BMJ Best Practice

Prolactinoma

Straight to the point of care

Last updated: Jul 22, 2022

Table of Contents

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.

THEORY

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

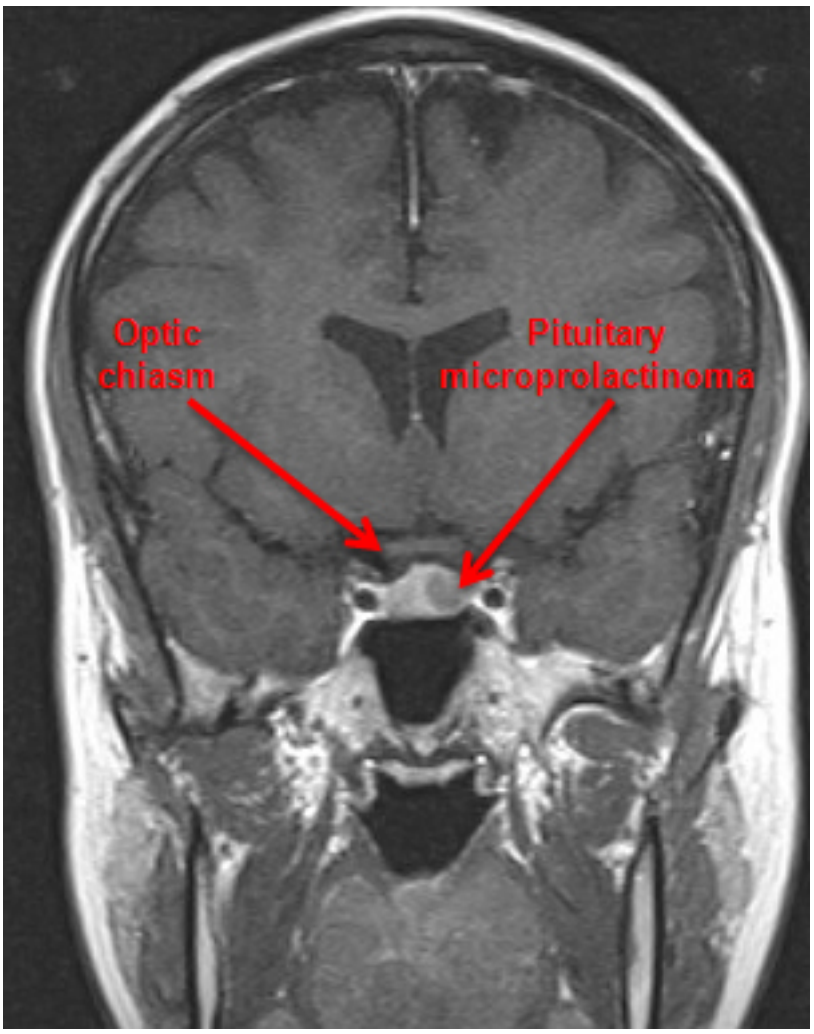
Microadenomas:

