# **BMJ** Best Practice Prolactinoma

Straight to the point of care



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# Summary

Prolactinomas represent approximately 50% of all pituitary adenomas, with a female preponderance.

Women usually present with amenorrhoea and galactorrhoea. Men may present with sexual dysfunction, hypogonadism, and sometimes gynaecomastia, all related to the hyperprolactinaemia.

Premenopausal women present earlier due to menstrual irregularity and hence usually have microprolactinomas. Men and post-menopausal women often present later with macroadenomas, which may be invasive or giant tumours.

Treatment with dopamine agonists usually results in prolactin normalisation, symptom improvement, and tumour shrinkage.

# Definition

Prolactinomas are benign lactotroph adenomas expressing and secreting prolactin.

# Epidemiology

Prolactinomas are the most common type of pituitary adenoma, constituting about 50% of these tumours.[1] [2] Prolactin-secreting adenomas are more frequent in women between 20 and 50 years old, mainly during the child-bearing years, with an estimated ratio of frequency between women and men of 10:1.[1] This sex imbalance is not apparent in the older population, after the fifth decade of life, when the frequency of prolactinomas is similar in men and women.[2] The annual incidence rate of prolactinomas is between 2 and 5 new cases/100,000.[2] The prevalence of symptomatic microprolactinomas and macroprolactinomas is approximately 40 and 10 per 100,000, respectively.[2]

# Aetiology

Human pituitary adenomas, including prolactinomas, are monoclonal in origin.[3] This suggests that pituitary tumours arise from the proliferation of single, mutated pituitary cells, where somatic cell mutations stimulate cellular growth rate. The majority of prolactinomas occur sporadically. A small percentage of patients may have multiple endocrine neoplasia syndrome type 1 (MEN-1) or familial isolated pituitary adenoma (FIPA). In studies of FIPA patients, prolactinomas associated with aryl hydrocarbon receptor-interacting protein (AIP) gene mutations were large, occurred at a young age (<30 years), were invasive, had suprasellar extension, and were resistant to dopamine agonist treatment.[4] [5] Consideration should be given to screening young patients (<40 years) presenting with large prolactinomas for AIP gene mutations and MEN-1.[6] [7]

# Pathophysiology

Prolactinomas are anterior pituitary lactotroph tumours. Hypersecretion of prolactin causes secondary hypogonadism via its inhibitory effects on gonadotrophin-releasing hormone and pituitary gonadotrophins. Dopamine is transported from the hypothalamus to the anterior pituitary by hypophysial portal vessels, where it inhibits prolactin secretion via dopamine receptors expressed by lactotrophs. Therefore, disruption of dopamine secretion or transport to the portal vessels can lead to hyperprolactinaemia.

# Classification

# **Classification according to tumour size**

Microadenomas:

- Small, intrasellar tumours, <10 mm in diameter
- Rarely increase in size
- Most common type in women.

Macroadenomas:

- Larger tumours, >10 mm in diameter
- Usually locally invasive into the suprasellar or parasellar regions
- Sometimes associated with aggressive compression of vital structures
- Men and post-menopausal women more commonly present with large and invasive adenomas, occasionally giant tumours (4 cm or greater)
- Almost invariably benign (malignant prolactinomas that metastasise outside the pituitary sella are very rare).

## Theory



Gadolinium-enhanced magnetic resonance imaging showing a left-sided 7 mm pituitary microprolactinoma From the collection of Dr Ilan Shimon



Gadolinium-enhanced magnetic resonance imaging showing a large pituitary macroadenoma in a 45-year-old man with hyperprolactinaemia From the collection of Dr Ilan Shimon

# Case history

# Case history #1

A 27-year-old woman presents with amenorrhoea. She had been taking the combined oral contraceptive pill for the last 9 years, stopping this 11 months ago. She is otherwise healthy, but on physical examination she has bilateral galactorrhoea. Laboratory work-up reveals an elevated prolactin level of 3000 mIU/L (150 micrograms/L). Normal prolactin levels are up to 500 mIU/L (25 micrograms/L). She also had low-normal gonadotrophin (luteinising hormone [LH], follicle-stimulating hormone [FSH]) levels. Magnetic resonance imaging (MRI) examination of the pituitary sellar region depicts a 6 mm right-sided pituitary mass, with no suprasellar or parasellar extension.

# Case history #2

A 45-year-old man presents with loss of libido and some erectile dysfunction. He is otherwise healthy. On physical examination he has mild bilateral gynaecomastia and normal testes. Laboratory work-up reveals a highly elevated prolactin level of 46,000 mIU/L (2300 micrograms/L). Normal prolactin levels are up to

# Other presentations

Prolactinomas, particularly where they are large tumours, can present with sudden headache, syncope, vomiting, fever, and visual impairment. All these symptoms may occur in the setting of pituitary apoplexy (a clinical syndrome resulting from acute haemorrhagic or ischaemic infarction of a pituitary adenoma). Occasionally, prolactinomas are incidentally detected during imaging evaluation (computed tomography or magnetic resonance imaging) of the brain for other unrelated medical conditions. Infrequently, prolactinoma may be a component of the familial syndrome of multiple endocrine neoplasia syndrome type 1, together with primary hyperparathyroidism and neuroendocrine tumours, most commonly in the gastrointestinal tract.

