Current PSYCHIATRY

Minimizing the impact of elevated prolactin in children and adolescents

Early identification, treatment can help lessen impaired development, other sequelae

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Hyperprolactinemia—increased levels of prolactin (PRL) in the blood that may be caused by hypothyroidism, pituitary disorders, atypical antipsychotics, or other conditions and medications—has numerous physiologic manifestations, including amenorrhea, infertility, abnormal bone resorption, increased risk of breast cancer, and compromised immunity. Evaluation of hyperprolactinemia in patients taking psychotropics—particularly children and adolescents, in whom hyperprolactinemia's adverse effects may be more pronounced—should include an examination for signs and symptoms of hyperprolactinemia and assessment to rule out other potential causes. This article reviews hyperprolactinemia's causes, symptoms, evaluation, and treatment, with an emphasis on younger patients.

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Causes of hyperprolactinemia

PRL is a circulating autocrine or paracrine factor (***Box 1, page 48***).[1,2] Its primary biologic activities can be broadly divided into 4 areas: reproductive, metabolic, osmoregulatory, and immunoregulatory (***Box 2, page 49***).[1,3-8]

Hyperprolactinemia has numerous physiologic and iatrogenic causes (***Table 1, page 50***).[9] Substantially increased serum PRL levels may be seen with:

- prolactinomas, which usually present as incidental findings on a brain CT or MRI or with symptoms of tumor mass
- a craniopharyngioma or other tumor that compresses the pituitary stalk or hypothalamus and in-

Prolactin elevation

Clinical Point

Atypical antipsychotics cause less elevation in prolactin levels than conventional antipsychotics

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Box 1

What controls production of prolactin?

Prolactin (PRL) is a lactogenic polypeptide hormone with a structure that resembles human growth hormone and human placental lactogen. A single gene on chromosome 6 encodes PRL, which is composed of 199 amino acids.[1]

PRL is produced primarily by lactotroph cells in the anterior pituitary gland, but also is produced and is active in breast tissue and mammary glands, placenta and decidua, bone marrow cells, lymphocytes (T cells and B cells), and other tissues. It has >300 biologic activities.[1]

PRL acts primarily through receptors that belong to the large class-1 cytokine receptor superfamily. PRL receptors have multiple isoforms in many different tissues.

Like most anterior pituitary hormones, PRL is under dual regulation by hypothalamic hormones delivered via the hypothalamic-pituitary portal circulation. Its production is stimulated and inhibited by several molecular factors. Under most conditions the predominant signal for PRL secretion from the pituitary is under inhibitory control. This is primarily mediated by the neurotransmitter dopamine, which is a tonic inhibitor of PRL expression and thus prevents its release. Other inhibitors of PRL are triiodothyronine (T3) and somatostatin.[2] Molecular stimulators of PRL production include thyrotropin-releasing factor, vasoactive intestinal peptide, peptide histidine isoleucine, gonadotropin-releasing hormone, and estrogen. These 5 molecular stimulators all enhance the growth of PRL-producing cells.[1] The balance between these stimulatory and inhibitory signals determines the amount of PRL released from the anterior pituitary.

terrupts the hypothalamic-dopaminergic inhibition of PRL release.[10]

Primary thyroid failure (hypothyroidism) can produce a compensatory increase in the discharge of central hypothalamic thyrotropin-releasing hormone, resulting in increased stimulation of PRL secretion.[10]

Medications can increase serum PRL (***Table 2, page 54***)[9] and cause clinical symptoms similar to those of physiologically induced hyperprolactinemia.

Conventional antipsychotics. The antipsychotic potency of phenothiazines, thioxanthenes, butyrophenones, and dibenzoxazepines generally parallels their potency in increasing PRL levels.[9] Although a dose-response relationship between PRL concentrations and conventional antipsychotics is likely, immediate and pronounced increases in PRL can occur even with low doses.