- 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

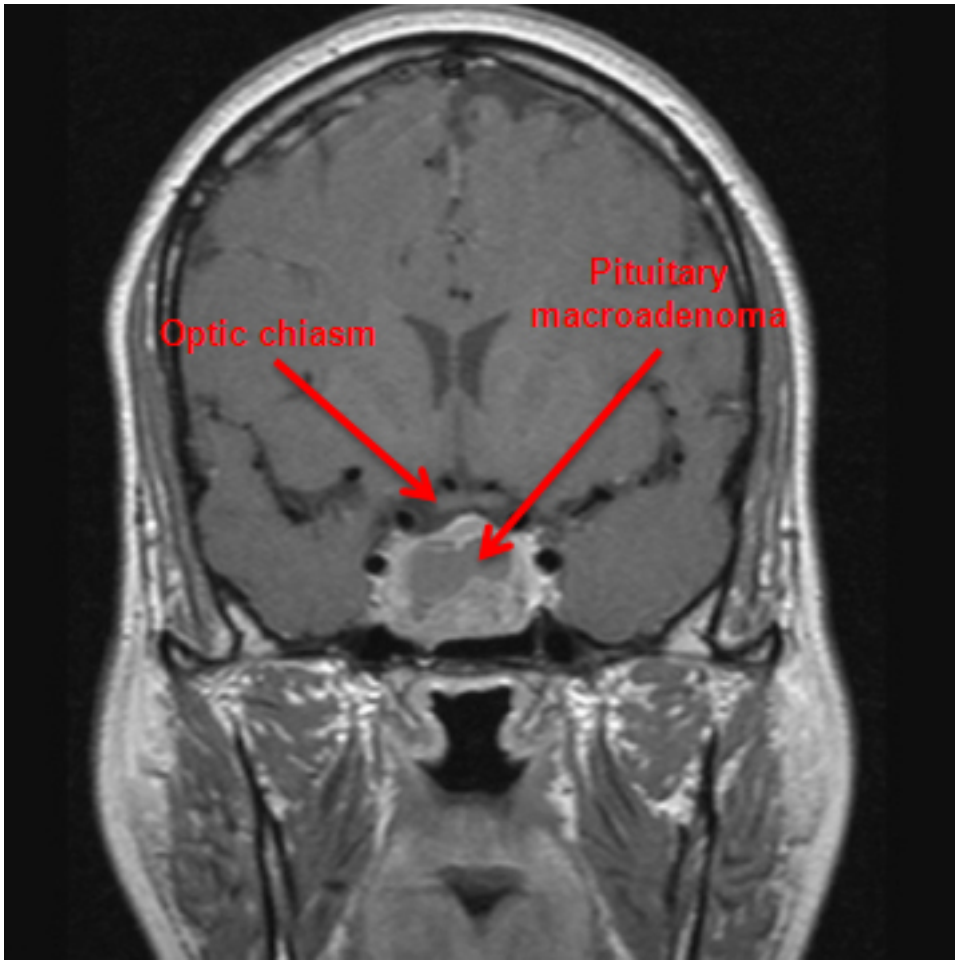
- Men and post-menopausal women more commonly present with large and invasive adenomas, occasionally giant tumours (4 cm or greater)
- Almost invariably benign (malignant prolactinomas that metastasise outside the pituitary sella are very rare).



Gadolinium-enhanced magnetic resonance imaging showing a left-sided 7 mm pituitary microprolactinoma

From the collection of Dr Ilan Shimon

THEORY



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 300 mIU/L (15 micrograms/L). He also has low testosterone, LH, and FSH levels. MRI examination of the pituitary sella depicts a large 32 mm pituitary macroadenoma with suprasellar extension and optic chiasmal compression. Visual field assessment reveals bi-temporal hemianopia.

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.

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.

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.

Investigations

1st test to order

Test	Result
serum prolactin • Blood sample should be collected at any time of day with minimal venepuncture stress. • 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) macroprolactinomas, 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]	**elevated**
pituitary MRI • 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]	**characteristic features of pituitary adenoma**
computerised visual-field examination • Performed in all patients with macroprolactinomas, particularly those with suprasellar extension and chiasmal compression.	**may reveal unilateral or bi-temporal hemianopia**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Non-functioning pituitary macroadenomas	• May be no differentiating signs or symptoms.	• 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). • 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.
Drug-induced hyperprolactinaemia	• There may be a drug history of antipsychotics, antidepressants, opiates, anti-emetics, oestrogens, H2 blockers, or verapamil.	• 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	• There may be weight gain, cold intolerance, dry skin, constipation, or lethargy. In mild or subclinical hypothyroidism, there may be no differentiating symptoms.	• Thyroid function tests confirm primary hypothyroidism. Hyperprolactinaemia should normalise following thyroid hormone replacement.
Renal insufficiency	• May be no clear differentiating signs or symptoms.	• Prolactin evaluation after renal improvement. • Elevated serum creatinine, reduced creatinine clearance.
Pregnancy	• May be no initial differentiating signs or symptoms.	• Pregnancy test is positive.
Polycystic ovarian syndrome	• Hirsutism or acne may be present. Body mass	• Testosterone may be elevated. Sex hormone

Condition	Differentiating signs / symptoms	Differentiating tests
	index may be >25 kg/m². 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

