waiting, discontinuing the antipsychotic, reducing the antipsychotic dose, switching antipsychotics, or adding aripiprazole or a dopamine agonist.

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reference range.<sup>3</sup> Various hormones and neurotransmitters can impact inhibition or stimulation of prolactin release.<sup>5</sup> For example, dopamine tonically inhibits prolactin release and synthesis, whereas estrogen stimulates prolactin secretion.<sup>1,5</sup> Prolactin also can be elevated under several physiologic and pathologic conditions, such as during stressful situations, meals, or sexual activity.<sup>1,5</sup> A prolactin level >250 ng/mL is usually indicative of a prolactinoma; however, some medications, such as strong D2 receptor antagonists (eg, risperidone, haloperidol), can cause significant elevation without evidence of prolactinoma.<sup>3</sup> In the absence of a tumor, medications are often identified as the cause of hyperprolactinemia.<sup>3</sup> According to the Endocrinology Society clinical practice guideline, medication-induced elevated prolactin levels are typically between 25 to 100 ng/mL.<sup>3</sup>

### Medication-induced hyperprolactinemia

Antipsychotics, antidepressants, hormonal preparations, antihypertensives, and gastrointestinal agents have been associated with hyperprolactinemia (*Table 1*,<sup>1,3,5-11</sup> *page 44*). These medication classes increase prolactin by decreasing dopamine, which facilitates disinhibition of prolactin synthesis and release, or increasing prolactin stimulating hormones, such as serotonin or estrogen.<sup>5</sup>

Antipsychotics are the most common medication-related cause of hyperprolactinemia.<sup>3</sup> Typical antipsychotics are more likely to cause hyperprolactinemia than atypical antipsychotics; the incidence among patients taking typical antipsychotics is 40% to 90%.<sup>3</sup> Atypical antipsychotics, except risperidone and paliperidone, are considered to cause less endocrinologic effects than typical antipsychotics through various mechanisms: serotonergic receptor antagonism, fast dissociation from D2 receptors, D2 receptor partial agonism, and preferential binding of D3 vs D2 receptors.<sup>1,5</sup> By having transient D2 receptor association, clozapine and quetiapine are considered to have less risk of hyperprolactinemia compared with other atypical antipsychotics.<sup>1,5</sup> Aripiprazole,

brexpiprazole, and cariprazine are partial D2 receptor agonists, and cariprazine is the only agent that exhibits preferential binding to D3 receptors.<sup>12,13</sup> Based on limited data, brexpiprazole and cariprazine may have prolactin-sparing properties given their partial D2 receptor agonism.<sup>12,13</sup> However, one study found increased prolactin levels in some patients after treatment with brexpiprazole, 4 mg/d.<sup>14</sup> Similarly, another study found that cariprazine could increase prolactin levels as much as 4.1 ng/mL, depending on the dose.<sup>15</sup> Except for aripiprazole, brexpiprazole, cariprazine, and clozapine, all other atypical antipsychotics marketed in the United States have a standard warning in the package insert regarding prolactin elevations.<sup>1,16,17</sup>

Because antidepressants are less well-studied as a cause of medication-induced hyperprolactinemia, drawing definitive conclusions regarding incidence rates is limited, but the incidence seems to be fairly low.<sup>6,18</sup> A French pharmacovigilance study found that of 182,836 spontaneous adverse drug events reported between 1985 and 2009, there were 159 reports of selective serotonin reuptake inhibitors (SSRIs) inducing hyperprolactinemia.<sup>6</sup> Fluoxetine and paroxetine represented about one-half of the cases; however, there were also cases associated with citalopram, escitalopram, sertraline, fluvoxamine, milnacipran, and venlafaxine. In comparison, there were only 11 reports of hyperprolactinemia associated with tricyclic antidepressants or monoamine oxidase inhibitors. Although patients were not always symptomatic, the most commonly reported symptoms were galactorrhea (55%), gynecomastia (29%), amenorrhea (11%), mastodynia (11%), and sexual disorders (4%).<sup>6</sup> Another study of 5,920 patients treated with fluoxetine found mastodynia in 0.25%, gynecomastia in 0.08%, and galactorrhea in 0.07% of patients.<sup>18</sup> Symptoms occurred in an extremely low percentage of patients, and the study is >20 years old.<sup>18</sup>

Mirtazapine and bupropion have been found to be prolactin-neutral.<sup>5</sup> Bupropion also has been reported to decrease prolactin levels, potentially via its ability to block dopamine reuptake.<sup>19</sup>