Prospective studies have shown that 3 to 9 weeks of treatment with an antipsychotic such as chlorpromazine increased mean baseline PRL levels up to 10-fold, even at therapeutic doses.[11] Conventional antipsychotics can cause marked increases in PRL, probably by blocking dopamine receptors in the tuberoinfundibular tract.[12] The blockage of D2 receptors removes the main inhibitory influence on PRL secretion and is associated with increased PRL release.[12]

Atypical antipsychotics cause less elevation in PRL levels than conventional antipsychotics. This may be because of their:

- highly selective mesolimbic and mesocortical dopamine receptor antagonism, which spares dopamine blockade within the tuberoinfundibular tract
- relatively lower D2 receptor affinity.[11]

Risperidone and its active metabolite paliperidone (9-hydroxyrisperidone) have a high affinity for D2 receptors and thus have potent D2 antagonistic effects.[12,13] At dosages of 8 mg/d to 11.8 mg/d, risperidone and paliperidone are associated with the greatest increase in PRL levels among atypical antipsychotics.[14]

The rate of risperidone metabolism depends on the patient's cytochrome P (CYP) 2D6 liver enzyme genotype. "Extensive" CYP2D6 metabolizers convert risperidone rapidly into 9-hydroxyrisperidone, whereas "poor" CYP2D6 metabolizers convert it much more slowly. Six percent to 8% of white individuals and a very low percentage of Asians have little or no CYP2D6 activity and are "poor metabolizers." CYP2D6 also is inhibited by various substrates and nonsubstrates, notably quinidine. Although extensive metabo-

Box 2

Prolactin: A versatile hormone with many roles

Prolactin (PRL) is best known for its regulatory role in reproductive processes. It inhibits secretion of the pituitary hormones (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]), which are responsible for gonadal function. PRL also influences normal breast development, lactation following childbirth, and corpus luteum development. It plays a critical role in inducing and maintaining mammary epithelial cell growth and differentiation.[1]

A recently observed correlation between elevated plasma PRL and breast cancer development suggests a mitogenic action in breast tissue. A prospective, case-control study of 851 women from the Nurses' Health Study cohort found a "modestly" increased relative risk of postmenopausal breast cancer associated with PRL plasma concentrations (1.34; 95% confidence interval, 1.02 to 1.76).[3]

PRL also acts as a physiologic sensor during lactation. It regulates ductal side branching and directly controls lobuloalveolar development and lactogenesis (synthesis of milk) in breast tissue. PRL is stimulated by suckling; it responds to demands for milk production by partitioning nutrients such as calcium away from adipose tissue and into the mammary glands.[1,4]

In reproduction, PRL can have a luteotropic or luteolytic action, depending on the stage of the reproductive cycle. It negatively modulates LH and FSH secretion by suppressing gonadotropin-releasing hormone and as a result suppresses ovulation during lactation.[3] PRL also maintains luteal vascularization in early pregnancy.[1]

PRL also has a role in bone development and bone mass maintenance. It has a direct inhibitory effect on osteoblast function, possibly through an effect on estrogen.[5] Although the mechanism is unclear, sustained plasma PRL elevation decreases bone formation, leading to reduced bone mineral density and increased risk of hip fracture.[6]

PRL is a stimulatory modulator of immune function and may be a "stress hormone." It is widely produced by lymphocytes. PRL and its receptors are expressed on diverse bone marrow-derived human cell types, including B cells, T cells, monocytes, natural killer cells, and cluster of differentiation 34 (CD34) human stem cells.[7] The widespread expression of PRL receptors on hematopoietic and immune cells implies a role in immunohematopoietic system development.