Theory

# Approach

Hyperprolactinaemia in premenopausal women results in galactorrhoea, menstrual irregularity, and infertility. Galactorrhoea is less common in post-menopausal women due to oestrogen deficiency. Men may also present with symptoms of secondary hypogonadism, such as reduced libido, impotence, and infertility. Later presentation in men and post-menopausal women means that these patients are more likely to present with locally invasive tumours which may compress adjacent structures in the suprasellar region (optic tracts or chiasm) or the parasellar cavernous sinuses (other cranial nerves), causing mass effect features (e.g., visual disturbances, ophthalmoplegia, headaches). Chronic hyperprolactinaemia with subsequent secondary hypogonadism may lead to osteoporosis.

## Hormonal determination

A single measurement of serum prolactin taken without significant venepuncture stress is sufficient to establish the diagnosis of hyperprolactinaemia. In cases of mild hyperprolactinaemia, it may be worth measuring several sequential prolactin measurements, separated by at least 20 minutes and taken via an indwelling cannula in order to minimise venepuncture stress. Secondary causes should be excluded by a careful history, examination, and pregnancy test. Mild prolactin level elevations, <2000 mIU/L (<100 micrograms/L), can occur with certain drugs, including typical and atypical antipsychotics (e.g., phenothiazines, risperidone, clozapine), opiates, anti-emetics (e.g., metoclopramide, domperidone), oestrogens, H2 blockers, and verapamil. Therefore it is important to take a full drug history.

Prolactin levels can be elevated in renal failure and in primary hypothyroidism, so renal and thyroid function should be checked prior to further investigating a raised prolactin level. Generally, prolactin levels associated with prolactinomas correspond with tumour size.[11] Most patients with a microprolactinoma will have a serum prolactin level between 2000 and 4000 mIU/L (100 and 200 micrograms/L), and a level of >5000 mIU/L (>250 micrograms/L) is almost certainly a macroprolactinoma.[12] In non-functioning pituitary adenomas, disconnection hyperprolactinaemia can occur. This is where prolactin is raised due to pituitary stalk compression impeding dopamine transport via the portal vessels to the anterior pituitary. In this setting, serum prolactin is normally <2000 mIU/L (<100 micrograms/L).[12]

In cases of significant hyperprolactinaemia, gonadotrophins (follicle-stimulating hormone, luteinising hormone) and estradiol/testosterone may be low, consistent with secondary hypogonadism. All patients, but particularly those with macroprolactinomas, should have assessment of the remainder of their pituitary function. Up to 50% of patients with growth hormone (GH)-secreting tumours causing acromegaly also have hyperprolactinaemia.[11] Therefore it is important to exclude this condition in patients with an elevated prolactin using clinical assessment, and random GH and insulin-like growth factor 1 measurement.

## **Pituitary imaging**

A gadolinium-enhanced magnetic resonance imaging is required to confirm the diagnosis of a prolactinoma. Computed tomography does not provide sufficient pituitary visualisation.

## Visual-field examination

Clinical visual-field examination is performed in all patients as part of the initial patient assessment. However, computerised visual field examination (perimetry) is also required in all patients with a macroadenoma with suprasellar extension to exclude the existence of optic chiasmal compression.

DIAGNOSIS

# History and exam

## Key diagnostic factors

## presence of risk factors (common)

• A key risk factor is female sex, aged between 20 and 50 years.

## amenorrhoea or oligomenorrhoea (common)

• Common presenting feature in women with prolactinoma.

## infertility (common)

• High prolactin inhibits ovulation in women.

#### galactorrhoea (common)

· Sometimes identified only during physical examination.

#### loss of sexual desire (libido) (common)

- Hyperprolactinaemia causes secondary hypogonadism.
- A particular clinical feature in men with prolactinoma.

## erectile dysfunction (common)

· Common presentation in men with prolactinoma.

## visual deterioration (e.g., temporal hemianopia) (common)

• Bilateral hemianopia occurs in patients with macroadenomas with suprasellar extension.

## Other diagnostic factors

#### osteoporosis (common)

• A consequence of low testosterone/estradiol level.

#### ophthalmoplegia (uncommon)

• Related to cranial nerve palsy.

#### headaches (uncommon)

• Related to pituitary apoplexy (a clinical syndrome resulting from acute haemorrhagic or ischaemic infarction of a pituitary adenoma).

# **Risk factors**

## Strong

#### female sex, 20 to 50 years of age

- Prolactin-secreting adenomas are more frequent in premenopausal women.
- There is a peak incidence between 20 to 50 years of age, and an estimated ratio of frequency between women and men of 10:1.[1]

## Weak

## genetic predisposition (e.g., presence of mutation resulting in multiple endocrine neoplasia-1 [MEN-1], familial isolated pituitary adenoma [FIPA])

Ninety-nine percent of prolactinomas are sporadic. However, pituitary adenomas, including
prolactinomas, can also occur as part of MEN-1 due to germline mutations in the gene encoding
menin (MEN-1). Prolactinomas also occur in the setting of FIPA due to inactivating germline mutations
of the gene encoding aryl hydrocarbon receptor-interacting protein, located close to that of MEN-1, on
chromosome 11q13.[8] [9]

#### oestrogen therapy

- •
- Medication-induced hyperprolactinaemia is associated with oestrogen therapy, but use of oral contraceptives or post-menopausal hormone replacement therapy does not increase susceptibility to prolactinoma development.[10]

#### male sex, 30 to 60 years of age

• Although prolactinomas are rare in men, if they do present in this age range it is usually with macroadenomas or they present incidentally.

