

## Management of hyperprolactinemia

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**INTRODUCTION** — Lactotroph adenomas (prolactinomas) are more amenable to pharmacologic treatment than any other kind of pituitary adenoma because of the availability of dopamine agonists, which usually decrease both the secretion and size of these tumors. For the minority of lactotroph adenomas that do not respond to dopamine agonists, other treatments must be used. Hyperprolactinemia due to nonadenoma causes should also be treated if it causes hypogonadism.

This topic will review the major issues concerning the therapy of hyperprolactinemia due to lactotroph adenomas and other causes, with the exception of treatment during pregnancy, which is discussed separately. The causes, clinical manifestations, and diagnosis of hyperprolactinemia are also discussed elsewhere. (See "[Management of lactotroph adenoma \(prolactinoma\) during pregnancy](#)" and "[Causes of hyperprolactinemia](#)" and "[Clinical manifestations and evaluation of hyperprolactinemia](#)".)

**INDICATIONS FOR TREATMENT** — There are two principal reasons why patients with hyperprolactinemia may need to be treated: existing or impending neurologic symptoms due to the large size of a lactotroph adenoma, and hypogonadism or other symptoms due to hyperprolactinemia, such as galactorrhea [1,2].

A third indication is in women with mild hyperprolactinemia and normal cycles who are trying to conceive as they may have subtle luteal phase dysfunction (see "[Clinical manifestations and evaluation of hyperprolactinemia](#)", section on '[Menstrual cycle dysfunction](#)'). Our approach to management is similar to that suggested by the Endocrine Society Guidelines [2].

**Adenoma size** — A lactotroph adenoma (prolactinoma) 1 cm or more in size is a macroadenoma. Treatment is usually essential when the tumor is large enough to cause neurologic symptoms, such as visual impairment or headache (see "[Causes, presentation, and evaluation of sellar masses](#)", section on '[Clinical manifestations](#)'). Treatment is usually desirable when the adenoma extends outside of the sella and abuts or elevates the optic chiasm, or invades the cavernous or sphenoid sinuses or the clivus; lesions of this size are likely to continue to grow and eventually cause neurologic symptoms.

Microadenomas are less than 1 cm in diameter. Studies of the natural history of microadenomas show that 95 percent do not enlarge during four to six years of observation [3,4]. The 5 percent that do enlarge should be treated because of the increase in size alone. (See ['Withdrawal of dopamine agonists'](#) below.)

Prolactin secretion by lactotroph adenomas is usually proportional to their size. Adenomas <1 cm in diameter are typically associated with serum prolactin values below 200 ng/mL (8.7 nmol/L), those approximately 1.0 to 2.0 cm in diameter with values between 200 and 1000 ng/mL (8.7 to 43.48 nmol/L), and those greater than 2.0 cm in diameter with values above 1000 ng/mL (43.48 nmol/L) and as high as 50,000 ng/mL (2173.91 nmol/L) ([figure 1](#)). There are exceptions to this generalization, however, as occasional patients have a large lactotroph adenoma but only modest hyperprolactinemia. Such adenomas are generally less well differentiated and respond less well to dopamine agonists than the more typical tumors.

In contrast to the extremely high serum prolactin concentrations that may be seen with lactotroph adenomas (in particular, macroadenomas), prolactin levels due to nonadenoma causes rarely exceed 200 ng/mL (8.7 nmol/L). (See ["Clinical manifestations and evaluation of hyperprolactinemia"](#), section on 'Serum prolactin concentrations'.)

**Symptoms** — Treatment of hyperprolactinemia is indicated when it causes hypogonadism by suppressing gonadotropin secretion or when it causes bothersome galactorrhea [1]. The clinical manifestations of hyperprolactinemia are reviewed in detail separately. (See ["Clinical manifestations and evaluation of hyperprolactinemia"](#).)

- In premenopausal women, serum prolactin concentrations >100 ng/mL (4.35 nmol/L) are likely to be associated with amenorrhea and low [estradiol](#) levels (which lead to eventual bone loss and osteoporosis if untreated). The symptoms correlate with the magnitude of the hyperprolactinemia. Moderate degrees of hyperprolactinemia (eg, serum prolactin values of 50 to 100 ng/mL [2.17 to 4.35 nmol/L]) cause either amenorrhea or oligomenorrhea, while women with milder degrees of hyperprolactinemia (20 to 50 ng/mL [0.87 to 2.17 nmol/L]) may have normal menstrual cycles or oligomenorrhea but infertility due to insufficient luteal phase [progesterone](#) secretion.
- Hyperprolactinemia in premenopausal women can also cause galactorrhea. The presence of galactorrhea alone does not require treatment unless the patient finds it bothersome.
- Postmenopausal women have markedly low [estradiol](#) levels, and galactorrhea is rare. Hyperprolactinemia in these women is clinically recognized only in the unusual situation when a lactotroph adenoma becomes so large as to cause headaches or impair vision.
- In men, hypogonadism can cause decreased libido and energy and eventually loss of sexual hair, loss of muscle mass, and osteoporosis. Hyperprolactinemia in men

may also be associated with erectile dysfunction, even when the serum testosterone concentration is normal. The mechanism is unknown, but the erectile dysfunction usually improves dramatically when the hyperprolactinemia is corrected [5-7]. Gynecomastia and galactorrhea may occur, but both are rare.

**OVERVIEW OF DOPAMINE AGONISTS** — A dopamine agonist drug should usually be the first treatment for patients with hyperprolactinemia of any cause, including lactotroph adenomas (prolactinomas) of all sizes, because these drugs decrease serum prolactin concentrations and decrease the size of most lactotroph adenomas [8,9]. Other approaches must be considered for the minority of patients whose adenomas are resistant to dopamine agonists or who cannot tolerate these drugs, and for those who are taking a medication (such as an antipsychotic drug) that cannot be discontinued. (See '[Intolerant or inadequate response](#)' below and '[Drug-induced hyperprolactinemia](#)' below.)

For most patients with hyperprolactinemia, [cabergoline](#) is our first choice of drug, and [bromocriptine](#) is our second choice. Pergolide had been used for Parkinson disease and hyperprolactinemia, but it was withdrawn from the market in the United States because of concerns about valvular heart disease. [Quinagolide](#) is available in some countries, but not the United States. (See '[Valvular heart disease](#)' below.)