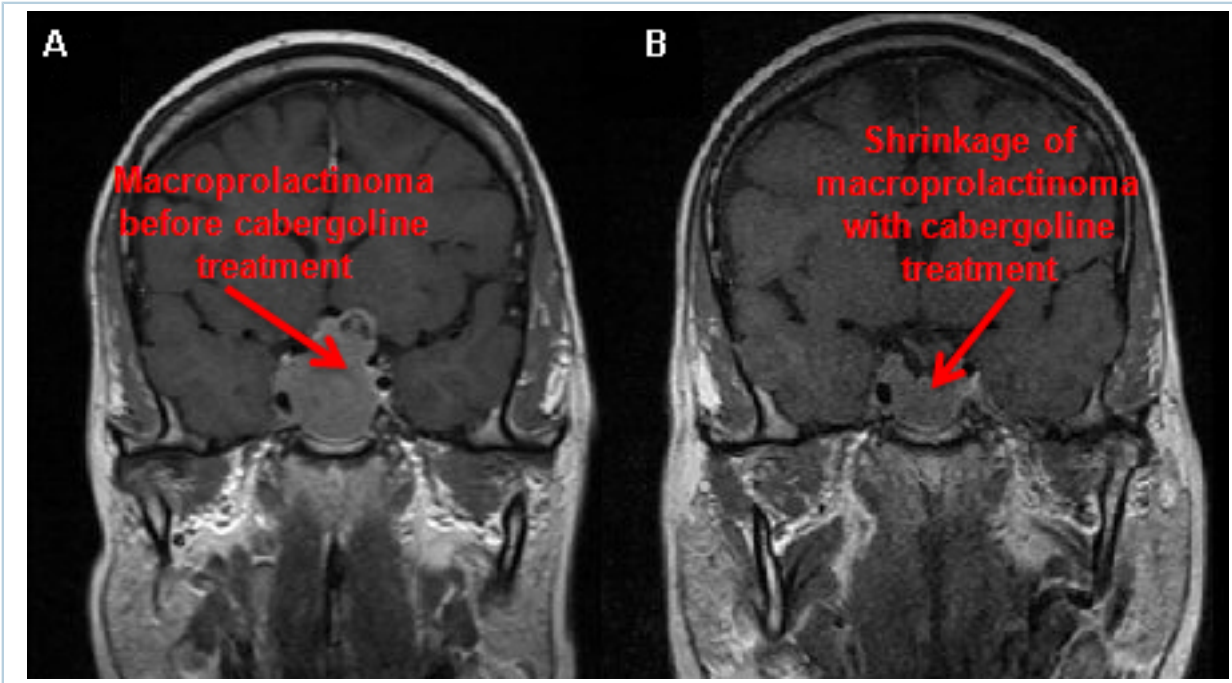
Medical treatment with dopamine agonists is the primary treatment in men and women for both microprolactinomas and macroprolactinomas.[11] [13] Dopamine agonists are potent inhibitors of prolactin secretion and synthesis. These agents reduce the volume of the lactotroph cells, thus decreasing the size 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]

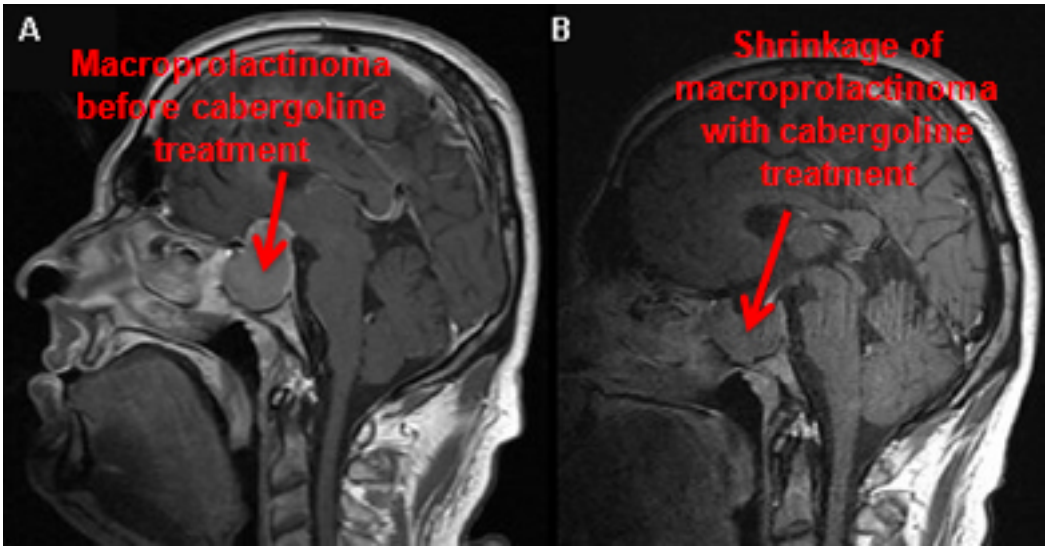
Because the dopamine agonists bromocriptine and cabergoline decrease prolactin levels and promote the return of a regular menstrual cycle and ovulation, pregnancy may occur whilst women are taking these medications. They are usually discontinued as soon as pregnancy is confirmed.[11] In those patients 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]