### Clinical Point

**Typical antipsychotics are more likely to cause hyperprolactinemia than atypical antipsychotics**



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Table 1

## Medication-induced hyperprolactinemia

Class	Medications	Mechanism(s) of action
Antipsychotics	Typical antipsychotics: Chlorpromazine, haloperidol, thioridazine, thiothixene <sup>5</sup> Prolactin-raising atypical antipsychotics: Paliperidone, risperidone <sup>1</sup>	Antipsychotic-associated D2 receptor antagonism <sup>5</sup>
Antidepressants	Serotonin reuptake inhibitors: Citalopram, escitalopram, fluoxetine, fluvoxamine, milnacipran, paroxetine, sertraline, venlafaxine <sup>6</sup> Tricyclic antidepressants: Amitriptyline, amoxapine, clomipramine, desipramine <sup>5</sup> Monoamine oxidase inhibitor: Clorgyline <sup>5</sup>	May release prolactin-regulating factors, such as vasoactive intestinal polypeptide or oxytocin <sup>7</sup> May inhibit the tuberoinfundibular dopamine system through the stimulation of GABAergic neurons <sup>8</sup> May cause indirect modulation of prolactin release by increasing serotonin <sup>8</sup>
Hormone preparations	Antiandrogens, <sup>5</sup> combined oral contraceptives, <sup>3</sup> estrogens <sup>3</sup>	Estrogen-stimulated lactotroph hyperplasia, which stimulates prolactin release <sup>9</sup>
Antihypertensives	Methyldopa, <sup>5</sup> reserpine, <sup>5</sup> tetrabenazine, <sup>10</sup> verapamil <sup>5</sup>	Methyldopa inhibits the conversion of levodopa to dopamine and can decrease dopamine synthesis by acting as a false neurotransmitter <sup>5,9</sup> Reserpine can inhibit the storage of hypothalamic catecholamines in secretory granules, which can lead to depletion of dopamine and other sympathetic biogenic amines <sup>5</sup> Tetrabenazine is thought to be a reversible depletor of dopamine <sup>10</sup> Verapamil blocks hypothalamic production of dopamine <sup>9</sup>
Gastrointestinal medications	Metoclopramide, <sup>9</sup> prochlorperazine <sup>11</sup>	Dopamine receptor antagonism <sup>9</sup>

GABA:  $\gamma$ -aminobutyric acid

## Clinical Point

A patient with a prolactin level >100 ng/mL should be referred to Endocrinology to rule out prolactinoma

## Managing medication-induced hyperprolactinemia

Screening for and identifying clinically significant hyperprolactinemia is critical, because adverse effects of medications can lead to nonadherence and clinical decompensation.<sup>20</sup> Patients must be informed of potential symptoms of hyperprolactinemia, and clinicians should inquire about such symptoms at each visit. Routine monitoring of prolactin levels in asymptomatic patients is not necessary, because the Endocrine Society Clinical Practice Guideline does not recommend treating patients with asymptomatic medication-induced hyperprolactinemia.<sup>3</sup>

In patients who report hyperprolactinemia symptoms, clinicians should

review the patient's prescribed medications and past medical history (eg, chronic renal failure, hypothyroidism) for potential causes or exacerbations, and address these factors accordingly.<sup>3</sup> Order a measurement of prolactin level. A patient with a prolactin level >100 ng/mL should be referred to Endocrinology to rule out prolactinoma.<sup>1</sup>

If a patient's prolactin level is between 25 and 100 ng/mL, review the patient's medications (*Table 1*<sup>1,3,5-11</sup>), because prolactin levels within this range usually signal a medication-induced cause.<sup>3</sup> For patients with antipsychotic-induced hyperprolactinemia, there are several management strategies (*Table 2*,<sup>1,3,4,9,16,17,21-27</sup> *page 45*):

Table 2

## Management strategies for antipsychotic-induced hyperprolactinemia

Strategy	Comments
Watch and wait	Tolerance and a decrease in prolactin levels may occur over time but will not occur in most patients <sup>1</sup>
Discontinue antipsychotic	Levels may return to normal 3 days after discontinuation, but medications with longer half-lives may require longer for prolactin levels and symptoms to normalize <sup>3,9</sup>
Reduce antipsychotic dose	Prolactin elevations may be dose-related; however, antipsychotics with a higher relative risk of increasing prolactin tend to raise prolactin levels even at low doses, which may be subtherapeutic depending on the indication <sup>1</sup>
Switch antipsychotic	Consider switching to a prolactin-sparing antipsychotic, such as aripiprazole, brexpiprazole, cariprazine, or clozapine. <sup>1,4</sup> Switching antipsychotics has been shown to decrease prolactin levels, but there is limited evidence available on the timeline of symptomatic improvement of prolactin-related adverse events. When switching from risperidone to aripiprazole, prolactin levels and symptoms may resolve within 4 weeks. <sup>21,22</sup> The long half-life of aripiprazole may explain why symptoms take at least 1 month to resolve. Two case reports describe probable aripiprazole-associated symptomatic hyperprolactinemia <sup>23,24</sup>
Add aripiprazole	A recent meta-analysis found that adjunctive aripiprazole increases the proportion of patients who had prolactin levels return to normal in antipsychotic-induced hyperprolactinemia with prolactin-raising antipsychotics, such as risperidone or haloperidol. <sup>25</sup> Lower doses (eg, 5 mg/d) may be sufficient. <sup>1,25</sup> Adjunctive therapy with brexpiprazole or cariprazine has not yet been studied <sup>16,17</sup>
Add a dopamine agonist	Bromocriptine and cabergoline have been shown to reduce prolactin levels and relieve symptoms of hypogonadism in patients with risperidone-induced hyperprolactinemia. <sup>26</sup> Patients resumed menstruation after 8 weeks of bromocriptine treatment. <sup>27</sup> Cabergoline is taken only once or twice weekly because of a longer elimination half-life, whereas bromocriptine is dosed multiple times a day <sup>4</sup>

