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Management of prolactinomas

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Prolactinomas are one of the most common hormone-secreting pituitary tumours. They are a primary cause of hyperprolactinemia. The clinical presentation of prolactinomas varies with gender. Medical therapy for prolactinomas is considered as first-line therapy for both microadenomas and macroadenomas. Bromocriptine has been used in the treatment of prolactinomas for over 20 years. More recently, a newer dopamine agonist, cabergoline, has proven to be more efficacious. Surgery, however, remains an option in certain cases. This issue of *Endocrinology Rounds* reviews the evidence for medical, surgical, and radiation treatment of prolactinomas and makes recommendations for clinical management.

Epidemiology

Prolactinomas account for approximately 30% to 40% of all pituitary adenomas, with 70% occurring in women.¹ Most prolactinomas are sporadic and likely arise from a spontaneous somatic mutation resulting in the monoclonal reproduction of a single cell. Prolactinomas are rarely associated with multiple endocrine neoplasia type 1 syndrome.²

Physiology of prolactin secretion

Prolactin is synthesized in the lactotroph cells of the anterior pituitary. Similar to other anterior pituitary hormones, its secretion is episodic. The predominant prolactin-inhibiting factor is dopamine. Dopamine, produced by the tuberoinfundibular neurons of the hypothalamus, tonically stimulates dopamine D₂ receptors.³ This suppresses adenylyl cyclase and lowers inositol phosphate production, which results in suppression of prolactin gene expression and changes in cell morphology. Prolactin release is stimulated by vasoactive intestinal peptide, thyrotropin releasing hormone, and prolactin releasing peptide. Suckling of the breast activates neural afferents to the hypothalamus, which increases prolactin release in the puerperium.

Causes of hyperprolactinemia

There are various causes of hyperprolactinemia. Prolactin levels are generally considered abnormal if >20 µg/L. Physiologic causes of hyperprolactinemia include pregnancy and nipple stimulation. Both physical and psychologic stress can also increase prolactin secretion; however, levels are rarely >40 µg/L. Pathologic causes of hyperprolactinemia are listed in Table 1.⁴ Prolactin levels >250 µg/L usually indicate the presence of a macroadenoma.⁴ If a specific cause of hyperprolactinemia is not identified after appropriate investigations, hyperprolactinemia is said to be idiopathic.

Clinical features of prolactinomas

Prolactin is known to inhibit the release of gonadotropin-releasing hormone (GnRH), presumably by altering GnRH pulsatility.³ This results in suppression of luteinizing and follicle-stimulating hormone secretion that may lead to hypogonadism. There are also possible direct effects of prolactin on the pituitary and ovary. The clinical presentation of a prolactinoma varies with gender. While most premenopausal women present with microadenomas, men usually present with macroadenomas.⁵ Premenopausal women commonly have symptoms of amenorrhea, oligomenorrhea, or infertility.⁶ Galactorrhea may also be present. There are data to suggest that women with hyperprolactinemic amenorrhea have lower trabecular bone density compared with normal women or women with hyperprolactinemia and normal menses.⁷



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TABLE 1: Pathologic causes of hyperprolactinemia

Pituitary disease	Medications
Prolactinomas	Phenothiazines
Acromegaly	Haloperidol
Cushing's disease	Monoamine-oxidase inhibitors
Empty sella syndrome	Tricyclic antidepressants
Hypothalamic disease	Selective serotonin re-uptake inhibitors
Neoplasms	Methyldopa
Inflammatory (eg. sarcoidosis)	Metoclopramide
Hypothalamic-pituitary stalk section	Verapamil
Hypothalamic-pituitary stalk compression	Protease inhibitors
	Opioids
Neurogenic	Comorbidities
Chest wall lesions	Hypothyroidism
Spinal cord lesions	Chronic renal failure
	Cirrhosis
Idiopathic	Adrenal insufficiency

Adapted from Molitch ME: Prolactin. In: Melmed S, ed. *The Pituitary*. Cambridge, MA: Blackwell Science, 2nd edition, 2002.

Men with prolactinomas may present with decreased libido, erectile dysfunction, infertility, or rarely, galactorrhea.⁶ There may also be symptoms from the mass effect of the tumour (eg, headache, visual compromise, or hypopituitarism).