## Diagnosis

# Investigations

## 1st test to order

Test	Result
<ul> <li>serum prolactin</li> <li>Blood sample should be collected at any time of day with minimal venepuncture stress.</li> <li>In asymptomatic patients with a high serum prolactin, macroprolactin should be measured. The majority (85%) of circulating prolactin is monomeric. Macroprolactin is a polymeric form, also known as 'big prolactin', which represents less than 5% of circulating prolactin. It consists of an antigen-antibody complex of monomeric prolactin and immunoglobulin G (IgG). Macroprolactin has limited bioavailability and bioactivity. Standard laboratory prolactin immunoassays do not reliably detect macroprolactin, and its presence needs to be confirmed by other methods, such as polyethylene glycol precipitation. In prolactinomas, serum prolactin concentration usually correlates with tumour size. In large (giant) macroprolactinnaes, serum prolactin concentrations may be so high that the antibodies used in immunoradiometric assays to measure prolactin are saturated, preventing formation of the prolactin antibody sandwich. The resultant loss of labelled antibody leads to falsely low values of prolactin. This assay artefact is termed the 'hook effect' and can be overcome by performing a 1:100 serum sample dilution. Elimination of a possible hook effect by dilution of serum prolactin samples is recommended where there is a discrepancy between tumour size and serum prolactin concentration.[11]</li> </ul>	elevated
<ul> <li>pituitary MRI</li> <li>A gadolinium-enhanced MRI of the pituitary is able to detect small microadenomas, and define the extension of invasive macroadenomas. Because approximately 12% of the normal population have asymptomatic pituitary adenomas, it is important to confirm a pathological elevation of prolactin prior to performing pituitary imaging.[11]</li> </ul>	characteristic features of pituitary adenoma
<ul> <li>computerised visual-field examination</li> <li>Performed in all patients with macroprolactinomas, particularly those with suprasellar extension and chiasmal compression.</li> </ul>	may reveal unilateral or bi- temporal hemianopia

# Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Non-functioning pituitary macroadenomas	<ul> <li>May be no differentiating signs or symptoms.</li> </ul>	<ul> <li>Usually mild hyperprolactinaemia up to 2000 mIU/L (100 micrograms/L) in the presence of a large pituitary mass compressing the pituitary stalk (disconnection hyperprolactinaemia).</li> <li>Pituitary MRI imaging demonstrates a macroadenoma. The mild elevation in prolactin for a pituitary adenoma this size makes this diagnosis, rather than a prolactinoma, more likely.</li> </ul>
Drug-induced hyperprolactinaemia	<ul> <li>There may be a drug history of antipsychotics, antidepressants, opiates, anti-emetics, oestrogens, H2 blockers, or verapamil.</li> </ul>	Prolactin evaluation after the patient stops the drug confirms decreasing prolactin levels. It may not be possible to discontinue certain medications, particularly antipsychotic medication. In this circumstance, pituitary MRI may help differentiate between drug-induced hyperprolactinaemia and elevated prolactin due to a sellar mass.[11]
Primary hypothyroidism	<ul> <li>There may be weight gain, cold intolerance, dry skin, constipation, or lethargy. In mild or subclinical hypothyroidism, there may be no differentiating symptoms.</li> </ul>	<ul> <li>Thyroid function tests confirm primary hypothyroidism.</li> <li>Hyperprolactinaemia should normalise following thyroid hormone replacement.</li> </ul>
Renal insufficiency	<ul> <li>May be no clear differentiating signs or symptoms.</li> </ul>	<ul> <li>Prolactin evaluation after renal improvement.</li> <li>Elevated serum creatinine, reduced creatinine clearance.</li> </ul>
Pregnancy	<ul> <li>May be no initial differentiating signs or symptoms.</li> </ul>	Pregnancy test is positive.
Polycystic ovarian syndrome	<ul> <li>Hirsutism or acne may be present. Body mass</li> </ul>	Testosterone may be     elevated. Sex hormone

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Condition	Differentiating signs / symptoms	Differentiating tests
	index may be >25 kg/m <sup>2</sup> . Menstrual irregularity may occur as with prolactinomas, but the history of oligo- or amenorrhoea is often longer in polycystic ovarian disease.	binding globulin may be low. Presence of ovarian cysts demonstrated on ultrasound.

# Criteria

## Serum prolactin level and prolactinoma size

Although a prolactinoma may be associated with any level of serum prolactin, usually the prolactin concentration reflects the size of the prolactinoma.[11] A prolactin level greater than 5000 mIU/L (250 micrograms/L) usually indicates the presence of a prolactinoma; however, some medications (e.g., risperidone, metoclopramide) also elevate prolactin levels.[11] A prolactin level greater than 10,000 mIU/L (500 micrograms/L) is almost certainly a macroprolactinoma.[11] In a patient with a serum prolactin <2000 mIU/L (<100 micrograms/L) and a macroadenoma (pituitary adenoma greater than 10 mm) on pituitary imaging, the diagnosis is likely to be a non-functioning pituitary adenoma causing disconnection hyperprolactinaemia (pituitary stalk compression).[11]

# Screening

The majority of pituitary tumours are sporadic. However, about 5% present in a familial setting. Consider screening young patients (<30 years at diagnosis) presenting with large prolactinomas for aryl hydrocarbon receptor-interacting protein (AIP) gene mutations and multiple endocrine neoplasia syndrome type 1.[6] [7] In studies of patients with familial isolated pituitary adenoma, prolactinomas associated with AIP gene mutations were large, occurred at a young age (<30 years), were invasive, had suprasellar extension, and were resistant to dopamine agonist treatment.[4] [5]

# Approach

The primary goal of treatment is to suppress and normalise prolactin levels, thus restoring ovulation in women and normalising testosterone and sexual function in men.