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: see disclaimer

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-menopausal 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**

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: see disclaimer

Ongoing

pre-menopausal women

asymptomatic microprolactinomas, normal menstrual cycle, and who do not desire pregnancy

1st **observation**

» Women who are asymptomatic and have normal menstrual cycles may be monitored and do not require treatment.[11]

symptomatic microprolactinomas who do not desire pregnancy

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 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 normal serum prolactin, significant reduction in

Ongoing

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]

» Both conventional radiotherapy and stereotactic radiotherapy do not achieve more

Ongoing

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.

microprolactinomas who desire pregnancy, or macroprolactinomas — **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 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]

» There is minimal risk of microprolactinoma enlargement in pregnancy and therefore dopamine agonists can be stopped once pregnancy is confirmed.[11] Because risk

Ongoing

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.

3rd **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]

» 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,

Ongoing

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.

» 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]

MANAGEMENT

Ongoing

» 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**

» 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.

3rd **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]

» 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.

men

microadenomas or macroadenomas **1st** **dopamine agonist**

Primary options

Ongoing

» 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.

» 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]

» 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]

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.

3rd **sellar radiotherapy**

Ongoing

» 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]

» 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.

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 trans-sphenoidal pituitary decompression.

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.

FOLLOW UP

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 therapy 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 anterior pituitary failure and/or diabetes insipidus requiring permanent hormonal replacement, particularly in cases of large and invasive macroprolactinomas.		
hypopituitarism associated with radiotherapy	**long term**	**high**
Pituitary radiotherapy is rarely used for prolactinomas as it is associated with significant long-term morbidity, including hypopituitarism.[32]		
cabergoline-associated valvular insufficiency	**long term**	**low**
When given in very high doses, such as for Parkinson's disease, cabergoline may result in valvular heart disease, particularly valvular regurgitation.[19] However, cabergoline is usually used at much lower doses to treat prolactinomas. Evidence does not support a significant clinical association between cabergoline treatment for prolactinomas and valvular heart disease.[20] 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-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 apoplexy	**variable**	**low**
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] 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] Many patients experience long-term symptoms, suggesting pituitary hormone dysfunction, before apoplexy.		

Complications	Timeframe	Likelihood
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] 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**
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-for-endocrinology-guidance)

Published by: Society for Endocrinology **Last published:** 2016

North America

ACR appropriateness criteria: neuroendocrine imaging (https://www.acr.org/Clinical-Resources/ACR-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 International Chapter of Clinical Endocrinology (ICCE) **Last published:** 2022

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

Published by: Society for Endocrinology **Last published:** 2016

North America

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

Published by: The Endocrine Society **Last published:** 2011

REFERENCES

Key articles

- Wildemberg LE, Fialho C, Gadelha MR. Prolactinomas. Presse Med. 2021 Dec;50(4):104080. Full text (https://www.sciencedirect.com/science/article/pii/S0755498221000191) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/34687915?tool=bestpractice.bmj.com)
- Melmed S, Casanueva FF, Hoffman AR, et al; Endocrine Society. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011 Feb;96(2):273-88. Full text (https://academic.oup.com/jcem/article/96/2/273/2709487) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/21296991?tool=bestpractice.bmj.com)
- Xia MY, Lou XH, Lin SJ, et al. Optimal timing of dopamine agonist withdrawal in patients with hyperprolactinemia: a systematic review and meta-analysis. Endocrine. 2018 Jan;59(1):50-61. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/29043560?tool=bestpractice.bmj.com)

