

Hyperprolactinemia: Monitoring children on long-term risperidone



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How to address evidence of potential for developmental effects with sustained use

Serum prolactin increases in children and adolescents when risperidone therapy begins, then decreases over time in many patients. When prolactin levels remain elevated, evidence suggests that children may experience adverse effects such as delayed sexual maturation or reduced bone growth because of hypothalamic-pituitary-gonadal axis (HPG) dysfunction.

To help you make informed prescribing decisions, we discuss what the evidence says about the effects of elevated prolactin in children and adolescents. We then suggest clinical steps to help you manage hyperprolactinemia when prescribing risperidone.

Pediatric indications

Based on short-term clinical trials of efficacy and tolerability, risperidone is FDA-approved for 3 pediatric indications:

- short-term treatment of acute mania or mixed episodes associated with bipolar I disorder in patients age 10 to 17
- schizophrenia treatment in patients age 13 to 17
- treatment of irritability (including aggression, self-injury, temper tantrums, and mood swings) associated with autistic disorder in patients age 5 to 16.

Recommended risperidone dosages are lower for children and adolescents than for adults (*Table 1*). Off-label pediatric uses described in case reports include psychotic, mood, disruptive, movement, and pervasive developmental disorders.

Table 1

Recommended risperidone dosing for pediatric indications*

Indication	Starting dose	Maximum dose
Acute mania or mixed episodes	0.5 mg once daily in morning or evening	2.5 mg/d
Irritability in autism	0.25 mg/d for patients weighing <20 kg	0.5 mg/d for patients weighing <20 kg
	0.5 mg/d for patients weighing ≥20 kg	1 mg/d for patients weighing ≥20 kg
Schizophrenia	0.5 mg once daily in morning or evening	3 mg/d

* FDA-approved dosages; individualize based on response and tolerability

Source: Drug facts and comparisons. St. Louis, MO: Wolters Kluwer Health; 2008:949-50

Table 2

Factors that regulate prolactin secretion

Effect	Factors	Mechanism
Inhibitory	Dopamine, gonadotropin-associated protein, acetylcholine	D2 receptor stimulation of lactotroph cells
Stimulatory	Serotonin, thyrotropin-releasing hormone, cholecystokinin	Through 5-HT _{1A} and 5-HT ₂

Clinical Point

Age- and sex-specific normal prolactin ranges vary from lab to lab, and levels show marked circadian variation

Prolactin physiology

Prolactin's primary physiologic function is to cause breast enlargement during pregnancy and milk secretion during lactation.¹ A polypeptide hormone, prolactin is secreted by lactotroph cells in the anterior pituitary, under the complex control of stimulatory and inhibitory factors (Table 2). Its pulsatile secretion peaks 13 to 14 times daily, with approximately 95 minutes between pulses.

Serum prolactin levels show marked circadian variation.² The reference value for serum prolactin is 1 to 25 ng/mL for women and 1 to 20 ng/mL for men. The higher prolactin levels seen in women begin after puberty and presumably are caused by estrogen's stimulatory effect.³ Age- and sex-specific normal prolactin ranges vary widely and from lab to lab (Table 3, page 66).

Risperidone is a strong dopamine D₂ and serotonin 5HT-2A antagonist with low affinity for alpha-1 and alpha-2 adrenergic receptors and histamine H₁ receptors.⁴ Antagonism of these receptors is thought to explain the drug's therapeutic effects and many of its side effects, including hyperprolactinemia.⁵ Prolactin release is

also influenced by thyrotropin-releasing hormone.⁶ A rare association between pituitary tumors and atypical antipsychotics has been proposed as a probable cause of sustained prolactin elevation.⁷

Pituitary prolactin secretion is regulated by neuroendocrine neurons in the hypothalamus, specifically in the tuberoinfundibular tract that extends from the arcuate nucleus of the mediobasal hypothalamus (tuberal region) and projects to the median eminence (infundibular region). Neurosecretory dopamine neurons of the arcuate nucleus inhibit prolactin secretion. Hence, prolactin secretion increases when antipsychotic therapy results in dopamine receptor blockade.