In addition, patients with macroprolactinomas are treated to achieve tumour size reduction and decrease mass effects, particularly visual defects. Intolerable galactorrhoea also requires active treatment.

Women with microprolactinomas, mild galactorrhoea, and normal menstrual cycles may be monitored and not treated.

## Treatment with dopamine agonists

Medical treatment with dopamine agonists is the primary treatment in men and women for both microprolactinomas and macroprolactinomas.[11] [13] Dopamine agonists are potent inhibitors of prolactin secretion and synthesis. These agents reduce the volume of the lactotroph cells, thus decreasing the size of both micro- and macroprolactinomas. This continuous treatment will normalise prolactin in about 90% of patients; restore gonadal function, libido, and fertility; and shrink the tumour.[11] Galactorrhoea should disappear.

Cabergoline is the recommended first-line dopamine agonist due to superior efficacy in normalising serum prolactin and reducing tumour size, better tolerability, and a more convenient dosing regimen.[11] [13] Treatment usually starts at low doses to avoid adverse effects, with a gradual dose escalation during the first months upon achieving control of the hyperprolactinaemia and tumour shrinkage. After these are achieved, and prolactin is stably controlled for 1-2 years, the dopamine agonist dose can be gradually decreased, provided it maintains normal prolactin levels and controls tumour size.

Women with microprolactinomas and amenorrhoea or menstrual irregularities, who do not desire pregnancy, may be offered oestrogen/progesterone treatment instead of a dopamine agonist.[11] Besides providing contraception, this treatment will achieve menstrual regularity. Oral oestrogen/progesterone treatment does not appear to promote growth of microprolactinomas.[11]

Because the dopamine agonists bromocriptine and cabergoline decrease prolactin levels and promote the return of a regular menstrual cycle and ovulation, pregnancy may occur whilst women are taking these medications. They are usually discontinued as soon as pregnancy is confirmed.[11] In those patients with large macroprolactinomas, particularly those abutting the optic chiasm, dopamine agonists may be continued throughout pregnancy.[14] [15] Due to its more widespread use, women are more likely to be receiving cabergoline rather than bromocriptine for treatment of their prolactinoma at the time of conception. Cabergoline has been introduced more recently than bromocriptine, and therefore, there are fewer safety data relating to maternal and fetal exposure to cabergoline compared with bromocriptine. Nevertheless, observational research has been unable to find an increase in miscarriage or fetal malformations in association with exposure to cabergoline in early pregnancy.[16] Bromocriptine is an alternative dopamine agonist that can be used for this indication.

Post-menopausal women with microadenoma or undetectable pituitary mass do not usually require any treatment. Galactorrhoea usually improves when endogenous oestrogen decreases post-menopausally.



Gadolinium-enhanced magnetic resonance imaging (coronal view) showing a 40 mm pituitary macroprolactinoma in a 41-year-old man before (A) and after (B) 2-month treatment with cabergoline From the collection of Dr Ilan Shimon



Gadolinium-enhanced magnetic resonance imaging (sagittal view) showing a 40 mm pituitary macroprolactinoma in a 41-year-old man before (A) and after (B) 2-month treatment with cabergoline From the collection of Dr Ilan Shimon

## Dopamine agonist resistance and intolerance

Patients in whom prolactin does not normalise on maximally tolerated doses of dopamine agonists, or tumour size is not reduced by 50%, are considered to be dopamine agonist resistant.[13] Resistance to cabergoline occurs in approximately 10% of patients with a microprolactinoma compared with 15% to 20% with a macroprolactinoma.[17]

This PDF of the BMJ Best Practice topic is based on the web version that was last updated: Jul 22, 2022. BMJ Best Practice topics are regularly updated and the most recent version of the topics can be found on <u>bestpractice.bmj.com</u>. Use of this content is subject to our<u>disclaimer (.</u> <u>Use of this content is subject to our)</u>. © BMJ Publishing Group Ltd 2025. All rights reserved. Patients resistant or intolerant to dopamine agonists should be referred for trans-sphenoidal surgery, in centres with experienced neurosurgeons, for prolactinoma resection.[11] [18] Surgery will immediately improve visual function in most cases of macroprolactinomas compressing the optic tract. Trans-sphenoidal surgery may be complicated, particularly in cases of large and invasive macroadenomas, and can result in anterior pituitary dysfunction and/or diabetes insipidus requiring permanent hormonal replacement.

Malignant prolactinomas exhibiting metastatic spread within or outside the central nervous system are rare. Radiotherapy is rarely used and is reserved for dopamine agonist-resistant or malignant prolactinomas.[11]

## Dopamine agonists and valvular heart disease

Reported associations between high doses of cabergoline used in the treatment of Parkinson's disease and cardiac valvulopathy has led to concerns about the safety of cabergoline treatment in patients with prolactinomas.[19] However, patients receiving cabergoline for hyperprolactinaemia are typically younger, female, and taking much lower doses than those used in Parkinson's disease. Evidence does not support a clinically significant association between cabergoline treatment for prolactinomas and valvular heart disease.[20] Recommendations on the timing and frequency of screening for cardiac valve disease in patients receiving cabergoline for hyperprolactinaemia vary.[21] [22] Patients should receive the lowest effective dose of cabergoline for the shortest possible duration. Echocardiographic surveillance may be performed on patients likely to receive moderate or high doses of cabergoline for a considerable duration.[22] [23]

## Dopamine agonists and psychiatric adverse effects

Although dopamine agonists are well tolerated by the majority of patients for prolactinoma management, a small number of patients may develop psychiatric disturbances, including impulse control disorders.[14] Further studies are needed to elucidate specific risk factors for the development of psychiatric disturbance with dopamine agonists, but currently, clinicians are advised to monitor carefully for mood disturbance and the development of impulse control disorders. For those patients with pre-existing psychiatric disorders, dopamine agonists should be used with caution in the management of prolactinoma, and alternative treatment options, such as trans-sphenoidal surgery, should be considered.