References

1. Wildemberg LE, Fialho C, Gadelha MR. Prolactinomas. Presse Med. 2021 Dec;50(4):104080. Full text (https://www.sciencedirect.com/science/article/pii/S0755498221000191) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/34687915?tool=bestpractice.bmj.com)
2. Chanson P, Maiter D. The epidemiology, diagnosis and treatment of prolactinomas: the old and the new. Best Pract Res Clin Endocrinol Metab. 2019 Apr;33(2):101290. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31326373?tool=bestpractice.bmj.com)
3. Herman V, Fagin J, Gonsky R, et al. Clonal origin of pituitary adenomas. J Clin Endocrinol Metab. 1990 Dec;71(6):1427-33. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/1977759?tool=bestpractice.bmj.com)
4. Tichomirowa MA, Barlier A, Daly AF, et al. High prevalence of AIP gene mutations following focused screening in young patients with sporadic pituitary macroadenomas. Eur J Endocrinol. 2011 Oct;165(4):509-15. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/21753072?tool=bestpractice.bmj.com)
5. Daly AF, Jaffrain-Rea ML, Ciccarelli A, et al. Clinical characterization of familial isolated pituitary adenomas. J Clin Endocrinol Metab. 2006 Sep;91(9):3316-23. Full text (https://academic.oup.com/jcem/article/91/9/3316/2656326) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16787992?tool=bestpractice.bmj.com)
6. Cazabat L, Bouligand J, Salenave S, et al. Germline AIP mutations in apparently sporadic pituitary adenomas: prevalence in a prospective single-center cohort of 443 patients. J Clin Endocrinol Metab. 2012 Apr;97(4):E663-70. Full text (https://academic.oup.com/jcem/article/97/4/E663/2834108) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/22319033?tool=bestpractice.bmj.com)
7. Cuny T, Pertuit M, Sahnoun-Fathallah M, et al. Genetic analysis in young patients with sporadic pituitary macroadenomas: besides AIP don't forget MEN1 genetic analysis. Eur J Endocrinol.

2013 Mar 15;168(4):533-41. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/23321498?tool=bestpractice.bmj.com)

8. Verges B, Boureille F, Goudet P, et al. Pituitary disease in MEN type 1 (MEN1): data from the France-Belgium MEN1 multicenter study. J Clin Endocrinol Metab. 2002 Feb;87(2):457-65. Full text (https://academic.oup.com/jcem/article/87/2/457/2846507) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/11836268?tool=bestpractice.bmj.com)

9. Vierimaa O, Georgitsi M, Lehtonen R, et al. Pituitary adenoma predisposition caused by germline mutations in the AIP gene. Science. 2006 May 26;312(5777):1228-30. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16728643?tool=bestpractice.bmj.com)

10. Heaney AP, Fernando M, Melmed S. Functional role of estrogen in pituitary tumor pathogenesis. J Clin Invest. 2002 Jan;109(2):277-83. Full text (https://www.jci.org/articles/view/14264) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/11805140?tool=bestpractice.bmj.com)

11. Melmed S, Casanueva FF, Hoffman AR, et al; Endocrine Society. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011 Feb;96(2):273-88. Full text (https://academic.oup.com/jcem/article/96/2/273/2709487) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/21296991?tool=bestpractice.bmj.com)

12. Vilar L, Fleseriu M, Bronstein MD. Challenges and pitfalls in the diagnosis of hyperprolactinemia. Arq Bras Endocrinol Metabol. 2014 Feb;58(1):9-22. Full text (https://www.scielo.br/j/abem/a/QrX3s6BHwjc4vFgWhCt7DDS/?lang=en) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/24728159?tool=bestpractice.bmj.com)

13. Samperi I, Lithgow K, Karavitaki N. Hyperprolactinaemia. J Clin Med. 2019 Dec 13;8(12):2203. Full text (https://www.mdpi.com/2077-0383/8/12/2203/htm) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31847209?tool=bestpractice.bmj.com)

14. Vilar L, Abucham J, Albuquerque JL, et al. Controversial issues in the management of hyperprolactinemia and prolactinomas - an overview by the Neuroendocrinology Department of the Brazilian Society of Endocrinology and Metabolism. Arch Endocrinol Metab. 2018 Mar-Apr;62(2):236-63. Full text (https://www.scielo.br/j/aem/a/YYhNDhks3xZndj8xG99bM3F/?lang=en) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/29768629?tool=bestpractice.bmj.com)