Antipsychotics vary in affinity for the D₂ dopamine receptor, rate of dissociation from the receptor, and ability to act on the receptor as both a dopamine agonist (which lowers serum prolactin) and a dopamine antagonist (which increases serum prolactin). Based on adult and pediatric data, the relative potency of antipsychotic drugs in inducing hyperprolactinemia is roughly risperidone > haloperidol > olanzapine > ziprasidone > quetiapine > clozapine > aripiprazole.⁸ Even though



Prolactin

Clinical Point

The prolactin level that triggers gonadal hypofunction appears to vary substantially among individual patients

Table 3

Sample age- and sex-specific reference ranges for serum prolactin (ng/mL)*

Age	Males	Females
0 to 1 month	3.7 to 81.2	0.3 to 95.0
1 to 12 months	0.3 to 28.9	0.2 to 29.9
1 to 3 years	2.3 to 13.2	1.0 to 17.0
4 to 6 years	0.8 to 16.9	1.6 to 13.1
7 to 9 years	1.9 to 11.6	0.3 to 12.9
10 to 12 years	0.9 to 12.9	1.9 to 9.6
13 to 15 years	1.6 to 16.6	3.0 to 14.4
Adult	2.1 to 17.7	2.8 to 29.2
Female: nonpregnant		2.8 to 29.2
Female: pregnant		9.7 to 208.5
Postmenopausal		1.8 to 20.3

* Reference values may vary from lab to lab
Source: LabCorp, Birmingham, AL

risperidone ranks highest in the hierarchy to cause hyperprolactinemia, it is accepted as the first-line antipsychotic in children and adolescents. This is probably because risperidone:

- has been in clinical use longer than other atypical antipsychotics except clozapine
- has received FDA approval for 3 pediatric indications.

Prolactin and the HPG axis

Elevated serum prolactin inhibits the hypothalamus' pulsatile release of gonadotrophin-releasing hormone (GnRH), which in turn decreases the pituitary's secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). In women, prolactin also blocks the feedback effect of estradiol on LH secretion (*Figure, page 71*). The prolactin level that triggers gonadal hypofunction appears to vary substantially among individuals.⁹

Symptoms of elevated prolactin can occur as a direct result of prolactin's physiologic effect on breast tissue or indirectly through hypogonadism related to decreased FSH and LH. Symptoms of hyperprolac-

tinemia—which can be seen more readily in sexually mature adolescents than in children—include:

- amenorrhea or oligorrhea
- breast enlargement or engorgement in females and males
- galactorrhea (females > males)
- decreased libido
- erectile dysfunction.

Although evidence is inconclusive, other problems may be associated with increased prolactin in children and adolescents. These include failure to enter or progress through puberty,⁸ increased risk of benign breast tumors,²² and reduced bone density.¹⁰

Bone changes. Decreased estrogen related to hyperprolactinemia may inhibit bone mineralization, causing osteopenia, osteoporosis, and increased fracture risk.¹⁰ The mechanism of bone density loss may be estrogen's osteoclast activating and osteoblast inhibiting action. The level and duration of prolactin elevation that can hamper bone growth has not been defined, although evidence suggests a pervasive effect:

- 65% of a group of 38 premenstrual patients developed osteoporosis or osteopenia when taking risperidone or typical antipsychotics for schizophrenia for a mean of 8 years.¹¹

- Bone loss has persisted 2 years after prolactin normalized in adolescents with prolactinomas.¹²

Hyperprolactinemia in children and adolescents

We suggest that children and adolescents receiving prolonged risperidone treatment can present with symptoms similar to those associated with hyperprolactinemia secondary to other causes, including:

- prolactinomas (the most common cause)¹³
- thyrotropin-releasing hormone stimulation in primary hypothyroidism
- hypoglycemia
- inherited endocrine syndromes
- physiologic stress
- medications.

The most common presenting symptoms of prolactinomas are headache, amenorrhea, and galactorrhea. A few patients have delayed puberty.¹³ In a review of hyperprolactinemia in children, Massart and Saggese¹⁴ proposed a correlation between elevated serum prolactin and underlying pathology:

- >100 ng/mL usually suggests organic pathology and requires MRI or CT confirmation
- <100 ng/mL usually indicates functional pathology.