## Dopamine agonist withdrawal

In view of concerns about the association of the long-term use of dopamine agonists with valvular heart disease, there has been emphasis on a trial of drug withdrawal in certain patients with prolactinoma to minimise exposure.[24] A trial of dopamine agonist withdrawal is most likely to be successful if attempted in patients in whom there has been restoration of normal serum prolactin, significant reduction in tumour size on magnetic resonance imaging, low maintenance doses of dopamine agonists, and a treatment duration of at least 2 years.[11] [25] Remission of hyperprolactinaemia in patients with prolactinoma following dopamine agonist withdrawal varies between studies, with greater success in microprolactinomas (approximately 40%) compared to macroprolactinomas (approximately 30%).[25] Because approximately one third of patients may develop secondary hypogonadism following recurrence of hyperprolactinaemia, regular monitoring of serum prolactin for the first year after drug withdrawal is recommended, with pituitary magnetic resonance imaging if hyperprolactinaemia recurs.[11]

# Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: <u>see disclaimer</u>

Ongoing (summary				
pre-menopausal women				
•	asymptomatic microprolactinomas, normal menstrual cycle, and who do not desire pregnancy	1st	observation	
	symptomatic microprolactinomas who do not desire pregnancy	1st	dopamine agonist	
		2nd	combined oral contraceptive	
		3rd	trans-sphenoidal surgery	
		4th	sellar radiotherapy	
••••••	microprolactinomas who desire pregnancy, or macroprolactinomas	1st	dopamine agonist	
		2nd	trans-sphenoidal surgery	
		3rd	sellar radiotherapy	
post-meno	pausal women			
	microadenomas	1st	observation	
•••••	macroadenomas	1st	dopamine agonist	
		2nd	trans-sphenoidal surgery	
		3rd	sellar radiotherapy	
men				
••••••	microadenomas or macroadenomas	1st	dopamine agonist	
		2nd	trans-sphenoidal surgery	
		3rd	sellar radiotherapy	

MANAGEMENT

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# **Treatment algorithm**

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: <u>see disclaimer</u>

## Ongoing

#### pre-menopausal women

 asymptomatic microprolactingmas	1st	observation
normal menstrual cycle, and who do not desire pregnancy		» Women who are asymptomatic and have normal menstrual cycles may be monitored and do not require treatment.[11]
 symptomatic	1st	dopamine agonist
microprolactinomas who do not desire pregnancy		Primary options
		» cabergoline: 0.25 mg orally twice weekly or 0.5 mg orally once weekly initially, increase by 0.5 mg/dose increments every 4 weeks, increase dose gradually until desired reduction in prolactin levels and/or tumour Adequate response to therapy (normalisation of serum prolactin and tumour shrinkage on magnetic resonance imaging) usually requires a dose of less than 2 mg/week.
		Secondary options
		» bromocriptine: 1.25 to 2.5 mg/day orally initially, increase by 2.5 mg/day increments every 2-7 days, increase dose gradually until desired reduction in prolactin levels and/or tumour
		» Medical treatment with dopamine agonists is considered the first-line therapy for prolactinomas.[11]
		» Even in women who do not desire pregnancy, dopamine agonists are considered initially to treat other symptoms (e.g., troublesome galactorrhoea).
		» The patient should be aware that treatment may result in return of fertility and alternative forms of contraception may be required.
		Treatment usually starts at low doses to avoid adverse effects, with a gradual dose escalation during the first months upon achieving control of the hyperprolactinaemia and tumour shrinkage.
		» A trial of dopamine agonist withdrawal is most likely to be successful if attempted in patients in whom there has been restoration of

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normal serum prolactin, significant reduction in tumour size on magnetic resonance imaging, maintenance of normal serum prolactin using a low dose of dopamine agonist, and a treatment duration of at least 2 years.[11] [25]

» Remission of hyperprolactinaemia in patients with prolactinoma following dopamine agonist withdrawal varies between studies, with greater success in microprolactinomas (approximately 40%) compared with macroprolactinomas (approximately 30%).[25]

» Cabergoline is the recommended first-line dopamine agonist due to superior efficacy in normalising serum prolactin and reducing tumour size, better tolerability, and more convenient dosing regimen.[11] [13]

#### 2nd combined oral contraceptive

» There are no controlled trials to compare the use of dopamine agonists and the combined oral contraceptive pill in women with microprolactinomas and oligo-/amenorrhoea. If women with microadenomas have no symptoms beside menstrual irregularities and do not desire pregnancy, then oestrogen with cyclical progesterone therapy may be considered (e.g., oestrogen/progesterone combined oral contraceptive pill), without dopamine agonist therapy. Besides providing contraception, this treatment is used to achieve menstrual regularity.

#### 3rd trans-sphenoidal surgery

» Trans-sphenoidal surgery may be considered for those who do not tolerate dopamine agonists or whose symptoms are not responding to dopamine agonists.[11] [18]

» Trans-sphenoidal surgery may be complicated and result in anterior pituitary failure and/or diabetes insipidus requiring permanent hormonal replacement, although this is more likely in cases of large and invasive macroadenomas.