Other functions of PRL include regulation of pancreatic islets growth and function during the perinatal period; osmoregulation in mammary glands, amniotic membranes, and the intestinal epithelial membrane; and maintenance of positive calcium deposition.[1] As a potent platelet aggregation co-activator, prolactin also may be a risk factor for both arterial and venous thrombosis.[8]

Clinical Point

Prolactin elevation is greater in children than adults in part because of increased density of D2 receptors in developing striatum

lizers have lower risperidone and higher 9-hydroxyrisperidone concentrations than poor metabolizers, the pharmacokinetics of the active moiety after single and multiple doses are similar in extensive and poor metabolizers.[15]

Clozapine, olanzapine, quetiapine, ziprasidone, and aripiprazole are associated with a much lower risk of PRL elevation than risperidone. In an 8-week open-label trial, aripiprazole (mean dose 9.4 ± 4.2 mg/d), did not increase serum PRL in 15 children and adolescents.[2]

Ziprasidone may cause only transient PRL elevation.[16] PRL abnormalities may be least likely with clozapine and quetiapine, possibly because of their relatively lower D2 receptor affinity. Amenorrhea, galactorrhea, or inhibition of ejaculation have not been reported with the use of these 2 antipsychotics.[16] Patients who developed hyperprolactinemia on conventional antipsychotics have been treated subsequently with clozapine without hyperprolactinemia recurrence.[16] Iloperidone has been associated with decreased PRL levels.[17]

Antidepressants that work by blocking catecholamine reuptake also cause hyperprolactinemia. This increase may be related to the antidopaminergic, stimulatory effects of estrogen. Numerous cases of galactorrhea and amenorrhea have been reported with the use of selective serotonin reuptake inhibitors (SSRIs).[16] Galactorrhea has been reported in women who took venlafaxine.[12] Less is known about the effects of nefazodone or bupropion on serum PRL. Mirtazapine can decrease serum PRL in men, probably through indirect 5-HT1 agonist and 5-HT2 and 5-HT3 antagonist activity.[16]

PRL elevation is greater in children and adolescents than adults because of increased density of D2 receptors in the

Prolactin elevation

Clinical Point

Hyperprolactinemia may lead to delayed puberty, amenorrhea, short stature, infertility, and osteopenia or osteoporosis

Table 1

Causes of hyperprolactinemia

Iatrogenic causes
Conventional antipsychotics (phenothiazines, thioxanthenes, butyrophenones, dibenzoxazepines)
Atypical antipsychotics (risperidone, olanzapine, ziprasidone, clozapine, quetiapine, aripiprazole, paliperidone)
SSRIs (fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram)
Antiretroviral agents (ritonavir, indinavir, zidovudine)
Gastrointestinal agents (omeprazole, ranitidine, cimetidine, famotidine)
Other medications (oral contraceptives, verapamil, methyldopa, reserpine, triptorelin, bendroflumethiazide)
Other causes
Tumors (prolactinoma, craniopharyngioma, other cerebral tumor)
Ectopic prolactin synthesis (bronchial carcinoma, acromegaly, empty sella syndrome, polycystic ovarian syndrome)
Chronic renal failure
Primary thyroid failure
Physiological causes (pregnancy, lactation, stress, sleep, sexual intercourse, head injury, surgery)

SSRIs: selective serotonin reuptake inhibitors

Source: Reference 9

developing striatum and differential D2 receptor sensitivity in the tuberoinfundibular tract.[16] Unfortunately, few studies have examined the consequences of elevated PRL in children and adolescents.

Clinical features

Adenomas. Primary hyperprolactinemia related to excessive secretion from the pituitary and other tissues causes multiple clinical effects, including:

- amenorrhea, oligomenorrhea, anovulatory cycles, galactorrhea, breast pain, breast enlargement, infertility, hirsutism, and loss of libido in females
- impotence, loss of libido, decrease in seminal fluid volume, galactorrhea, and gynecomastia in males.[12]

Preclinical studies of risperidone suggested an association with pituitary adenomas in female mice.[18] To determine if there was a similar association in humans, Szarfman et al[18] retrospectively evaluated data on 7 antipsychotics—aripiprazole, clozapine, olanzapine, quetiapine, risperidone, ziprasidone, and haloperidol—and found 77 pituitary tumors associated with use of these medications. Risperidone was associated with 54 of the pituitary tumors—including 3 in adolescents age 14 to 16. No pituitary tumors were reported with aripiprazole. Approximately one-half of the pituitary tumors were benign. Symptoms included visual field defects, headaches, pituitary hemorrhage, convulsions, and coma.