15. Maiter D. Prolactinoma and pregnancy: from the wish of conception to lactation. Ann Endocrinol (Paris). 2016 Jun;77(2):128-34. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/27130071?tool=bestpractice.bmj.com)

16. O'Sullivan SM, Farrant MT, Ogilvie CM, et al. An observational study of pregnancy and post-partum outcomes in women with prolactinoma treated with dopamine agonists. Aust N Z J Obstet Gynaecol. 2020 Jun;60(3):405-11. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31583693?tool=bestpractice.bmj.com)

17. Maiter D. Management of dopamine agonist-resistant prolactinoma. Neuroendocrinology. 2019;109(1):42-50. Full text (https://www.karger.com/Article/FullText/495775) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/30481756?tool=bestpractice.bmj.com)

REFERENCES

18. Donoho DA, Laws ER Jr. The role of surgery in the management of prolactinomas. Neurosurg Clin N Am. 2019 Oct;30(4):509-14. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31471058?tool=bestpractice.bmj.com)

19. De Vecchis R, Esposito C, Ariano C. Cabergoline use and risk of fibrosis and insufficiency of cardiac valves: meta-analysis of observational studies. Herz. 2013 Dec;38(8):868-80. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/23743769?tool=bestpractice.bmj.com)

20. Stiles CE, Lloyd G, Bhattacharyya S, et al. Incidence of cabergoline-associated valvulopathy in primary care patients with prolactinoma using hard cardiac endpoints. J Clin Endocrinol Metab. 2021 Jan 23;106(2):e711-20. Full text (https://academic.oup.com/jcem/article/106/2/e711/6009022) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/33247916?tool=bestpractice.bmj.com)

21. Caputo C, Prior D, Inder WJ. The need for annual echocardiography to detect cabergoline-associated valvulopathy in patients with prolactinoma: a systematic review and additional clinical data. Lancet Diabetes Endocrinol. 2015 Nov;3(11):906-13. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/25466526?tool=bestpractice.bmj.com)

22. Steeds RP, Stiles CE, Sharma V, et al. Echocardiography and monitoring patients receiving dopamine agonist therapy for hyperprolactinaemia: a joint position statement of the British Society of Echocardiography, the British Heart Valve Society and the Society for Endocrinology. Echo Res Pract. 2019 Mar 1;6(1):G1-8. Full text (https://echo.biomedcentral.com/track/pdf/10.1530/ERP-18-0069.pdf) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/30825409?tool=bestpractice.bmj.com)

23. Gamble D, Fairley R, Harvey R, et al. Screening for valve disease in patients with hyperprolactinaemia disorders prescribed cabergoline: a service evaluation and literature review. Ther Adv Drug Saf. 2017 Jul;8(7):215-29. Full text (https://journals.sagepub.com/doi/10.1177/2042098617703647) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/28845230?tool=bestpractice.bmj.com)

24. Dekkers OM, Lagro J, Burman P, et al. Recurrence of hyperprolactinemia after withdrawal of dopamine agonists: systematic review and meta-analysis. J Clin Endocrinol Metab. 2010 Jan;95(1):43-51. Full text (https://academic.oup.com/jcem/article/95/1/43/2835124) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/19880787?tool=bestpractice.bmj.com)

25. Xia MY, Lou XH, Lin SJ, et al. Optimal timing of dopamine agonist withdrawal in patients with hyperprolactinemia: a systematic review and meta-analysis. Endocrine. 2018 Jan;59(1):50-61. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/29043560?tool=bestpractice.bmj.com)

26. Lasolle H, Vasiljevic A, Borson-Chazot F, et al. Pasireotide: a potential therapeutic alternative for resistant prolactinoma. Ann Endocrinol (Paris). 2019 Apr;80(2):84-8. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/30318256?tool=bestpractice.bmj.com)

27. Coopmans EC, van Meyel SWF, Pieterman KJ, et al. Excellent response to pasireotide therapy in an aggressive and dopamine-resistant prolactinoma. Eur J Endocrinol. 2019 Aug;181(2):K21-7. Full text (https://eje.bioscientifica.com/view/journals/eje/181/2/EJE-19-0279.xml) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31167168?tool=bestpractice.bmj.com)