» Dopamine agonist therapy may need to be continued following surgery if symptomatic hyperprolactinaemia persists.

#### 4th sellar radiotherapy

» Radiotherapy is rarely used and is reserved for situations where medical and surgical treatments have failed, and for the rare cases of malignant prolactinomas.[11]

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microprolactinomas who desire pregnancy, or macroprolactinomas 1st

» Both conventional radiotherapy and stereotactic radiotherapy do not achieve more than 20% to 40% prolactin normalisation rate in patients with prolactinomas.[17] Thus, most prolactin-secreting adenomas are radioresistant, and this mode of therapy is not an acceptable primary treatment for prolactinomas.

» Pituitary radiotherapy is associated with significant long-term morbidity, including hypopituitarism (up to 50% after 10-20 years), cerebrovascular accidents, optic nerve damage, cognitive deterioration, and secondary radiationinduced brain malignancies.

#### dopamine agonist

#### **Primary options**

» cabergoline: 0.25 mg orally twice weekly or 0.5 mg orally once weekly initially, increase by 0.5 mg/dose increments every 4 weeks, increase dose gradually until desired reduction in prolactin levels and/or tumour Adequate response to therapy (normalisation of serum prolactin and tumour shrinkage on magnetic resonance imaging) usually requires a dose of less than 2 mg/week.

#### **Secondary options**

» bromocriptine: 1.25 to 2.5 mg/day orally initially, increase by 2.5 mg/day increments every 2-7 days, increase dose gradually until desired reduction in prolactin levels and/or tumour

» Medical treatment with dopamine agonists is considered the first-line therapy for prolactinomas in women.[11]

» Treatment usually starts at low doses to avoid adverse effects, with a gradual dose escalation during the first months with the aim of achieving control of the hyperprolactinaemia and tumour shrinkage.

» Macroprolactinomas usually require higher doses of dopamine agonist compared with microprolactinomas.

» Cabergoline is the recommended first-line dopamine agonist due to superior efficacy in normalising serum prolactin and reducing tumour size, better tolerability, and more convenient dosing regimen.[11] [13]

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### Management

## Ongoing

» There is minimal risk of microprolactinoma enlargement in pregnancy and therefore dopamine agonists can be stopped once pregnancy is confirmed.[11] Because risk of enlargement of macroprolactinomas in pregnancy is greater (20% to 30%), dopamine agonists may be continued throughout pregnancy or recommenced if visual fields deteriorate.[15] Prolactin increases in pregnancy and therefore serum prolactin measurements are not useful in monitoring prolactinoma patients during pregnancy. Both bromocriptine and cabergoline have been shown to be safe in pregnancy.[14] [15]

» A trial of dopamine agonist withdrawal is most likely to be successful if attempted in patients in whom there has been restoration of normal serum prolactin, significant reduction in tumour size on magnetic resonance imaging, low maintenance doses of dopamine agonists, and a treatment duration of at least 2 years.[11] [25]

» Remission of hyperprolactinaemia in patients with prolactinoma following dopamine agonist withdrawal varies between studies, with greater success in microprolactinomas (approximately 40%) compared with macroprolactinomas (approximately 30%).[25] Therefore, in a woman with a prolactinoma who is planning pregnancy, it may be sensible to defer plans for a trial of dopamine agonist withdrawal until she has completed her family.

#### 2nd trans-sphenoidal surgery

» Trans-sphenoidal surgery may be considered for those who do not tolerate dopamine agonists or whose symptoms are not responding to dopamine agonists.[11] [18]

» Trans-sphenoidal surgery may be complicated and result in anterior pituitary failure and/or diabetes insipidus requiring permanent hormonal replacement, although this is more likely in cases of large and invasive macroadenomas.

» Dopamine agonist therapy may need to be continued following surgery if symptomatic hyperprolactinaemia persists.

#### sellar radiotherapy

» Radiotherapy is rarely used and is reserved for situations where medical and surgical treatments have failed, and for the rare cases of malignant prolactinomas.[11]

3rd

21

» Both conventional radiotherapy and stereotactic radiotherapy do not achieve more than 20% to 40% prolactin normalisation rate in patients with prolactinomas.[17] Thus, most prolactin-secreting adenomas are radioresistant, and this mode of therapy is not an acceptable primary treatment for prolactinomas.
» Pituitary radiotherapy is associated with significant long-term morbidity, including hypopituitarism (up to 50% after 10-20 years), cerebrovascular accidents, optic nerve damage, cognitive deterioration, and secondary radiation- induced brain malignancies.

#### post-menopausal women

 microadenomas	1st	observation
		» Post-menopausal women with microadenoma or undetectable pituitary mass do not usually require any treatment.
		» Any galactorrhoea usually improves when oestrogens decrease post-menopausally.
 macroadenomas	1st	dopamine agonist
		Primary options
		» cabergoline: 0.25 mg orally twice weekly or 0.5 mg orally once weekly initially, increase by 0.5 mg/dose increments every 4 weeks, increase dose gradually until desired reduction in prolactin levels and/or tumour Adequate response to therapy (normalisation of serum prolactin and tumour shrinkage on magnetic resonance imaging) usually requires a dose of less than 2 mg/week.
		Secondary options
		» bromocriptine: 1.25 to 2.5 mg/day orally initially, increase by 2.5 mg/day increments every 2-7 days, increase dose gradually until desired reduction in prolactin levels and/or tumour
		» Medical treatment with dopamine agonists is considered the first-line therapy.[11]
		» Treatment usually starts at low doses to avoid adverse effects, with a gradual dose escalation during the first months with the aim of achieving control of the hyperprolactinaemia and tumour shrinkage.