Other adverse effects reported in the study were hyperprolactinemia, galactorrhea, amenorrhea, and gynecomastia. The incidence of adverse effects with risperidone was >10-fold higher than with haloperidol or olanzapine and >25-fold higher than with clozapine, ziprasidone, quetiapine, and aripiprazole.

Hyperprolactinemia secondary to macroadenoma or microadenoma in children and adolescents is rare and difficult to diagnose because typically it is suspected only when symptoms of tumor expansion occur. The usual initial symptoms of microadenomas are menstrual disturbances and galactorrhea in girls and galactorrhea and gynecomastia in boys.[19]

Decreased bone mass. Long-term hyperprolactinemia may lead to delayed puberty, primary amenorrhea, short stature, infertility, and osteopenia and/or osteoporosis due to decreased bone mass density (BMD).[16] The risk of osteoporosis and/or osteopenia is directly related to the duration of hyperprolactinemia. A serum PRL level twice the upper limit of normal can result in osteopenia.

Breast cancer risk may be increased in hyperprolactinemia because of the effects of PRL on breast tissue and mammary gland development. A study of premenopausal (n = 235) and postmenopausal women (n = 851) reported a positive correlation between elevated PRL levels and breast cancer risk.[3] "Crosstalk" between PRL and estradiol in activating AP-1 activity may promote

continued on page 54

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Prolactin elevation

Clinical Point

The degree of change in serum prolactin levels over time may be more important than absolute prolactin level

Table 2

Relative risk of hyperprolactinemia with common psychotropics

Medication	Effect on prolactin serum levels
Antipsychotics	
Phenothiazines	++
Butyrophenones	++
Thioxanthenes	++
Risperidone	++
Quetiapine	+
Olanzapine	+
Clozapine	0
Ziprasidone	0
Aripiprazole	0
SSRIs	
Paroxetine	+/-
Citalopram	+/-
Fluvoxamine	+/-
Fluoxetine	CR

0: no hyperprolactinemia effect; +/-: increased but not to abnormal levels; +: increased to abnormal in small percentage of patients; ++: increased to abnormal in >50% of patients; CR: isolated case reports of hyperprolactinemia but generally no increase to abnormal

SSRIs: selective serotonin reuptake inhibitors

Source: Adapted from reference 9

carcinogenesis. Furthermore, tamoxifen, a common treatment for breast cancer, lowers PRL concentrations.[3]

Not all patients with hyperprolactinemia develop problems. Whether hyperprolactinemia secondary to antipsychotic treatment adversely affects bone density or sexual maturation is unknown. Furthermore, sexual side effects—such as a decrease or loss of libido, erectile dysfunction, impotence, and ejaculatory or orgasmic difficulties—do not show a strong correlation with PRL levels.[11]

Effects of hyperprolactinemia may be more pronounced in adolescents because PRL synthesis and release are stimulated by estrogen. In adolescent females elevated estrogen levels can be related to:

- increased estrogen levels in menstruating females
- increased estrogen levels in females taking oral contraceptives.[16]

Therefore, adolescent females taking antipsychotics are at high risk for increased PRL levels and resultant effects. For example, the BMD of adolescent girls with 6 months of hypothalamic-pituitary-gonadal (HPG) axis dysfunction caused by hyperprolactinemia was reduced by 2 standard deviations (SDs) below the population mean.[16] A BMD 1 SD below the mean age-population value may double the risk for fractures.[16] Unfortunately, there are no studies that measure estrogen levels or BMDs of children taking psychotropics[16] or that assess PRL in pubertal girls taking atypical antipsychotics or SSRIs.