It is thought that gender differences in tumour size may be related to a delay of diagnosis in males, however, there may also be inherent differences in the propensity of these tumours to grow. Delgrange et al retrospectively investigated the differences in clinical and pathological features of 45 men and 51 women with prolactinomas.⁸ Basal prolactin levels (2789 ± 573 ng/mL versus 292 ± 74 ng/mL, $P < 0.001$) and tumour diameter (26 ± 2 mm versus 10 ± 1 mm, $P < 0.001$) were significantly higher in men than in women. Men were more likely to have macroadenomas (89% versus 29%, $P < 0.001$). The frequencies of bromocriptine-resistant tumours (30% versus 5%, $P < 0.01$) and invasive macroadenomas (52% versus 27%, $P < 0.001$) were also significantly higher in men than in women. Males with macroadenomas demonstrated higher proliferating cell indexes compared to females with macroadenomas, however, this was not statistically significant.

The issue of macroprolactinemia

Prolactin circulates in different forms. The monomeric 23,000 kDa form accounts for 85% of total prolactin in normal individuals. Other forms in the serum include the 50,000 kDa big prolactin and the 100,000 kDa big big prolactin. Big big prolactin is a complex of prolactin and an IgG antibody against prolactin. Macroprolactinemia, first described 25 years ago, is a condition where most of the prolactin is big big prolactin. Because of its large size, big big prolactin is confined to the vascular compartment and lacks full biologic activity.⁹

Many patients with macroprolactinemia traditionally lack the usual symptoms of amenorrhoea, infertility, and galactorrhea.¹⁰ However, there have been recent reports that macroprolactinemia can be associated with the typical

symptoms of hyperprolactinemia. A prospective study examining the clinical features of 106 patients with macroprolactinemia demonstrated that 25% of patients with macroprolactinemia had menstrual disorders versus 37% of those with hyperprolactinemia and normal chromatography ($P = 0.03$).¹¹ It was unclear if these findings were related to macroprolactinemia or secondary to another disorder in the presence of coincidental macroprolactinemia. Pituitary adenomas were present in 6% of those with macroprolactinemia who underwent imaging, one-third of which were prolactinomas. This was contrary to the classical finding of a normal MRI in patients with macroprolactinemia.

Detection of macroprolactinemia in routine clinical practice has been a major issue. Gel filtration chromatography used in clinical research studies is costly and time-consuming. Other methods such as polyethylene glycol precipitation of macroprolactin have also been studied, however, this method is neither specific nor quantitative. Measuring monomeric prolactin is difficult in the presence of macroprolactinemia. A recent study by Smith et al, examined the detection of prolactin in sera containing macroprolactin by 9 different commercial immunoassays.¹² The differences in the measured prolactin levels ranged from 2.3- to 7.8-fold. Therefore, commercial immunoassays have variable degrees of reactivity to macroprolactin. At this time, no assay will reliably detect only monomeric prolactin in the presence of macroprolactin.

Treatment of prolactinomas

There are 2 major reasons for the treatment of prolactinomas:

- Hypogonadism or other symptoms of hyperprolactinemia
- Effects of tumour size such as headaches, visual compromise, or panhypopituitarism.

The following discussion examines the role of medical therapy, surgical therapy and radiation therapy in prolactinomas.

Medical therapy: dopamine agonists

Bromocriptine

Dopamine agonists are the mainstay of treatment of prolactinomas. Bromocriptine is an ergot derivative that binds to dopamine (D_1 and D_2) receptors, resulting in a decrease of prolactin synthesis. There is evidence that bromocriptine decreases prolactin mRNA and DNA synthesis, cell multiplication, and tumour growth.¹³ In a review of 13 small studies, bromocriptine treatment achieved normoprolactinemia in 82% of hyperprolactinemic women and a return of menses in 84%.¹⁴ In lactotroph macroadenomas, 71% of patients achieved normoprolactinemia and 76% had a reduction in their tumours after bromocriptine treatment.

After initiation of therapy, a reduction in prolactin level usually precedes a reduction in tumour size. The timeline for shrinkage in tumour size is highly variable. Visual fields may improve within 24-72 hours. Changes

may be noted on subsequent scanning at 6 weeks or even up to 6 months to a year.¹⁵ Bromocriptine resistance, however, occurs in 5% to 15% of patients and may be due to low tumour expression of D₂ receptors and mRNA levels.¹

Issues with long-term treatment with dopamine agonists

One caveat for using dopamine agonists in the management of prolactinomas is the potential need for long-term treatment. Doses, however, can often be reduced as the tumour shrinks. Liuzzi et al followed a cohort of 38 patients with macroprolactinomas.¹⁷ Bromocriptine and lisuride doses were decreased after 2 years of therapy. In 55% of patients, doses were decreased substantially with maintenance of normoprolactinemia. Only one patient withdrew from therapy completely. After long-term treatment with bromocriptine, withdrawal of therapy is associated with highly variable rates of normoprolactinemia ranging from 6.6% to 44% depending on the study. A recent, retrospective study examined the characteristics of patients who maintained normoprolactinemia after bromocriptine withdrawal.¹⁸ A multivariate analysis demonstrated that gender, age, tumour size, pretreatment serum prolactin levels, initial bromocriptine dose, and duration of treatment did not predict the persistence of normoprolactinemia.