- [Cabergoline](#) – As noted, when starting dopamine agonist therapy, we suggest cabergoline as our first choice among the available options because of its efficacy and favorable side-effect profile [2]. It is an ergot dopamine agonist that is administered once or twice a week and has much less tendency to cause nausea than [bromocriptine](#) [10,11]. It may also be effective in patients resistant to bromocriptine [12]. At the high doses used for the treatment of Parkinson disease, cabergoline is associated with an increased risk of valvular heart disease [13,14], but at the lower doses generally used for the treatment of hyperprolactinemia, cabergoline does not appear to be associated with this risk. (See '[Valvular heart disease](#)' below and '[Pharmacologic treatment of Parkinson disease](#)', section on '[Valvular heart disease](#)'.)

- [Bromocriptine](#) – Bromocriptine is an ergot derivative that has been used for approximately three decades for treatment of hyperprolactinemia. It should be given twice a day to have optimal therapeutic effect [8]. As noted, it is more likely to cause nausea than [cabergoline](#).

- **Pergolide** – Pergolide is also an ergot derivative and had been used primarily for the treatment of Parkinson disease [15]. At the high dose used for Parkinson disease (>3 mg/day), pergolide was associated with an increased risk of valvular heart disease [13,14]. In the United States, pergolide was voluntarily withdrawn from the market in March 2007 due to this risk [16]. Much lower doses were used for hyperprolactinemia. (See '[Pharmacologic treatment of Parkinson disease](#)', section on '[Valvular heart disease](#)' and '[Valvular heart disease](#)' below.)

●**Other** – [Quinagolide](#) (CV 205-502), a nonergot dopamine agonist that is given once or twice a day, is available in some countries but not the United States [17-19]. The starting dose is 0.075 mg once a day, which can be increased to twice a day and a maximum total daily dose of 0.9 mg. It is generally considered a second-line drug if [cabergoline](#) is available, but unlike cabergoline, it is not an ergot derivative so valvular heart disease is not a concern.

**Efficacy** — Dopamine agonists decrease prolactin secretion ([figure 2](#)) and reduce the size of the lactotroph adenoma ([image 1](#)) in more than 90 percent of patients. Both effects are mediated by the binding of the drug to cell-surface dopamine receptors, leading to reductions in the synthesis and secretion of prolactin and in adenoma cell size [20]. A review of 13 studies, as an example, showed that [bromocriptine](#) reduced the serum prolactin concentration to normal in 229 of 280 women (82 percent) with hyperprolactinemia, and in 12 studies, in 66 of 92 patients (71 percent) with lactotroph macroadenomas [8].

[Cabergoline](#) may be superior to [bromocriptine](#) in decreasing the serum prolactin concentration [10,12]. This was illustrated in a trial of 459 women with hyperprolactinemia and amenorrhea who had microadenomas or no obvious cause; the patients who were randomized to cabergoline were more likely to have a reduction of serum prolactin to normal (83 versus 52 percent in the bromocriptine group) ([figure 2](#)) [10]. In addition, a meta-analysis of three trials and six observational studies reported that cabergoline was more effective than bromocriptine in reducing the risk of persistent hyperprolactinemia, amenorrhea, and galactorrhea (relative risk [RR] 2.88, 1.85, and 3.41, respectively) [9].

Overall, the greater the decrease in serum prolactin concentration, the greater the decrease in adenoma size, although there is considerable variation from patient to patient. The effect on adenoma size is most apparent in patients with lactotroph macroadenomas ([image 1](#)) [21].

The therapeutic efficacy of dopamine agonists may be blunted by the concurrent use of drugs known to raise serum prolactin concentrations, including neuroleptic drugs, [metoclopramide](#), sulpiride, [domperidone](#), [methyldopa](#), [verapamil](#), and [cimetidine](#).

[Quinagolide](#) appears to have equivalent therapeutic effects to [cabergoline](#) in reducing serum prolactin and adenoma size [18,22]. It is available in some countries but not the United States.

**Time course of clinical response** — The fall in serum prolactin typically occurs within the first two to three weeks of therapy with a dopamine agonist ([figure 2](#)) [10]; in patients with macroadenomas, it always precedes any decrease in adenoma size [18]. The decrease in adenoma size can, in many patients, be detected by imaging within six weeks after initiation of treatment; in some patients, however, a decrease is not apparent for six

months ([image 1](#)) [21]. These benefits occur even in patients who have impaired visual fields before therapy, occurring in 9 of 10 such patients in each of two reports [23,24].

Following the decrease in serum prolactin and adenoma size in patients with macroadenomas, visual and pituitary function often return to normal. Vision usually begins to improve within days after the initiation of treatment [21,23]. There is recovery of menses and fertility in women and of testosterone secretion, sperm count, and erectile function in men [8,10,25-27]. Patients with macroadenomas who are hypothyroid and/or hypoadrenal may also have a return of these functions to normal [28].

**Adverse effects** — The principal side effects of dopamine agonist drugs are nausea, postural hypotension, and mental fogginess. Less common side effects include nasal stuffiness, depression, Raynaud phenomenon, alcohol intolerance, and constipation. Nausea appears to be more common with [bromocriptine](#) than [cabergoline](#).

Side effects are more likely to occur when treatment is initiated or the dose is increased. They can be avoided in most patients by starting with a small dose (eg, one-half of the lowest strength pill of [bromocriptine](#) once a day or half a pill of [cabergoline](#) twice a week) and by giving it with food or at bedtime. A small percentage of patients have side effects even at the lowest doses. In women, nausea can be avoided by intravaginal administration [29].

Cerebrospinal fluid (CSF) rhinorrhea may occur during dopamine agonist treatment for very large lactotroph adenomas that extend inferiorly and invade the floor of the sella [30,31]. Although uncommon, early recognition and neurosurgical evaluation of this complication is important because of the potential risk of bacterial meningitis.

**Valvular heart disease** — [Cabergoline](#) and pergolide have been associated with valvular heart disease in patients with Parkinson disease [13,14]. The association appears to be dose dependent, and the pergolide doses used for Parkinson disease were much higher than those used for hyperprolactinemia. In the United States, pergolide was voluntarily withdrawn from the market in March 2007 due to this risk [16]. (See "[Pharmacologic treatment of Parkinson disease](#)", [section on 'Valvular heart disease'](#).)