28. Souteiro P, Karavitaki N. Dopamine agonist resistant prolactinomas: any alternative medical treatment? Pituitary. 2020 Feb;23(1):27-37. Full text (https://link.springer.com/

article/10.1007/s11102-019-00987-3) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31522358?tool=bestpractice.bmj.com)

29. Raverot G, Sturm N, de Fraipont F, et al. Temozolomide treatment in aggressive pituitary tumors and pituitary carcinomas: a French multicenter experience. J Clin Endocrinol Metab. 2010 Oct;95(10):4592-9. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/20660056?tool=bestpractice.bmj.com)

30. Valea A, Sandru F, Petca A, et al. Aggressive prolactinoma (review). Exp Ther Med. 2022 Jan;23(1):74. Full text (https://www.spandidos-publications.com/10.3892/etm.2021.10997) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/34934445?tool=bestpractice.bmj.com)

31. Shimon I. Giant prolactinomas. Neuroendocrinology. 2019;109(1):51-6. Full text (https://www.karger.com/Article/FullText/495184) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/30404098?tool=bestpractice.bmj.com)

32. Tirosh A, Shimon I. Management of macroprolactinomas. Clin Diabetes Endocrinol. 2015 Jul 20;1:5. Full text (https://clindiabetesendo.biomedcentral.com/articles/10.1186/s40842-015-0006-4) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/28702224?tool=bestpractice.bmj.com)

33. Baldeweg SE, Vanderpump M, Drake W, et al. Society For Endocrinology endocrine emergency guidance: emergency management of pituitary apoplexy in adult patients. Endocr Connect. 2016 Sep;5(5):G12-5. Full text (https://ec.bioscientifica.com/view/journals/ec/5/5/G12.xml) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/27935817?tool=bestpractice.bmj.com)

34. Albani A, Ferraù F, Angileri FF, et al. Multidisciplinary management of pituitary apoplexy. Int J Endocrinol. 2016 Dec 15;2016:7951536. Full text (https://www.hindawi.com/journals/ije/2016/7951536) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/28074095?tool=bestpractice.bmj.com)

35. Lubina A, Olchovsky D, Berezin M, et al. Management of pituitary apoplexy: clinical experience with 40 patients. Acta Neurochir (Wien). 2005 Feb;147(2):151-7. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/15570437?tool=bestpractice.bmj.com)