Cabergoline

Cabergoline is a nonergot dopamine agonist that has more specificity for D₂ receptors than bromocriptine. Doses are given once or twice weekly due to its prolonged half-life. There are several studies examining the use of cabergoline in the treatment of hyperprolactinemia.

- A randomized, multicentre, 24-week trial compared cabergoline with bromocriptine in the treatment of women with hyperprolactinemic amenorrhea.¹⁹ Treatment was double-blind for the first 8 weeks and open-label for the next 16 weeks. Four hundred and fifty-nine women were randomized to either cabergoline or bromocriptine. Sixty percent of patients had a microprolactinoma, 36% had idiopathic hyperprolactinemia, and 2% had an empty sella. Clinical success, defined as the occurrence of at least 2 consecutive menses with biochemical evidence of ovulation on at least 1 occasion, occurred in 72% of the patients in the cabergoline group versus 52% in the bromocriptine group ($P < 0.001$). Normalization of prolactin levels was achieved in 83% in the cabergoline group versus 58% in the bromocriptine group (Table 2). In terms of side effects, 68% of patients in the cabergoline group reported adverse events versus 78% of patients in the bromocriptine group ($P = 0.03$). The main adverse events included nausea, vomiting, constipation, headache, dizziness, abdominal pain, and fatigue. Only 3% of women discontinued treatment because of intolerance in the cabergoline group versus 12% in the bromocriptine group ($P < 0.001$). It was concluded that cabergoline is more effective in normalizing prolactin and better tolerated than bromocriptine in women with hyperprolactinemia.

- Cabergoline has also been studied in the treatment of macroadenomas. A retrospective review of 455 patients

TABLE 2: Cabergoline versus bromocriptine in hyperprolactinemic amenorrhea

	Bromocriptine	Cabergoline	P value
Clinical success	52%	72%	$P < 0.001$
Normalization of prolactin	58%	83%	$P < 0.05$
Adverse events	78%	68%	$P = 0.03$
Discontinuation of treatment from intolerance	12%	3%	$P < 0.001$

Adapted from Webster J, Piscitelli G, Polli A, et al. A comparison of cabergoline and bromocriptine in the treatment of hyperprolactinemic amenorrhea. *N Engl J Med* 1994;331:904-909.

revealed that treatment with cabergoline normalized serum prolactin levels in 92% of patients with idiopathic hyperprolactinemia or a microprolactinoma, and 77% of patients with macroadenomas.²⁰ Tumour shrinkage occurred in 67% of patients.

- The question of whether previous treatment with bromocriptine or quinagolide impairs response to cabergoline treatment was examined by Colao et al.²¹ This prospective study followed 110 patients with macroprolactinomas treated with cabergoline. Patients were divided into 4 groups based on prior treatment:

- treatment naïve patients had no previous exposure to dopamine agonists;
- the intolerant group had previous treatment with bromocriptine that was stopped because of moderate to severe side effects;
- the resistant group included patients who did not normalize their prolactin after treatment with bromocriptine (15 mg/day) or quinagolide (0.6 mg/day) for 3 months; and
- the responsive group consisted of patients who had achieved normoprolactinemia with bromocriptine or quinagolide. These patients were withdrawn from their medications 15 to 30 days prior to the study.

Normal prolactin levels were achieved in 80.7% of the treatment naïve group, 94.7% of the intolerant group, 51.3% of the resistant group, and 82.1% of the responsive group. Significant tumour shrinkage (defined as >80% reduction in pretreatment tumour volume) was higher in treatment naïve patients (92.3%) than intolerant patients (42.1%), resistant patients (30.3%), or responsive patients (38.4%). This study suggests that first line treatment of macroprolactinomas with cabergoline results in higher tumour shrinkage than when patients are treated with other dopamine agonists prior to cabergoline treatment. It was unclear, however, whether all treatment groups were similar at the beginning of the study with respect to prolactin levels and tumour size.