In contrast to the excess risk of cardiac valvulopathy associated with high-dose [cabergoline](#) use for Parkinson disease, most studies suggest that low-dose cabergoline for hyperprolactinemia is **not** associated with excess risk [32-41]. In one report of 50 patients with lactotroph adenoma treated with cabergoline, moderate tricuspid regurgitation was more frequent (54 percent) than in 50 age- and gender-matched subjects (18 percent) [34]. However, in a review of nine studies published through 2008, the majority did not demonstrate an increased risk of valvular regurgitation with cabergoline [32]. Most patients were using standard doses of cabergoline for hyperprolactinemia (0.5 to 1.5 mg/week). Additional reassuring data come from a prospective study of 40 patients with newly diagnosed hyperprolactinemia treated with a

median cumulative dose of 149 mg over five years [42]. Patients were evaluated by transthoracic echocardiography before initiating cabergoline and after 24 and 60 months of therapy; none of the patients developed significant valvulopathy.

Based upon the available data, we suggest using the lowest dose of [cabergoline](#) necessary to lower prolactin to normal. We also suggest ordering cardiac ultrasonography approximately every two years in patients who take larger than typical doses of cabergoline (eg, greater than 2 mg per week). There are no available data for cabergoline use in patients with preexisting valvular heart disease. However, for patients with a lactotroph adenoma and mild valvular heart disease, we feel it is reasonable to use cabergoline therapy since the doses used in this setting have not been associated with an increased risk of valvular heart disease.

Withdrawal of therapy is discussed below. (See '[Withdrawal of dopamine agonists](#)' below.)

## **MICROADENOMAS**

**Initial therapy (dopamine agonists)** — Given the high rate of efficacy and low rate of side effects with dopamine agonists, as well as the consequences of hypogonadism, we recommend that these agents be used in patients with lactotroph microadenomas who have any degree of hypogonadism. Decreasing the size of the pituitary adenoma is **not** a treatment goal in these patients.

- [Cabergoline](#) is the best initial choice in most circumstances because it is most likely to be effective and least likely to cause side effects. Our approach is consistent with the 2011 Endocrine Society hyperprolactinemia clinical guidelines [2]. The initial dose should be 0.25 mg twice a week or 0.5 mg once a week, if a patient finds that more convenient.
- For a woman who wishes to become pregnant, [bromocriptine](#) might be a better first choice because there is more evidence that bromocriptine does not cause birth defects [43]. However, data to-date suggest that [cabergoline](#) is also safe in early pregnancy [44,45]. (See "[Management of lactotroph adenoma \(prolactinoma\) during pregnancy](#)".)
- If [bromocriptine](#) is used, we suggest a starting dose of 1.25 mg after dinner or at bedtime for one week, then increase to 1.25 mg twice a day (after breakfast and after dinner or at bedtime).

**Response to therapy** — After one month of therapy, the patient should be evaluated for side effects and serum prolactin should be measured. Subsequent treatment depends upon the response:

**Prolactin normalized** — If the serum prolactin concentration is normal and no side effects have occurred, the initial dose should be continued. In this setting, gonadal function will probably return within a few months. (See '[Long-term follow-up](#)' below.)

Of note, in some patients, dopamine agonist therapy may result in restoration of normal gonadal function (eg, normal menstrual cycles in women) even if serum prolactin levels remain slightly high. In this case, the reproductive outcome (menstrual function) can be followed rather than the absolute prolactin level to determine treatment dose.

Similarly, when treating women with bothersome galactorrhea, the goal of therapy is to lower the serum prolactin low enough to resolve the galactorrhea. This may not require lowering prolactin into the normal range for the galactorrhea to remit.

### **Prolactin improved but not normal**

- If the serum prolactin concentration has not decreased to normal but no side effects have occurred, the dose should be increased gradually to as much as 1.5 mg of [cabergoline](#) two or three times a week or 5 mg of [bromocriptine](#) twice a day. Whatever dose results in a normal serum prolactin value should be continued. (See '[Prolactin normalized](#)' above.)
- If the [cabergoline](#) dose is increased above 2 mg per week, we suggest cardiac ultrasonography every two years in patients to monitor for valvular heart disease.

### **Intolerant or inadequate response**

#### **•To initial therapy:**

•If the serum prolactin concentration does not decrease sufficiently to restore normal gonadal function in response to [bromocriptine](#) (if it was chosen as initial therapy) and if compliance seems good, changing to [cabergoline](#) may be effective. The cabergoline dose should then be adjusted until the serum prolactin concentration is normal. (See '[Prolactin normalized](#)' above.)

Approximately 25 percent of patients are resistant to [bromocriptine](#) [10,12], and most (80 percent) can achieve normal prolactin concentrations with [cabergoline](#) therapy [12,46]. It is estimated that 10 percent of patients are resistant to cabergoline [2].

•If the patient cannot tolerate the first dopamine agonist administered because of side effects, another can be tried. In women, nausea can be avoided by vaginal administration [47].

#### **•To all dopamine agonists:**

•Patients who do not respond to typical doses of dopamine agonists, eg, 2 mg of [cabergoline](#) a week, may respond to higher doses [46], but higher doses may be associated with higher risk of valvular heart disease.

•If dopamine agonists have been unsuccessful or the patient cannot tolerate them, transsphenoidal surgery or ovulation induction with [clomiphene](#) citrate can be considered (for women wishing to become pregnant). For women not pursuing pregnancy, estrogen and [progesterone](#) replacement can be considered; men can consider testosterone therapy. (See '[Role of](#)

[transsphenoidal surgery](#)' below and ["Overview of ovulation induction"](#) and ["Role of estrogen in women"](#) below.)

**Role of estrogen in women** — Estrogen, along with a progestin, can be considered as sole therapy in women who have lactotroph microadenomas causing hyperprolactinemia and hypogonadism but who cannot tolerate or do not respond to dopamine agonists and do not want to become pregnant. Estrogen is also a reasonable option for women with hyperprolactinemia and amenorrhea due to other causes, including antipsychotic agents. (See ["Clinical manifestations and evaluation of hyperprolactinemia"](#) and ["Drug-induced hyperprolactinemia"](#) below.)

Since estrogen treatment might pose a slight risk of increasing the size of the adenoma, the serum prolactin concentration should be measured periodically in these patients. Estrogen should **not** be used as the sole treatment for lactotroph macroadenomas.

Estrogen and progestin can be administered separately in low doses as they would be for the treatment of hypogonadism of any etiology, or estrogen can be administered in the form of an oral contraceptive. (See ["Overview of the use of estrogen-progestin contraceptives"](#).)