What the evidence says. Using the key words “risperidone and hyperprolactinemia in children and adolescents” in a PubMed search, we identified 7 prospective, cross-sectional, and retrospective studies.¹⁴⁻²⁰ We then analyzed these studies in terms of subjects’ age, sex, primary psychiatric disorder, dosage of risperidone used, prolactin elevation pattern, reported clinical consequences, and interventions used to ameliorate asymptomatic or symptomatic hyperprolactinemia.

Prolactin and antipsychotics. In a cross-sectional study, Staller¹⁵ compared serum prolactin at baseline and after 6 months in 50 children treated with atypical antipsychotics. Patients taking risperidone showed greater increases in prolactin than those taking quetiapine or olanzapine. Saito et

al¹⁶ reached a similar conclusion in a prospective study of 40 children treated with atypical antipsychotics for 4 to 15 weeks.

Ups and downs. Prolactin levels increase sharply in the first weeks of risperidone treatment, peak at around 6 to 8 weeks, and then trend downward toward normal.¹⁷ In a post hoc analysis of pooled data from 5 clinical trials totaling 700 patients age 5 to 15, Findling et al¹⁷ reported that mean serum prolactin:

- peaked in the first 1 to 2 months of patients’ starting risperidone, 0.02 to 0.06 mg/kg/d
- returned to within or close to normal range by 3 to 5 months.

No correlation was seen between prolactin elevation and side effects that could be attributed to prolactin.

In a 2-part study, Anderson et al¹⁸ examined the short- and long-term effects of risperidone treatment on prolactin in children age 5 to 17 with autism. In the initial double-blind, placebo-controlled trial, 101 children were randomly assigned to risperidone 1.8 mg/d, or placebo. After 8 weeks, 63 children continued with open-label risperidone, mean dose 1.96 mg/d, for up to a total 22 months. Serum prolactin was measured at baseline (9.3 ± 7.5 ng/mL) and then at 2, 6, and 22 months.

Serum prolactin increased sharply in children treated with risperidone in the placebo-controlled trial. After 8 weeks, prolactin levels were 4 times higher with risperidone treatment than with placebo (39.0 ± 19.2 ng/mL vs 10.1 ± 8.8 ng/mL [$P < 0.0001$]). In the open-label risperidone continuation trial, prolactin levels remained significantly higher than at baseline but decreased over time to:

- 32.4 ± 17.8 ng/mL in 43 children who remained in the study at 6 months ($P < 0.0001$)
- 25.3 ± 15.6 ng/mL in 30 children who remained at 22 months ($P < 0.0001$).

In this study, a sharp rise in serum prolactin in the first 2 months trended down to the upper limit of normal at 22 months. None of the children showed known clinical manifestations of elevated prolactin, including gynecomastia, galactorrhea, or menstrual disturbance.

Clinical Point

Prolactin levels peak at around 6 to 8 weeks of risperidone treatment, then trend downward toward normal



Prolactin

Clinical Point

In patients with mild or no symptoms, consider waiting 6 to 12 months for symptoms to resolve and elevated prolactin to diminish

A double-blind, placebo-controlled trial by Hellings et al¹⁸ examined risperidone's effect on aggression and self-injury in children, adolescents, and adults with mental retardation and pervasive developmental disorders. In a subset of 10 children and adolescents whose serum prolactin was measured during the trial, prolactin remained elevated during at least 26 weeks of risperidone treatment. Mean prolactin levels were:

- 13.2 ± 8.6 ng/mL at baseline
- 31.0 ± 11.6 ng/mL during acute risperidone therapy
- 37.9 ± 10.4 ng/mL during maintenance therapy.

Clinical features. Higher risperidone dosages—rather than longer duration of use—appear more likely to cause symptomatic elevated serum prolactin. A case series of 3 adolescents with symptomatic prolactin elevation showed:

- gynecomastia and galactorrhea in 2 adolescent males age 17 and 18, receiving risperidone, 4 mg/d and 5 mg/d, respectively
- amenorrhea within 2 to 6 weeks of starting treatment in a female patient age 15 receiving risperidone, 6 mg/d.²⁰

Holzer et al²¹ described 5 adolescents who showed symptoms of elevated prolactin after 3 to 15 months while taking risperidone, 2 to 6 mg/d, as treatment for psychosis.