• **Watch and wait** may be warranted when the patient is experiencing mild hyperprolactinemia symptoms.

• **Discontinue.** If the patient can be maintained without an antipsychotic, discontinuing the antipsychotic would be a first-line option.<sup>3</sup>

• **Reduce the dose.** Reducing the antipsychotic dose may be the preferred strategy for patients with moderate to severe hyperprolactinemia symptoms who responded to the antipsychotic and do not wish to start adjunctive therapy.<sup>4</sup>

• **Switching** to a prolactin-sparing antipsychotic may help normalize prolactin levels and may be preferred when the risk of relapse is low.<sup>3</sup> Dopamine agonists can treat medication-induced hyperprolactinemia, but may worsen psychiatric symptoms.<sup>28,29</sup> Therefore, this may be the preferred strategy

if the offending medication cannot be discontinued or switched, or if the patient has a comorbid prolactinoma.

Less data exist on managing hyperprolactinemia that is induced by a medication other than an antipsychotic; however, it seems reasonable that the same strategies could be implemented. Specifically, for SSRI-induced hyperprolactinemia, if clinically appropriate, switching to or adding an alternative antidepressant that may be prolactin-sparing, such as mirtazapine or bupropion, could be attempted.<sup>8</sup> One study found that fluoxetine-induced galactorrhea ceased within 10 days of discontinuing the medication.<sup>30</sup>

**CASE CONTINUED**

Because Ms. E has been on the same medication regimen for 3 years and recently developed galactorrhea, it seems unlikely that her

**Clinical Point**

**Switching to a prolactin-sparing antipsychotic may normalize prolactin levels and may be preferred when risk of relapse is low**

## Clinical Point

For SSRI-induced hyperprolactinemia, consider adding or switching to mirtazapine or bupropion

hyperprolactinemia is medication-induced. However, a tumor-related cause is less likely because the prolactin level is <100 ng/mL. Based on the literature, the only possible medication-induced cause of her galactorrhea is risperidone. Ms. E agrees to a trial of adjunctive oral aripiprazole, 5 mg/d, with close monitoring of her type 2 diabetes mellitus. Because of the long elimination half-life of aripiprazole, 1 month is required to monitor for improvement in galactorrhea. Ms. E is advised to use breast pads as a nonpharmacologic strategy in the interim. After 1 month of treatment, Ms. E denies galactorrhea symptoms and no longer requires the use of breast pads.

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## Related Resource

- Peuskens J, Pani L, Detraux J, et al. The effects of novel and newly approved antipsychotics on serum prolactin levels: a comprehensive review. *CNS Drugs*. 2014;28(5):421-453.

### Drug Brand Names

Amitriptyline • Elavil	Methyldopa • Aldomet
Amoxapine • Asendin	Metoclopramide • Reglan
Aripiprazole • Abilify	Milnacipran • Savella
Brexpiprazole • Rexulti	Mirtazapine • Remeron
Bromocriptine • Cyclost	Olanzapine • Zyprexa
Bupropion • Wellbutrin	Paliperidone • Invega
Cabergoline • Dostinex	Paroxetine • Paxil
Cariprazine • Vraylar	Pramipexole • Mirapex
Chlorpromazine • Thorazine	Prazosin • Minipress
Citalopram • Celexa	Prochlorperazine • Compazine
Clomipramine • Anafranil	Quetiapine • Seroquel
Clorgyline • Aurorix	Risperidone • Risperdal
Clozapine • Clozaril	Sertraline • Zoloft
Desipramine • Norpramin	Tetrabenazine • Xenazine
Escitalopram • Lexapro	Thioridazine • Mellaril
Fluoxetine • Prozac	Thiothixene • Navane
Fluvoxamine • Luvox	Valproic acid • Depakote
Haloperidol • Haldol	Venlafaxine • Effexor
Lamotrigine • Lamictal	Verapamil • Calan
Lithium • Lithobid	Ziprasidone • Geodon
Medroxyprogesterone • Provera	
Metformin • Glucophage	