**Role of testosterone in men** — For men with hyperprolactinemia causing hypogonadism who cannot tolerate or who do not respond to dopamine agonists, testosterone treatment can be considered for those who are not interested in fertility and human chorionic gonadotropin (hCG) for those who are. (See ["Testosterone treatment of male hypogonadism"](#) and ["Induction of fertility in men with secondary hypogonadism"](#).)

**Transsphenoidal surgery** — Transsphenoidal surgery should be considered in patients with microadenomas when dopamine agonist treatment has been unsuccessful in lowering the serum prolactin concentration, symptoms or signs due to hyperprolactinemia persist even after several months of treatment, and gonadal steroid replacement is not an option, eg, when pregnancy is desired. The role of surgery in patients with macroadenomas is reviewed below. (See ["Role of transsphenoidal surgery"](#) below.)

**Long-term follow-up** — Patients with microadenomas who achieve normal serum prolactin concentrations should be treated for at least one year. Serum prolactin measurements should be obtained at least every 12 months [[1,2](#)].

After approximately one year of treatment (if prolactin is normal), the dose can often be decreased. If the prolactin has been normal for two or more years and no adenoma is seen on magnetic resonance imaging (MRI), discontinuation of the drug can be considered. (See ["Withdrawal of dopamine agonists"](#) below.)

Dopamine agonists should be stopped in women who become pregnant. (See ["Management of lactotroph adenoma \(prolactinoma\) during pregnancy"](#), section on ["Dopamine agonist therapy"](#).)



**Withdrawal of dopamine agonists** — In a patient who had idiopathic hyperprolactinemia (no pituitary mass at baseline) and whose serum prolactin decreased to low normal in response to dopamine agonist treatment, we suggest attempting to decrease the dose gradually, as long as the prolactin remains within the normal range. If a patient has a normal prolactin for two years while taking a low dose (eg, 0.25 mg twice a week) of [cabergoline](#), we suggest a trial of discontinuation of the drug. We suggest a similar approach for patients who had hyperprolactinemia and a microadenoma prior to treatment in whom prolactin fell to normal and who have not had evidence of an adenoma by MRI for at least two years. We suggest considering this approach even if the patient had a macroadenoma prior to treatment, as long as the serum prolactin has been normal and no adenoma has been detectable by MRI for at least two years. This approach is consistent with that of the Endocrine Society 2011 clinical guidelines [2].

If the drug is discontinued, prolactin should be measured after three months and yearly thereafter. If the prolactin increases substantially (eg, to >100 ng/mL), especially in a patient who originally had a macroadenoma, an MRI should be performed.

We recommend not stopping the dopamine agonist if the prolactin increases above normal while gradually decreasing the drug.

If serum prolactin increases after a withdrawal attempt, we suggest resuming [cabergoline](#) therapy at the same dose that previously kept the prolactin normal and decreased the adenoma size to undetectable.

Several studies have reported the consequences of discontinuation of dopamine agonist treatment in patients who have hyperprolactinemia. Recurrence of hyperprolactinemia and increase in adenoma size have been variable [48-53].

In one prospective study of 200 cabergoline-treated patients with hyperprolactinemia (25 with idiopathic hyperprolactinemia, 105 with microadenomas, and 70 with macroadenomas), therapy was withdrawn when serum prolactin concentrations were normal and MRI showed no adenoma (or >50 percent reduction with no cavernous sinus invasion and >5 mm distance from the optic chiasm) [48]. After two to five years of observation, the following results were seen:

- Hyperprolactinemia recurred in 24, 31, and 36 percent of patients with idiopathic hyperprolactinemia, microadenomas, and macroadenomas, respectively (eg, a remission rate [persistent normoprolactinemia] of 64 to 76 percent).
- Adenoma regrowth was not seen in any patient.
- Hyperprolactinemia in patients with adenomas was more likely to recur if an adenoma remnant was seen on MRI than if it was not when treatment was stopped (78 versus 33 percent for macroadenomas, and 42 versus 26 percent for microadenomas).

Most patients with a macroadenoma remnant had tumor recurrence by seven years of follow-up [54]. However, giant adenomas (>3 cm) may behave more aggressively, as shown by case reports of rapid, substantial regrowth within weeks of discontinuation of dopamine agonist medication [55,56].

In contrast, a number of other studies report higher rates of recurrent hyperprolactinemia (eg, lower rates of remission) [49,52,56]. In a meta-analysis of 19 studies with a total of 743 patients, the overall rate of remission (persistent normoprolactinemia) after withdrawal of dopamine agonist therapy was only 21 percent (32, 21, and 16 percent for idiopathic hyperprolactinemia, microprolactinomas, and macroprolactinomas, respectively) [53].

Other findings included:

- Higher rate of remission in studies in which [cabergoline](#) was used (35 percent in four studies) than in those in which [bromocriptine](#) was used (20 percent in 12 studies).
- Higher rates of remission in studies with treatment duration longer than 24 months (34 percent) compared with studies with shorter treatment duration (16 percent).
- Higher rate of remission in studies where a 50 percent tumor reduction was achieved in all patients before stopping therapy (55 percent remission rate was seen).

In summary, hyperprolactinemia may recur in a considerable number of patients after stopping dopamine agonist therapy. The probability of remission is best the longer the serum prolactin has been normal and no adenoma has been seen by MRI, preferably for at least two years.

**Menopause** — After menopause, the drug can be discontinued and the serum prolactin concentration can be allowed to rise. Imaging should be performed if the value rises above 200 ng/mL to determine if the adenoma has increased to a clinically important size. If so, drug therapy should be resumed.

## MACROADENOMAS

**Initial therapy** — Treatment of patients with lactotroph macroadenomas, no matter how large or how severe the neurologic sequelae, should also be initiated with a dopamine agonist, starting with [cabergoline](#) [2], as described above for patients with microadenomas. (See '[Microadenomas](#)' above.) Patients whose macroadenomas are largely cystic should also be treated initially with a dopamine agonist since this treatment shrinks most of these [57].

**Titration of dose and monitoring** — The serum prolactin should be measured and the [cabergoline](#) dose should be increased once a month, if necessary, until the serum prolactin concentration becomes normal.

If vision was abnormal before therapy, it should be reassessed within one month, although improvement may occur within a few days. A magnetic resonance imaging (MRI) should be repeated in 6 to 12 months to determine if the size of the adenoma has decreased.

In most patients with lactotroph macroadenomas:

- The size of the adenoma decreases to approximately the same degree as the serum prolactin concentration, although the relationship varies from patient to patient.
- The decrease in size usually cannot be demonstrated until weeks or months after the prolactin secretion has decreased ([image 1](#)).
- The size of the adenoma can continue to decrease for years.