Long-term health risks?

Some evidence suggests an association between elevated serum prolactin and carcinogenesis and infertility in adults. No studies have examined these long-term risks in children and adolescents who develop hyperprolactinemia from risperidone treatment. A link may be possible, however, if prolactin elevation affects postpubertal and HPG axis development.

Breast cancer. Halbriech et al²² reviewed mammograms and charts of 275 female psychiatric hospital patients age >40 and 928 women of similar age at a hospital radiology clinic. The incidence of breast cancer among psychiatric patients was:

- >3.5 times higher than among radiology clinic patients

- 9.5 times higher than in the general population.

The authors speculated that the observed increased breast cancer incidence in psychiatric patients could be associated with medications, although high rates of cigarette smoking and alcohol consumption also might have played a role.

A case-control study by Hankinson et al²³ of blood samples collected from women in the Nurses' Health Study found a statistically significant association between hyperprolactinemia and breast cancer. This analysis included 306 postmenopausal women diagnosed with breast cancer and 448 controls matched for age, postmenopausal hormone use, and time of day and month when blood samples were drawn.

Several putative mechanisms have been proposed to explain a possible role of prolactin in breast carcinoma. Breast tissue—whether normal or cancerous—expresses the prolactin receptor, but the density of prolactin receptors is higher in tumor tissue. In several mouse models, prolactin induces tumor formation and increases tumor growth rates.^{23,24}

Infertility. As noted, hyperprolactinemia can cause HPG axis dysfunction.⁹ A retrospective review by Sigman and Jarow²⁵ linked endocrine disorders with infertility in 10% of 1,035 consecutive men attending 2 infertility centers. Hyperprolactinemia accounted for infertility in 0.4% of that population. No studies have associated hyperprolactinemia with female infertility.