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» Remission of hyperprolactinaemia in patients with prolactinoma following dopamine agonist withdrawal varies between studies, with greater success in microprolactinomas (approximately 40%) compared to macroprolactinomas (approximately 30%).[25]

» Cabergoline is the recommended first-line dopamine agonist due to superior efficacy in normalising serum prolactin and reducing tumour size, better tolerability, and more convenient dosing regimen.[11] [13]

#### 2nd trans-sphenoidal surgery

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3rd

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#### men

microadenomas or macroadenomas

1st

#### dopamine agonist

#### **Primary options**

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#### **Secondary options**

» bromocriptine: 1.25 to 2.5 mg/day orally initially, increase by 2.5 mg/day increments every 2-7 days, increase dose gradually until desired reduction in prolactin levels and/or tumour

» Medical treatment with dopamine agonists is considered the first-line therapy.[11]

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MANAGEMENT

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#### sellar radiotherapy

3rd

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# Emerging

## Novel somatostatin receptor 5 (SSTR5)-selective analogues

Prolactinomas express SSTR5 among the other recognised human SSTRs. Octreotide and lanreotide, the clinically available somatostatin analogues, bind poorly to SSTR5 and have proven to be ineffective for treatment of prolactinoma.[1] The novel somatostatin analogue pasireotide has a more universal SSTR binding profile, with improved binding affinity to SSTR1, SSTR2, SSTR3, and SSTR5. Pasireotide has achieved biochemical and tumour control in several case reports of patients with highly aggressive, dopamine agonist-resistant prolactinoma.[26] [27] However, further studies are required to determine its role in treatment of prolactinoma.[28]

## Temozolomide

Temozolomide is an alkylating agent that can be given orally and is used to treat patients with astrocytoma or glioblastoma. The effectiveness of temozolomide in reducing tumour size and serum prolactin in aggressive or malignant prolactinomas resistant to conventional therapies has been reported. The DNA repair enzyme O6-methyl-guanine-DNA methyltransferase (MGMT) protects tumour cells from alkylating agents. Prolactinomas with absent MGMT protein expression appear to be more likely to respond to temozolomide, although positive responses have also been observed in patients with prolactinomas that are MGMT-immunopositive.[29] Although results appear encouraging, data from these small case studies must be confirmed in larger, prospective clinical trials. Malignant or aggressive prolactinomas, particularly if resistant to dopamine agonists, may benefit from temozolamide (used off-label).[11] [30]

# Patient discussions

- Women with prolactinomas should be instructed that dopamine agonist treatment may restore ovulation and fertility within a very short time, thus contraception should be used to prevent unplanned pregnancy.
- Patients with large macroprolactinomas must be warned about symptoms suggesting acute apoplexy (severe headache, vomiting, visual impairment, ocular palsy due to acute haemorrhagic or ischaemic infarction of the adenoma) while treated medically. Apoplexy may require urgent transsphenoidal pituitary decompression.

**Follow up** 

# Monitoring

## Monitoring

- Periodic measurement of serum prolactin.
- Initially, pituitary magnetic resonance imaging is recommended every year (more frequently in macroadenomas or in patients where serum prolactin continues to rise despite dopamine agonist treatment). The frequency of imaging can reduce once there is suppression of serum prolactin into the normal range and a stable tumour remnant.
- Regular visual field examination (perimetry) is required in patients with visual field disturbance secondary to optic chiasmal compression, until maximal improvement is achieved. Patients with macroprolactinomas should also have regular perimetry to monitor for development of new field defects suggesting tumour growth and optic chiasmal compression.
- In patients with macroprolactinomas, pituitary hormone axes (testosterone, thyroid function tests) should be assessed every 3-6 months if hypopituitarism is treated with hormone replacement (thyroid hormone, glucocorticoids, testosterone/oestrogen). Hypopituitarism may sometimes resolve with successful tumour shrinkage by a dopamine agonist.
- Patients using high-dose cabergoline for a long time should be monitored by echocardiography for the rare adverse effect of valvulopathy.