Once serum prolactin has normalized:

- If the clinical picture is stable (no evidence of tumor growth on MRI and no symptoms such as headaches or visual symptoms), serum prolactin should be checked in six months, and if normal, it should then be measured yearly.
- Serum prolactin should be measured at any point if the clinical picture changes (eg, if there are recurrent or new symptoms).

**Candidates for stopping therapy** — If the serum prolactin concentration has been normal for at least one year and the adenoma has decreased markedly in size, the dose of the dopamine agonist can be decreased gradually, as long as the serum prolactin remains normal [58]. Discontinuation can be considered in those patients who had macroadenomas of modest size (eg, 1.0 to 1.5 cm), whose serum prolactin concentrations have been normal for more than two years, and whose adenomas can no longer be visualized by MRI.

If the drug is discontinued, the prolactin concentration and the size of the adenoma by MRI must be monitored.

Discontinuation should probably **not** be considered if the adenoma was initially >2 cm, if it can still be visualized by MRI during treatment, or if the prolactin has not become normal during treatment. The agonist should not be discontinued entirely, even after menopause, because hyperprolactinemia will probably recur, and the adenoma may increase in size [48,55,56]. (See '[Withdrawal of dopamine agonists](#)' above.)

**Inadequate response or drug intolerance** — We recommend the following approach in patients who do not have a complete response to dopamine agonist therapy:

- If the patient cannot tolerate the first agonist tried or the adenoma does not respond to it, another agonist should be tried.
- If the patient cannot tolerate or the adenoma does not respond to agonist therapy, transsphenoidal surgery should be performed, and if a significant amount of adenoma tissue remains after surgery, radiation therapy should be administered (see '[Radiation therapy of pituitary adenomas](#)', section on '[Lactotroph adenomas \(prolactin-secreting adenomas\)](#)'). Surgery can also be considered for the woman who

has a giant adenoma and is contemplating pregnancy. (See ['Role of transsphenoidal surgery'](#) below.)

**Role of transsphenoidal surgery** — Transsphenoidal surgery should be considered when:

- Dopamine agonist treatment has been unsuccessful in lowering the serum prolactin concentration or size of the adenoma, and symptoms or signs due to hyperprolactinemia or adenoma size persist after several months of treatment at high doses.
- A woman has a giant lactotroph adenoma (eg, >3 cm) and wishes to become pregnant even if the adenoma responds to a dopamine agonist. The rationale for this approach is that if the patient becomes pregnant and discontinues the agonist for the duration of pregnancy, the adenoma may increase to a clinically important size before delivery.

Surgery is usually successful in substantially reducing serum prolactin concentrations in patients with lactotroph adenomas, sometimes to normal [59-62]. It is a safer procedure when performed by an experienced surgeon [63]. (See ["Transsphenoidal surgery for pituitary adenomas and other sellar masses"](#), section on 'Lactotroph adenomas'.)

Surgery, however, has the following limitations:

- Not all of the adenoma tissue is excised in many patients, particularly those with macroadenomas. (See ["Transsphenoidal surgery for pituitary adenomas and other sellar masses"](#), section on 'Lactotroph adenomas'.)
- The adenoma and hyperprolactinemia may recur within several years after surgery. (See ["Transsphenoidal surgery for pituitary adenomas and other sellar masses"](#), section on 'Lactotroph adenomas'.)

Complications are the same as may occur during and after transsphenoidal surgery for any kind of pituitary adenoma.

**Postoperative radiation therapy** — Radiation is primarily used to prevent regrowth of residual tumor in a patient with a very large macroadenoma after transsphenoidal debulking of lactotroph adenomas that are resistant to [cabergoline](#). It should not be used for the primary treatment of patients with macroadenomas or at all for those with microadenomas. While data suggest that radiation therapy (single dose or multiple fraction) appears to be effective in controlling growth of most pituitary macroadenomas, the effect on aggressive lactotroph adenomas that do not respond to dopamine agonists and cannot be entirely resected surgically is less well known. (See ["Radiation therapy of pituitary adenomas"](#), section on 'Lactotroph adenomas (prolactin-secreting adenomas)').

Complications of radiation include transient nausea, lassitude, loss of taste and smell, loss of scalp hair at the radiation portals during and shortly after the treatment, and possible

damage to the optic nerve and neurologic dysfunction [1]. There is also a 50 percent chance of loss of anterior pituitary hormone secretion during the subsequent 10 years [64].

**PREGNANCY** — The management of lactotroph adenomas before, during, and after pregnancy is reviewed in detail separately. (See "[Management of lactotroph adenoma \(prolactinoma\) during pregnancy](#)".)

**TREATMENT OF NONADENOMA CAUSES** — Treatment of hyperprolactinemia due to an abnormality other than a lactotroph adenoma varies depending on the cause:

**Idiopathic hyperprolactinemia** — In a substantial number of patients whose serum prolactin concentration is between 20 and 100 ng/mL (100 mcg/L SI units), no cause can be found; they are considered to have idiopathic hyperprolactinemia. Although many of these patients may have microadenomas not visible on imaging studies, in most of them the serum prolactin concentrations change little during follow-up for several years. Serum prolactin should be measured yearly. (See "[Causes of hyperprolactinemia](#)".)

In patients with idiopathic hyperprolactinemia (no pituitary mass at baseline) whose serum prolactin decreased to low normal in response to dopamine agonist treatment, we suggest attempting to decrease the dose gradually, as long as the prolactin remains within the normal range. If a patient has a normal prolactin for two years while taking a low dose (eg, 0.25 mg of [cabergoline](#) twice a week), we suggest a trial of discontinuation of the drug. (See "[Withdrawal of dopamine agonists](#)" above.)

**Hypothalamic and pituitary disease** — Any disease in or near the hypothalamus or pituitary that interferes with the secretion of dopamine or its delivery to the hypothalamus can cause hyperprolactinemia, including tumors and infiltrative diseases of the hypothalamus, section of the hypothalamic-pituitary stalk (eg, due to head trauma or surgery), and adenomas of the pituitary other than lactotroph adenomas. If removal of the adenoma or mass is not possible, the hyperprolactinemia should be treated with a dopamine agonist.