- As previously mentioned, bromocriptine resistance may occur in 5%-15% of patients. A small prospective study by Colao et al examined the effectiveness of cabergoline in patients with prolactinomas resistant to bromocriptine or quinagolide.²² Cabergoline achieved normalization of prolactin levels in 15 of 19 patients with

macroprolactinomas and in all 8 patients with microprolactinomas in whom previous bromocriptine and quinagolide had been unsuccessful.

- Experience with cabergoline is still somewhat limited and its prevalence of resistance is still unclear. A recent retrospective study of 207 patients examined the resistance to cabergoline versus bromocriptine in the treatment of hyperprolactinemia.²³ If prolactin levels remained elevated, bromocriptine doses were progressively increased to 15-20 mg/day and cabergoline doses were increased to 5-7 mg/week. Cabergoline for 24 months achieved prolactin normalization and tumour reduction in a higher number of macroprolactinomas (82.1% versus 46.4%) and microprolactinomas (90% versus 56.8%) when compared with bromocriptine.

In summary, cabergoline is preferred over bromocriptine since it is more effective in normalizing prolactin and in reducing tumour size. It also appears more effective in patients with no previous dopamine agonist therapy when compared to patients who have had previous therapy. Lastly, it is better tolerated than bromocriptine.

Quinagolide

Quinagolide is a nonergot dopamine agonist that has a 35-fold greater D₂ activity than bromocriptine. It requires once-a-day dosing. In a small study, quinagolide was shown to normalize prolactin in 82% of patients with idiopathic hyperprolactinemia, 73% of patients with microadenomas, and 67% of patients with macroadenomas.²⁴ In patients with microadenomas, 55% had a decrease in tumour size versus 75% of patients with macroadenomas. In a recent, open-label, crossover study, quinagolide decreased prolactin levels by 74.3%, whereas cabergoline decreased levels by 86% ($P < 0.05$).²⁵

Pergolide

Pergolide is an ergot derivative commonly used in the treatment of Parkinson's disease. At this time, it has not been approved by the FDA for treatment of hyperprolactinemia. It is 100 times more potent than bromocriptine and requires once- or twice-a-day dosing. A recent case series was published reviewing 22 patients with macroprolactinomas treated with pergolide.²⁶ Prolactin levels normalized in 15 and approached normal in 2 others. Significant tumour shrinkage was observed in all 22 patients. Previous studies of pergolide in micro- and macroadenomas have demonstrated high rates of prolactin normalization.^{27,28}

Surgical therapy

Transsphenoidal surgery for the initial treatment of prolactinomas has fallen out of favour due to the success of dopamine agonists. Overall surgical success rates have been published in a review of 34 published

series.²⁹ Curative surgical rates, defined as normoprolactinemia within 1 to 12 weeks after surgery, were 73.7% for microadenomas and 32.4% for macroadenomas. The recurrence of hyperprolactinemia or microadenomas was 21.0% and 19.8% for macroadenomas, respectively. In one surgical series of 44 patients, recurrence rates were as high as 50% for microadenomas and 80% for macroadenomas.³⁰

A recent retrospective review of 120 patients examined the early and long-term outcomes after transsphenoidal surgery.³¹ Reasons for surgery included resistance to dopamine agonists, drug intolerance, partial response to therapy, diagnostic uncertainty, patient's preference, and tumour apoplexy. Normalization of prolactin levels 5 days after surgery occurred in 78% of patients with microadenomas and in 50.8% of patients with macroadenomas. There was no difference in surgical results in patients who had been previously treated with a dopamine agonist. Univariate analysis demonstrated that high preoperative prolactin levels, larger tumour size, male sex, younger age at surgery, invasiveness into the cavernous sinus, and dural infiltration were associated with a negative surgical outcome. Other surgical series have demonstrated that both small tumour size and lower basal prolactin levels are associated with successful surgical outcomes.^{32,33} In the recent study by Losa et al, recurrence of hyperprolactinemia was documented in 16.9% of patients with normal postoperative prolactin levels.³¹ All recurrences occurred within 3 years of surgery. Sex, age, previous dopamine agonist therapy, and preoperative prolactin levels were not predictors of higher relapse rates. In other studies, a high postoperative prolactin level has been associated with recurrence.^{33,34}

One must also take into account that surgery in itself has inherent risks. Mortality and major morbidity rates for transsphenoidal surgery are 0.5% and 1.5%, respectively.³⁵