Evaluation of hyperprolactinemia

Blood samples to measure PRL levels must be collected under standardized conditions. A morning fasting serum PRL level should be obtained between 8 AM and 10 AM (3 hours after waking up). It is best to avoid emotional stress or strenuous exercise for at least 30 minutes before the blood draw because these conditions can raise PRL. Avoid nipple stimulation for 24 hours before testing because this also can raise PRL levels. A woman having abnormal nipple discharge should not do anything to cause more discharge before the test. Serum PRL levels should be monitored every 6 months in pubertal girls taking psychotropics until they experience sexual maturity or regular menstrual cycles so that abnormalities can be identified early and irreversible BMD loss is minimized.[16]

Absolute PRL level is not useful in guiding treatment because it is not consistently correlated with adverse effects. However, the degree of change of serum PRL levels over time or the change of PRL levels from baseline may be important in diagnosing asymptomatic hyperprolactinemia.[16] Suspect pathologic hyperprolactinemia in patients (except newborns and pregnant women) with plasma PRL levels consistently >15 to 25 ng/mL.[12] This finding occurs in <1% of the population, but the rate is higher among individuals with specific symptoms attributable to hyperprolactinemia. For example, 9% of women with amenorrhea, 25% of women with galactorrhea, and 70% of women with both amenorrhea and

Table 3

Presenting symptoms of hyperprolactinemia

Adult females	Adult males	Prepubertal children (male and female)
Amenorrhea	Decreased in seminal fluid volume	Delayed puberty
Anovulatory cycle	Galactorrhea	Galactorrhea
Breast enlargement	Gynecomastia	Gynecomastia
Breast pain	Impotence	Osteopenia or osteoporosis
Galactorrhea	Loss of libido	Primary amenorrhea (females only)
Hirsutism		Short stature
Infertility		
Loss of libido		
Oligomenorrhea		

Source: Adapted from reference 12

galactorrhea have hyperprolactinemia. The prevalence is approximately 5% among men with impotence or infertility.[10]

If hyperprolactinemia is detected, the degree of PRL elevation can help determine etiology. In the absence of pregnancy and breast-feeding, a serum PRL level of >600 ng/mL is highly suggestive of a macroprolactinoma.[12] PRL concentrations >250 ng/mL suggest a microprolactinoma or a nonfunctioning adenoma.[12] Antipsychotics usually produce moderate PRL elevation (up to 6 times the upper limit of the reference range of 100 ng/mL).[12] In 1 study, the median time to onset of galactorrhea was 20 days after initiating antipsychotics in female patients.[12] Hyperprolactinemia-induced HPG axis dysfunction causes delayed pubertal development or loss of bone mineral deposit.[16] Measuring BMD in

Clinical Point

In pubertal girls taking agents that modulate prolactin, consider monitoring prolactin levels every 6 months until patients achieve sexual maturity

Prolactin elevation

Clinical Point

If reducing the antipsychotic dosage fails to reduce hyperprolactinemia, consider switching to a low-potency D2 agent or aripiprazole

Related Resource

- Ali J, Khemka M. Hyperprolactinemia: Monitoring children on long-term risperidone. Current Psychiatry. 2008;7(11):64-72.