**Drug-induced hyperprolactinemia** — A number of drugs, especially antipsychotics and some antihypertensives ([verapamil](#), [methyldopa](#)), can cause hyperprolactinemia ([table 1](#)) (see "[Causes of hyperprolactinemia](#)", [section on 'Drug induced'](#)"). If the hyperprolactinemia is asymptomatic, no treatment is necessary. If symptoms are present and the hyperprolactinemia is due to a drug other than an antipsychotic agent, we suggest discontinuing the drug as a trial. If discontinuation is not feasible, options include switching to a drug with a similar action that does not cause hyperprolactinemia, adding estrogen or testosterone for the hypogonadal symptoms and/or low bone mass, or cautious administration of a dopamine agonist, as described in the following section.

**Antipsychotic drug use** — If an antipsychotic drug is causing hyperprolactinemia and hypogonadism but cannot be discontinued because it is essential, several possible treatment options can be considered:

- Addition of a dopamine agonist. This option should be undertaken **very** cautiously in consultation with the treating psychiatrist since it might counteract the dopamine antagonist property of the antipsychotic drug.
- Change to an antipsychotic drug that does not raise prolactin, such as [quetiapine](#). This course should only be considered in conjunction with the treating psychiatrist.
- Addition of the antipsychotic drug [aripiprazole](#) to the existing antipsychotic drug. This drug has both dopamine agonist and antagonist properties and dampens hyperprolactinemia when added to other antipsychotic drugs such as [risperidone](#) [65].
- Addition of an estrogen and progestin to treat the estrogen deficiency and prevent bone loss in women. This approach will not treat the hyperprolactinemia.

**Hypothyroidism** — If hyperprolactinemia is solely the result of hypothyroidism, it will remit as the hypothyroidism is corrected, so no other treatment is necessary. (See ["Causes of hyperprolactinemia", section on 'Hypothyroidism'](#) and ["Treatment of primary hypothyroidism in adults"](#).)

**Macroprolactinemia** — Macroprolactinemia or "big prolactin" is a benign condition that does **not** require treatment, as it does not result from a pituitary adenoma or cause hypogonadism. Macroprolactin is an umbrella term used to describe aggregates of prolactin and antibodies, some antiprolactin autoantibodies, to prolactin, that range in size from approximately 150 to 170 kD (the most common form of native prolactin in serum is 23 kD in size). Macroprolactinemia is sometimes misdiagnosed and treated as ordinary hyperprolactinemia. Misdiagnosis can be avoided by asking the laboratory to pretreat the serum with polyethylene glycol to precipitate the macroprolactin before the immunoassay for prolactin. (See ["Causes of hyperprolactinemia", section on 'Macroprolactinemia'](#).)

**INFORMATION FOR PATIENTS** — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5<sup>th</sup> to 6<sup>th</sup> grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10<sup>th</sup> to 12<sup>th</sup> grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see ["Patient education: Prolactinoma \(The Basics\)"](#))
- Beyond the Basics topics (see ["Patient education: High prolactin levels and prolactinomas \(Beyond the Basics\)"](#))

**SUMMARY AND RECOMMENDATIONS** — Based upon the treatments now available, we make the following recommendations:

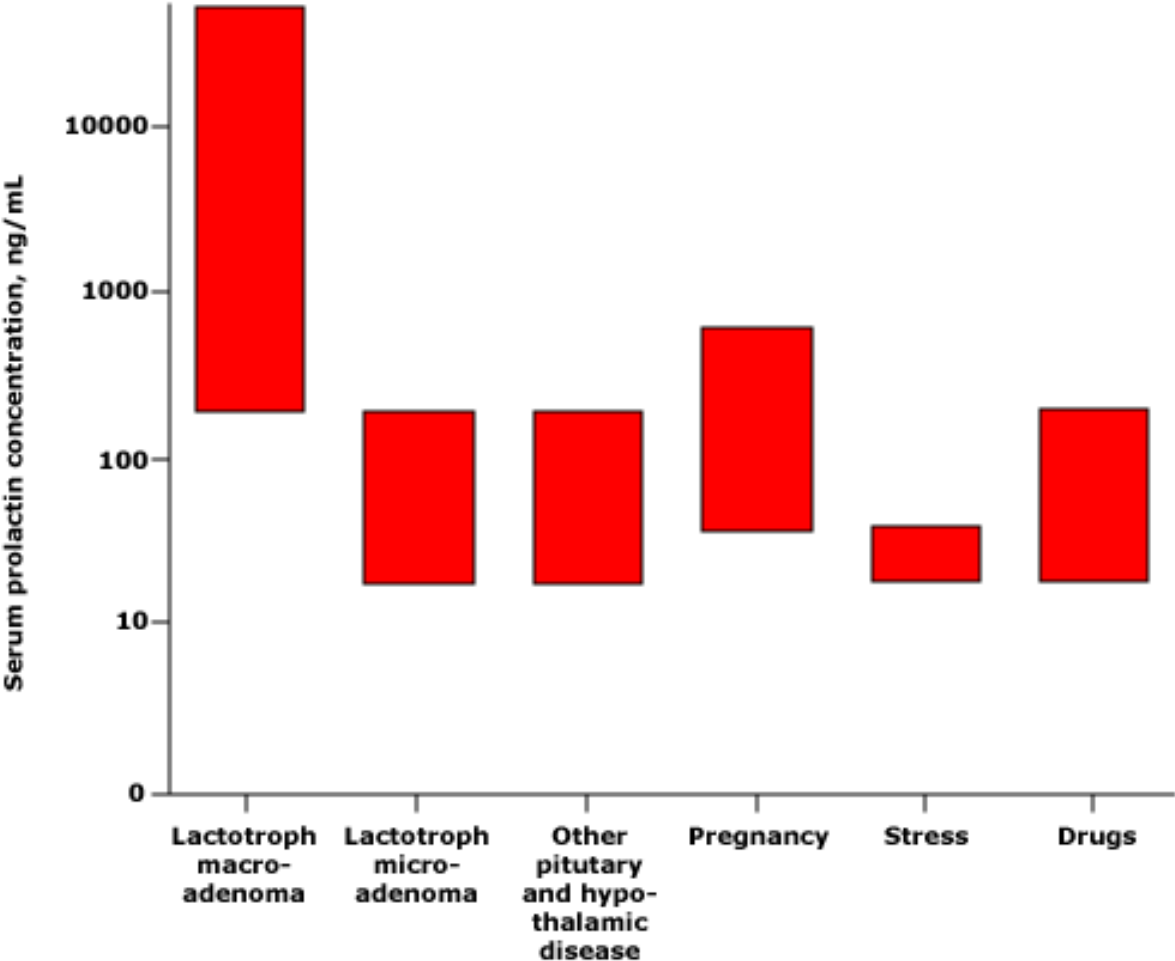
- For patients with lactotroph microadenomas and any degree of hypogonadism, we recommend initial treatment with a dopamine agonist ([Grade 1B](#)). (See '[Microadenomas](#)' above.)
- For women with hyperprolactinemia and galactorrhea (but normal menstrual cycles), we suggest dopamine agonist therapy only if the galactorrhea is bothersome.
- We recommend [cabergoline](#) as the initial choice of dopamine agonists in most circumstances because it is most likely to be effective and least likely to cause side effects ([Grade 1B](#)). (See '[Overview of dopamine agonists](#)' above.)
- Because of a possible association between high-dose [cabergoline](#) use for Parkinson disease and valvular heart disease, we suggest using the lowest dose of cabergoline necessary to lower prolactin to normal ([Grade 2B](#)). (See '[Valvular heart disease](#)' above.)
- For patients who require higher than usual doses of [cabergoline](#) (eg, greater than 2 mg per week), we suggest ordering cardiac ultrasonography every two years. (See '[Valvular heart disease](#)' above.)
- For patients whose serum prolactin decreases to low normal in response to dopamine agonist treatment, we suggest decreasing the dose gradually, as long as the prolactin remains within the normal range ([Grade 2C](#)).
- For patients who had idiopathic hyperprolactinemia (negative magnetic resonance imaging [MRI]) and have had a normal prolactin while taking a low dose of dopamine agonist for at least two years, we suggest a trial of stopping the drug ([Grade 2C](#)). We suggest a similar approach for patients who had lactotroph adenomas and have also had no evidence of the adenoma by MRI for at least two years ([Grade 2C](#)).
- If the drug is discontinued, prolactin should be measured after three months and yearly thereafter. If the prolactin increases substantially, eg, to >100 ng/mL, especially in a patient who originally had a macroadenoma, an MRI should be performed.
- If the patient cannot tolerate the first dopamine agonist administered or serum prolactin concentrations do not normalize, we suggest switching to a second dopamine agonist ([Grade 2C](#)). (See '[Overview of dopamine agonists](#)' above.) Starting doses and upward titration of dose based upon clinical response are reviewed above. (See '[Microadenomas](#)' above.)
- In women with lactotroph microadenomas seeking fertility whose serum prolactin concentrations do not normalize with dopamine agonist therapy (and who therefore do not ovulate), we suggest ovulation induction with [clomiphene](#) citrate or gonadotropin therapy ([Grade 2B](#)). (See '[Overview of ovulation induction](#)'.)
- For patients with lactotroph macroadenomas, no matter how large or how severe the neurologic sequelae, we recommend initial treatment with a dopamine agonist ([Grade 1B](#)). Dosing is the same as that for microadenomas. (See '[Microadenomas](#)' above.)