Radiation therapy

Radiation therapy has been surpassed by both medical therapy and surgery in terms of successful clinical outcomes. With radiotherapy alone, few patients achieve normal prolactin levels after a number of years. When radiation is used in combination with bromocriptine, 22% achieved normal prolactin levels after a mean of 4 years in one series.³⁶ In patients with prolactinomas who were treated with radiation therapy postoperatively or as a part of salvage therapy, only 25% had normalization of prolactin levels at 10 years.³⁷ Gamma knife radiosurgery, a technique that permits conformation of the radiation to the tumour shape, limits radiation exposure to the surrounding field in comparison to conventional radiotherapy, but experience is very limited in the treatment of prolactinomas. In a retrospective review, 20 patients

underwent gamma knife radiosurgery after unsuccessful surgery and/or medical treatment for prolactinoma.³⁸ Five patients (25%) had normalization of their prolactin values and 11 patients had normalization on reduced medical treatment. Treatment failed in 3 patients. The major side effect of radiation therapy is hypopituitarism.

Issues in pregnancy

In pregnancy, estrogens stimulate lactotroph DNA synthesis and mitotic activity that results in lactotroph hyperplasia. There is an increase in the size of the pituitary gland by the second month, which peaks in the first week postpartum. Prolactin levels in normal pregnant individuals gradually increase in pregnancy and may increase by as much as 10-fold. Molitch reviewed the data from a number of case series and reported that the risk of significant symptoms (headaches, visual symptoms or both) from tumour enlargement during pregnancy was 1.3% for microadenomas.³⁹ Patients with macroadenomas who had no previous surgery or irradiation were more likely to have symptomatic tumour enlargement than those with microadenomas.

Treatment of prolactinomas during pregnancy

Bromocriptine use has been shown to be safe during the first 3-4 weeks of gestation. Data from over 6000 women demonstrated that there was no increase in spontaneous abortions, ectopic pregnancies, trophoblastic disease, multiple pregnancies, or congenital malformations.⁴⁰ Bromocriptine, however, has not been well-studied in pregnant women throughout gestation. Reports from just over 100 women revealed that 2 of the offspring had congenital abnormalities (an undescended testicle and a talipes deformity).³⁹ Experience with cabergoline has been limited in pregnancy; however, outcome data in 255 women indicated that it did not appear to increase risk of preterm, ectopic, multiple birth deliveries, or congenital malformations.^{41,42}

General recommendations

Microadenomas: Medical management is first-line therapy for microadenomas, preferably with cabergoline since it is more effective in decreasing prolactin levels, reducing tumour size, and is better tolerated than bromocriptine. In asymptomatic postmenopausal women, there is little role for therapy. Surgery can be an option in patients with microadenomas if there is medication intolerance, resistance, or noncompliance. **Macroadenomas:** Medical management is also first-line therapy for macroadenomas. Cabergoline is again recommended over bromocriptine. Surgery is imperative in patients with visual loss or other forms of neurologic compromise not responding to medical treatment within 48 hours. Surgery may also be considered

in patients with medication intolerance, resistance, or noncompliance. However, surgical cure rates in macroadenomas are low and therapy with a dopamine agonist will likely be required in the postoperative period.

Recommendations for management in pregnancy

Microadenomas: Given that microadenomas have a low risk of symptomatic tumour enlargement during pregnancy, dopamine agonists should be stopped when the pregnancy is discovered. If the patient becomes symptomatic, formal visual field testing and an MRI should be done. Prolactin levels should be measured at 2- to 3-month intervals.

Macroadenomas: For macroadenomas, the risk of symptomatic tumour enlargement is much higher. Optimum management is unclear. In general, dopamine agonists should be stopped when the pregnancy is discovered. Patients should have formal visual field testing and monitoring of prolactin levels at 2-3 month intervals. If suspicion of tumour enlargement is present, MRI and visual field testing should be done. In patients with tumour enlargement, bromocriptine therapy should be considered at the lowest possible dose associated with a clinical response. Cabergoline has been less well-studied in pregnancy. Transsphenoidal surgery is an option, but any surgery during pregnancy is associated with an increase in fetal loss.⁴³

Summary

Dopamine agonist therapy is the recommended first-line treatment for both microprolactinomas and macroprolactinomas. There is evidence to support the use of cabergoline over bromocriptine because it is more effective in normalizing prolactin secretion and reducing tumour size. Cabergoline is also better tolerated than bromocriptine. Currently, bromocriptine is the only dopamine agonist that has been well-studied during the first weeks of gestation. Surgery remains an option for microprolactinomas and macroprolactinomas in patients with medication intolerance, resistance, or noncompliance. Radiation treatment, however, has a very limited role.

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