# Complications

Complications	Timeframe	Likelihood		
visual field impairment	short term	high		
Visual field defects (bilateral hemianopia) are commonly identified in untreated patients with large macroprolactinomas compressing the optic chiasm.[32]				
However, rapid improvement can occur if dopamine agonist there	apy is initiated as early	/ as possible.		
anterior pituitary failure and/or diabetes insipidus	long term	high		
Trans-sphenoidal surgery may be complicated and result in ante insipidus requiring permanent hormonal replacement, particularl macroprolactinomas.	rior pituitary failure an y in cases of large and	d/or diabetes d invasive		
hypopituitarism associated with radiotherapy	long term	high		
Pituitary radiotherapy is rarely used for prolactinomas as it is ass morbidity, including hypopituitarism.[32]	sociated with significar	nt long-term		
cabergoline-associated valvular insufficiency	long term	low		
<ul> <li>disease, particularly valvular regurgitation.[19] However, cabergoline is usually used at much lower doses to treat prolactinomas.</li> <li>Evidence does not support a significant clinical association between cabergoline treatment for prolactinomas and valvular heart disease.[20]</li> <li>Patients should receive the lowest effective dose of cabergoline for the shortest possible duration. Echocardiographic surveillance may be performed on patients likely to receive moderate or high doses of cabergoline for a considerable duration.[22] [23]</li> </ul>				
dopamine-agonist psychiatric disturbances	variable	low		
Although dopamine agonists are well tolerated by the majority of patients for prolactinoma management, a small number of patients may develop psychiatric disturbances, including impulse control disorders.[14] Further studies are needed to elucidate specific risk factors for the development of psychiatric disturbance with dopamine agonists, but currently clinicians are advised to monitor carefully for mood disturbance and the development of impulse control disorders. For those patients with pre-existing psychiatric disorders, dopamine agonists should be used with caution in the management of prolactinoma, and alternative treatment options, such as trans-sphenoidal surgery, should be considered.				
pituitary apoplex y	variable	low		
<ul> <li>Patients may present with acute symptoms, including severe headache, vomiting, visual impairment, ocular palsy, or death, due to acute haemorrhage into or ischaemic infarction of a large pituitary prolactinoma (pituitary apoplexy).[33] [34]</li> <li>Pituitary apoplexy may occur as the presenting sign. Triggers such as the use of anticoagulants, oestrogen administration, or use of dopamine agonist treatment have been reported.[34]</li> <li>Many patients experience long-term symptoms, suggesting pituitary hormone dysfunction, before apoplexy.</li> </ul>				
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FOLLOW UP

## Follow up

Likelihood

## Complications

Some patients with apoplexy of a prolactinoma, with mild symptoms and no visual deficit, improve spontaneously and can be managed conservatively with dopamine agonists and supportive care.[35]

Timeframe

Patients with symptomatic apoplexy may be referred for trans-sphenoidal surgery.[33]

Dopamine agonists are usually required if a patient remains hyperprolactinaemic despite trans-sphenoidal surgery for pituitary apoplexy.

cerebrospinal fluid leakage	variable	low
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Rhinorrhoea may occur as a presenting sign of large invasive macroprolactinomas or during medical treatment with high-dose dopamine agonist for these tumours.[32]

Sometimes this complication requires surgical intervention to decrease the risk for bacterial meningitis.

# Prognosis

This benign disease follows a progressive improving course while medically treated. Since the introduction of bromocriptine in the 1970s into the treatment of prolactinomas, the course of this condition has changed and the prognosis improved. Today, even when large invasive macroadenomas or giant prolactinomas are diagnosed with chiasmal compression and bilateral temporal hemianopia, continuous treatment with relatively large doses of dopamine agonists will result in prolactin normalisation, tumour shrinkage or disappearance, and rapid visual improvement.[31] In some patients, dopamine agonist treatment may be withdrawn after several years without tumour recurrence.[25]

# **Diagnostic guidelines**

## Europe

Clinical practice guidelines for the management of aggressive pituitary tumours and carcinomas (https://www.ese-hormones.org/publications/guidelines)

Published by: European Society of Endocrinology

Last published: 2018

## International

Emergency management of pituitary apoplexy in adult patients (https:// www.endocrinology.org/clinical-practice/clinical-guidance/society-forendocrinology-guidance)

Published by: Society for Endocrinology

Last published: 2016

## North America

ACR appropriateness criteria: neuroendocrine imaging (https://www.acr.org/ Clinical-Resources/Clinical-Tools-and-Reference/Appropriateness-Criteria)

Published by: American College of Radiology

Last published: 2018

Diagnosis and treatment of hyperprolactinemia (https://www.endocrine.org/ clinical-practice-guidelines/neuroendocrinology)

Published by: The Endocrine Society

Last published: 2011

# **Treatment guidelines**

## Europe

Clinical practice guidelines for the management of aggressive pituitary tumours and carcinomas (https://www.ese-hormones.org/publications/guidelines)

Published by: European Society of Endocrinology

Last published: 2018

## International

Position statement for clinical practice: prolactin-secreting tumors (https://eje.bioscientifica.com/view/journals/eje/186/3/EJE-21-0977.xml)

**Published by:** Italian Association of Clinical Endocrinologists (AME) and Last published: 2022 International Chapter of Clinical Endocrinology (ICCE)

Emergency management of pituitary apoplexy in adult patients (https:// www.endocrinology.org/clinical-practice/clinical-guidance/society-forendocrinology-guidance)

Published by: Society for Endocrinology

Last published: 2016

## North America

Diagnosis and treatment of hyperprolactinemia (https://www.endocrine.org/ clinical-practice-guidelines/neuroendocrinology)

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# Images



Optic chiasm Pituitary nicroprolactinoma

*Figure 1: Gadolinium-enhanced magnetic resonance imaging showing a left-sided 7 mm pituitary microprolactinoma* 

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Figure 2: Gadolinium-enhanced magnetic resonance imaging showing a large pituitary macroadenoma in a 45-year-old man with hyperprolactinaemia

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Figure 3: Gadolinium-enhanced magnetic resonance imaging (coronal view) showing a 40 mm pituitary macroprolactinoma in a 41-year-old man before (A) and after (B) 2-month treatment with cabergoline

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Figure 4: Gadolinium-enhanced magnetic resonance imaging (sagittal view) showing a 40 mm pituitary macroprolactinoma in a 41-year-old man before (A) and after (B) 2-month treatment with cabergoline

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This approach is in line with the guidance of the International Bureau of Weights and Measures Service.

#### Figure 1 – BMJ Best Practice Numeral Style

5-digit numerals: 10,000

4-digit numerals: 1000

numerals < 1: 0.25

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