- We suggest transsphenoidal surgery when dopamine agonist treatment has been unsuccessful in lowering the serum prolactin concentration or size of the macroadenoma, and symptoms or signs due to hyperprolactinemia or adenoma size persist during treatment (**Grade 1B**). (See '[Role of transsphenoidal surgery](#)' above.)
- We also suggest transsphenoidal surgery in women with giant lactotroph adenomas (>3 cm) who wish to become pregnant, even if the adenoma responds to a dopamine agonist (**Grade 2C**). The rationale for this approach is that if such a patient becomes pregnant and discontinues the agonist for the duration of pregnancy, the adenoma may increase to a clinically important size before delivery. (See '[Role of transsphenoidal surgery](#)' above.)
- In patients with large macroadenomas who have undergone transsphenoidal debulking and in whom considerable residual adenoma remains in a location not readily accessible to surgery, we suggest radiation therapy to prevent regrowth of residual adenoma (**Grade 2C**). We recommend not using radiation therapy for the primary treatment of patients with macroadenomas or at all for those with microadenomas (**Grade 1B**). (See '[Postoperative radiation therapy](#)' above.)
- In premenopausal women who have lactotroph microadenomas causing hyperprolactinemia and hypogonadism but who cannot tolerate or do not respond to dopamine agonists and do not want to become pregnant, we suggest estrogen and progestin replacement to prevent bone loss (**Grade 2B**). (See '[Role of estrogen in women](#)' above.)
- We also suggest gonadal steroid replacement therapy in patients with hyperprolactinemia and hypogonadism due to antipsychotic agents (estradiol-progestin in women and testosterone in men) if addition of a dopamine agonist is not possible or if a satisfactory antipsychotic regimen that does not cause hyperprolactinemia cannot be found (**Grade 2C**). (See '[Antipsychotic drug use](#)' above.)

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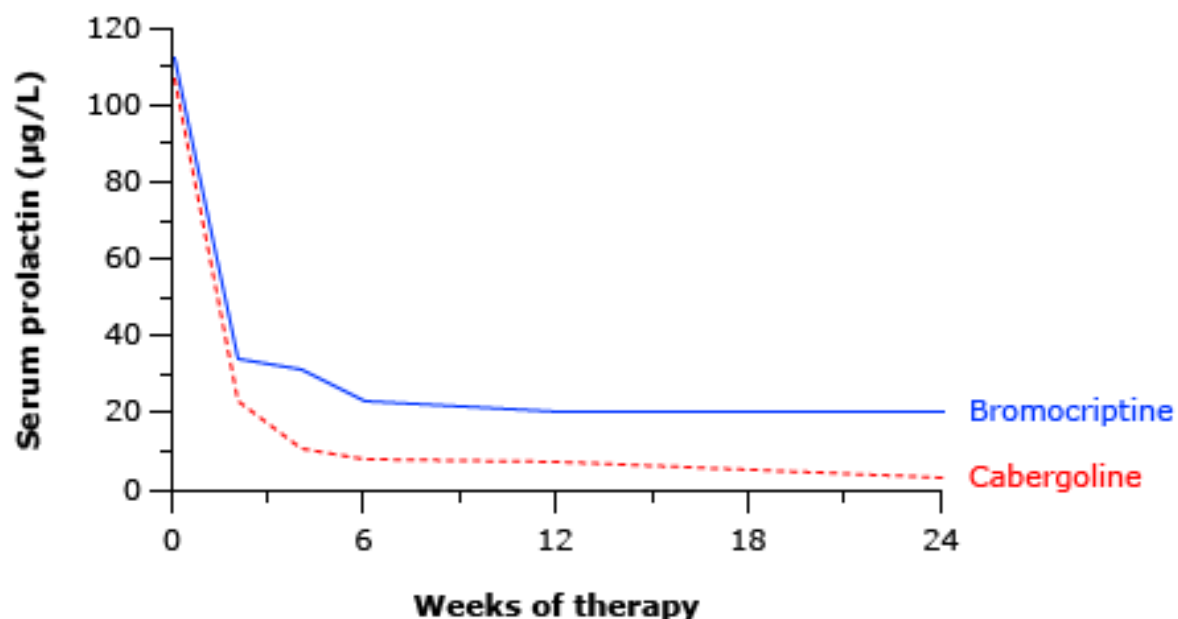
# Ranges of serum prolactin concentrations in several causes of hyperprolactinemia



The serum prolactin concentration is much higher in most patients who have lactotroph macroadenoma than in patients with any other cause of hyperprolactinemia. The prolactin concentrations among other causes overlap with each other.