Drug Brand Names

Amantadine • Symmetrel
Aripiprazole • Abilify
Bendroflumethiazide • Naturetin
Bromocriptine • Parlodel
Bupropion • Wellbutrin
Cabergoline • Dostinex
Chlorpromazine • Thorazine
Cimetidine • Tagamet
Citalopram • Celexa
Clozapine • Clozaril
Famotidine • Pepcid
Fluoxetine • Prozac
Fluvoxamine • Luvox
Haloperidol • Haldol
Iloperidone • Fanapt
Indinavir • Crixivan
Methyldopa • Aldomet
Mirtazapine • Remeron
Nefazodone • Serzone
Olanzapine • Zyprexa
Omeprazole • Prilosec
Paliperidone • Invega
Paroxetine • Paxil
Quetiapine • Seroquel
Quinidine • Quinidex
Ranitidine • Zantac
Reserpine • Serpasil
Risperidone • Risperdal
Ritonavir • Norvir
Sertraline • Zoloft
Tamoxifen • Nolvadex
Triptorelin • Trelstar
Venlafaxine • Effexor
Verapamil • Calan, Isoptin
Zidovudine • Retrovir
Ziprasidone • Geodon

Disclosure

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

Acknowledgment

The authors wish to thank Yunyoung C. Chang, BS, for her assistance with this article.

children and adolescents with hyperprolactinemia is important during this critical time of skeletal development.[16]

Managing hyperprolactinemia

Before starting any antipsychotic, inform patients and families of possible side effects, including hyperprolactinemia. Educate them about recognizing the signs and symptoms of hyperprolactinemia (***Table 3, page 55***).[12] Although PRL blood levels typically are not routinely measured in pubertal girls who take PRL-modulating agents, consider monitoring serum PRL levels every 6 months until patients achieve sexual maturity and menstrual cycle regularity.[16]

If laboratory testing detects elevated PRL levels in a child or adolescent, determine if the patient had sexual intercourse, nipple stimulation, stress (including venipuncture), sleep disturbances, seizures, head injury, or surgery before the blood sample was obtained. This information will help to determine if the PRL elevation is caused by one of these factors.

To treat hyperprolactinemia, address the underlying medical cause(s). If patients using antipsychotics have signs and symptoms of hyperprolactinemia, consider discontinuing the drug or reducing the dosage.[11] If dose change fails to reduce hyperprolactinemia, consider a switch to a low-potency D2 agent or aripiprazole. Shim et al[20] studied the effects of adjunctive treatment with aripiprazole on hyperprolactinemia and psychopathology in schizophrenia patients maintained on haloperidol. In this study, aripiprazole reversed hyperprolactinemia in both sexes but plasma levels of haloperidol were not significantly altered. The authors hypothesized that decreased PRL levels may have been the result of pharmacodynamic interaction at dopamine receptors rather than pharmacokinetic interaction between aripiprazole and haloperidol. Additional studies are needed to confirm these findings.

If a medication switch is contraindicated, pharmacologic treatment for hyperprolactinemia may be required.[11] Bromocriptine, cabergoline, and amantadine have been used to treat hyperprolactinemia.[11] Bromocriptine lowers PRL levels and restores normal gonadal function for men and women with hyperprolactinemia regardless of etiology, but may worsen psychiatric symptoms and can cause nausea, headaches, dizziness, and orthostatic hypotension.[11] In a pilot study, amantadine, 300 mg/d, used to treat neuroleptic-induced extrapyramidal effects also decreased PRL levels and reduced galactorrhea.[11]

Osteoporosis can be minimized by exercising, taking adequate calcium and vitamin D, and avoiding caffeinated drinks.[9] Simmons et al[21] found bisphosphonate treatment in children and adolescents improved bone density and fragility within 2 to 4 years. Unfortunately, information about optimal duration and long-term effects of bisphosphonate therapy is limited.[22]

Surgical treatment may be necessary to remove a pituitary tumor that causes hyperprolactinemia. For some patients, referral to pediatric endocrinologist for further treatment may be needed.

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Clinical Point

Bromocriptine, cabergoline, and amantadine have been used to treat hyperprolactinemia

Bottom Line

Hypothyroidism, pituitary disorder, antipsychotics, and other conditions and medications can cause hyperprolactinemia, which can substantially effect growth and development in children and adolescents. Treatment should focus on addressing underlying medical causes and/or medication reduction or discontinuation.