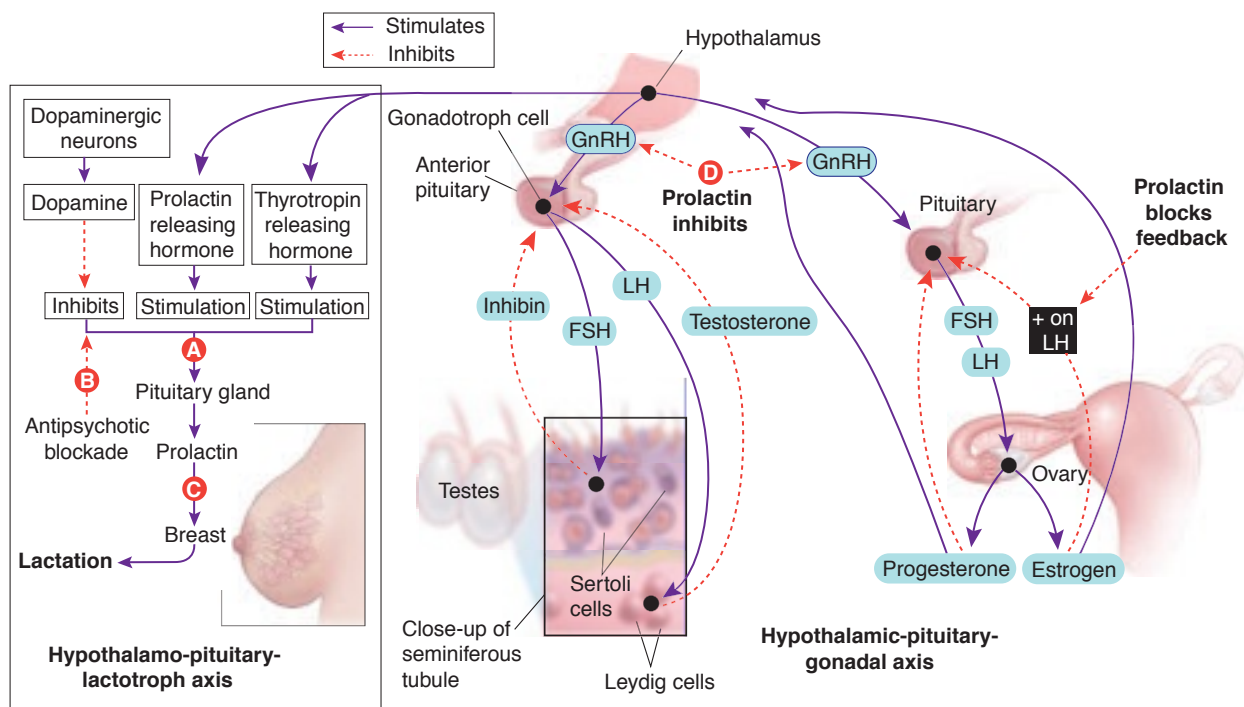
Targeting hyperprolactinemia

When prescribing risperidone, consider obtaining a baseline serum prolactin level, especially in sexually mature patients. Repeat after 2 months, and ask the patient about menstruation, nipple discharge, sexual functioning, and pubertal development. Sexual side effects may be difficult to ascertain in patients receiving antipsychotics because of psychiatric comorbidities in this population.

Elevation without symptoms. If serum prolactin is elevated after 2 months but

Figure

Mechanism by which increased prolactin might affect gonadal maturation



Prolactin secretion is controlled by stimulatory and inhibitory influences (A). Antipsychotic blockade of dopamine's inhibitory influence (B) increases serum prolactin and its effect on mammary tissue (C). In the brain, hyperprolactinemia inhibits the release of gonadotropin-releasing hormone (GnRH) by the hypothalamus, which results in decreased follicle-stimulating hormone (FSH) and luteinizing hormone (LH) secretion by the pituitary (D). FSH and LH are important determinants of male and female gonadal maturation by their direct action on testes and ovaries within the hypothalamic-pituitary-gonadal axis.

Source: Developed by Manpreet Khemka, MBBS, and Jeffrey Ali, MD, MSc. CURRENT PSYCHIATRY Illustration by Rob Flewell

the patient has no clinical symptoms, repeat evaluation after another 2 months without altering the risperidone dosage. As discussed, serum prolactin tends to decline and may normalize with continued antipsychotic therapy in adults and children. A reasonable approach may be to wait 6 to 12 months for symptoms to resolve and hyperprolactinemia to diminish in patients who benefit from risperidone and have no or mild prolactin-related symptoms.⁸

Elevation with symptoms. Intervene if serum prolactin is elevated and your patient has clinical symptoms of hyperprolactinemia. Consider gradually tapering risperidone over 2 weeks and switching to a prolactin-sparing antipsychotic such as aripiprazole. If serum prolactin is >200 ng/mL or is persistently elevated despite

switching to a prolactin-sparing antipsychotic, obtain an MRI of the sella turcica to look for a pituitary adenoma or parasellar tumor.

Use of dopamine agonists. Few studies have evaluated the safety and efficacy of using dopamine agonists such as cabergoline or amantadine to resolve the effects of hyperprolactinemia.^{26,27} Further research is warranted before this approach can be recommended.

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Prolactin

Clinical Point

If serum prolactin is >200 ng/mL or remains elevated despite switching antipsychotics, order an MRI to look for a pituitary adenoma

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Related Resources

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Drug Brand Names

Amantadine • Symmetrel	Olanzapine • Zyprexa
Aripiprazole • Abilify	Quetiapine • Seroquel
Cabergoline • Dostinex	Risperidone • Risperdal
Clozapine • Clozaril	Ziprasidone • Geodon
Haloperidol • Haldol	

Disclosure

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

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Bottom Line

Risperidone treatment, particularly at high dosages, can increase serum prolactin and affect the hypothalamic-pituitary-gonadal (HPG) axis. To reduce risks of HPG dysfunction and bone growth changes in children and adolescents, monitor prolactin when initiating risperidone. Prolactin levels and clinical symptoms guide decisions about maintaining risperidone or switching to a prolactin-sparing antipsychotic.

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