## Dopamine agonist drugs lower serum prolactin concentrations in lactotroph adenoma (prolactinoma)

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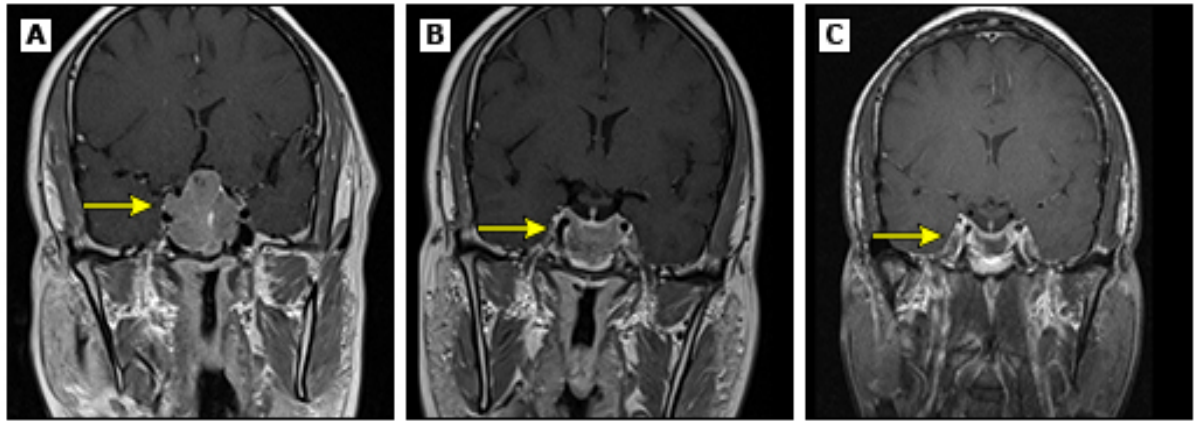
Serum prolactin concentrations in women with hyperprolactinemic amenorrhea treated with bromocriptine and cabergoline. Both drugs lowered serum prolactin concentrations into the normal range (upper limit of normal equals 20 mcg/L).

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*Data from: Webster J, Piscitelli MD, Polli A, et al. A comparison of cabergoline and bromocriptine in the treatment of hyperprolactinemic amenorrhea. Cabergoline Comparative Study Group. N Engl J Med 1994; 331:904.*

## Shrinkage of a lactotroph macroadenoma in response to dopamine agonist treatment

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Shrinkage of a lactotroph adenoma in response to treatment with the dopamine agonist cabergoline as shown by post-gadolinium magnetic resonance imaging. A 37-year-old man presented with headaches and was found to have an enormous sellar mass (A, arrow) and a prolactin of 7248 ng/mL. He was treated with cabergoline and after two months the prolactin had decreased to 745 ng/mL and the size of the mass had decreased markedly (B, arrow). After 12 months of cabergoline treatment, the prolactin had decreased to 9.2 ng/mL and the mass had decreased even further (C, arrow).

*Courtesy of Julia Kharlip, MD.*

## Medications that cause hyperprolactinemia

Medication class	Frequency of prolactin elevation*	Mechanism
<b>Antipsychotics, first generation</b>		
Chlorpromazine	Moderate	Dopamine D <sub>2</sub> receptor blockade within hypothalamic tuberoinfundibular system
Fluphenazine	High	
Haloperidol	High	
Loxapine	Moderate	
Perphenazine	Moderate	
Pimozide	Moderate	
Thiothixene	Moderate	
Trifluoperazine	Moderate	
<b>Antipsychotics, second generation</b>		
Aripiprazole	None or low	Dopamine D <sub>2</sub> receptor blockade
Asenapine	Moderate	
Clozapine	None or low	
Iloperidone	None or low	
Lurasidone	None or low	
Olanzapine	Low	
Paliperidone	High	
Quetiapine	None or low	
Risperidone	High	
Ziprasidone	Low	
<b>Antidepressants, cyclic</b>		
Amitriptyline	Low	Not well understood. Possibly by GABA stimulation and indirect modulation of prolactin release by serotonin.
Desipramine	Low	
Clomipramine	High	
Nortriptyline	None	
<b>Antidepressants, SSRI</b>		
Citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline	None or low (rare reports)	Same as for cyclic antidepressants
<b>Antidepressants, other</b>		
Bupropion, venlafaxine, mirtazapine, nefazodone, trazodone	None	Not applicable
<b>Antiemetic and gastrointestinal</b>		
Metoclopramide	High	Dopamine D <sub>2</sub> receptor blockade
Domperidone (not available in United States)	High	
Prochlorperazine	Low	
<b>Antihypertensives</b>		
Verapamil	Low	Not well understood. Specific to verapamil. May involve calcium influx inhibition within tuberoinfundibular dopaminergic neurons.
Methyldopa	Moderate	Decreased conversion of L-dopa to dopamine; suppression of dopamine synthesis
Most other antihypertensives (including other calcium channel blockers)	None	Not applicable
<b>Opioid analgesics</b>		
Methadone, morphine, others	Transient increase for several hours following dose	Potentially an indirect effect of mu opiate receptor activation

Medication induced hyperprolactinemia can cause decreased libido and erectile dysfunction in men and galactorrhea and amenorrhea in women.

GABA: gamma-aminobutyric acid; SSRI: selective serotonin reuptake inhibitor.

\* Frequency of increase to abnormal prolactin levels with chronic use: high >50 percent; moderate: 25 to 50 percent; low: <25 percent; none or low: case reports. Effect may be dose-dependent.

Data from:

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