Images

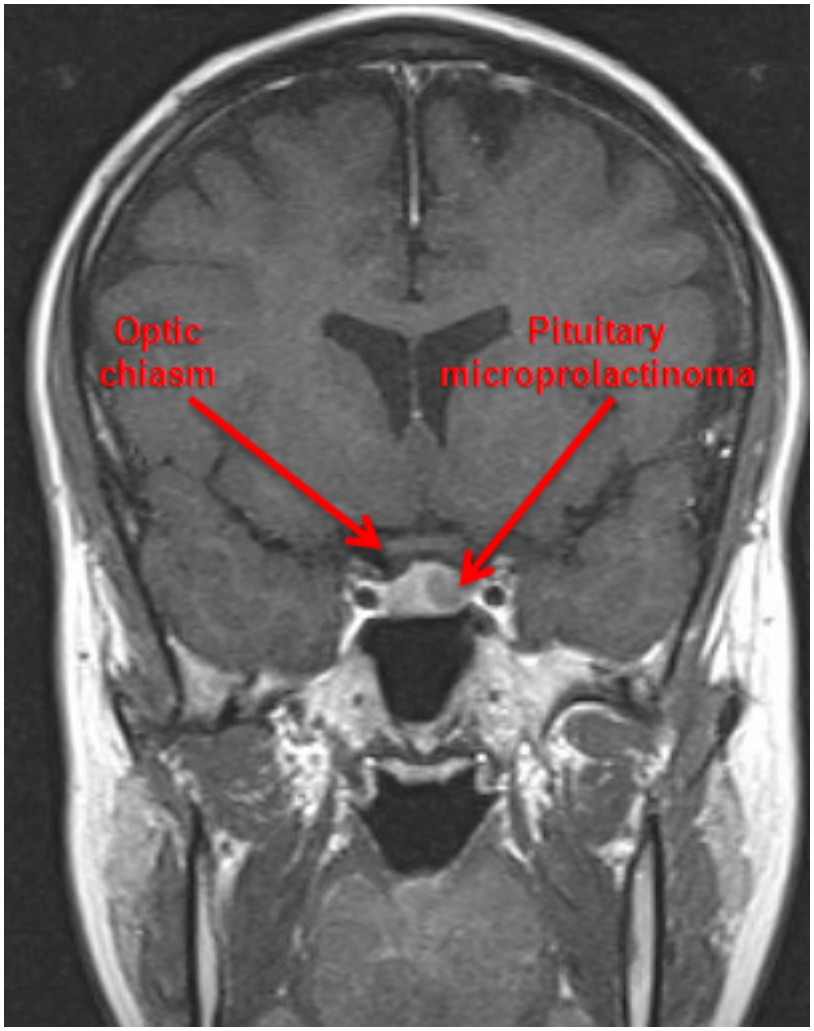


Figure 1: Gadolinium-enhanced magnetic resonance imaging showing a left-sided 7 mm pituitary microprolactinoma

From the collection of Dr Ilan Shimon

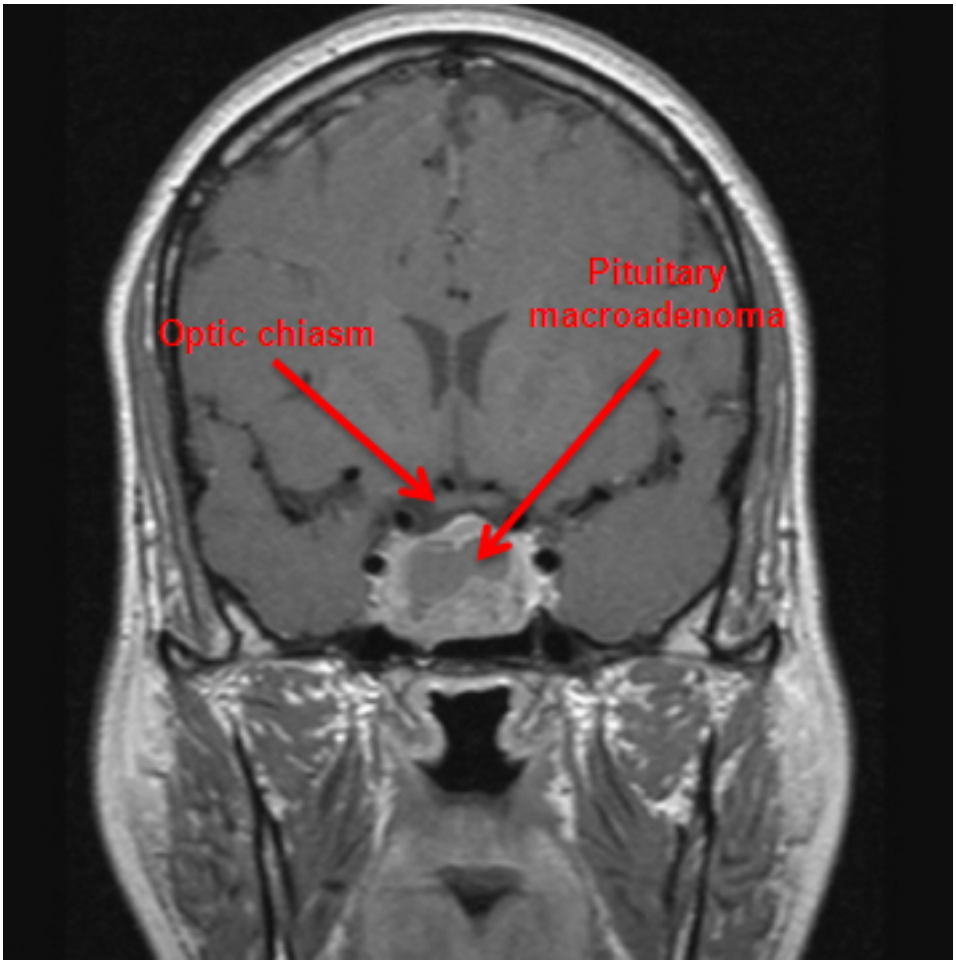


Figure 2: Gadolinium-enhanced magnetic resonance imaging showing a large pituitary macroadenoma in a 45-year-old man with hyperprolactinaemia

From the collection of Dr Ilan Shimon

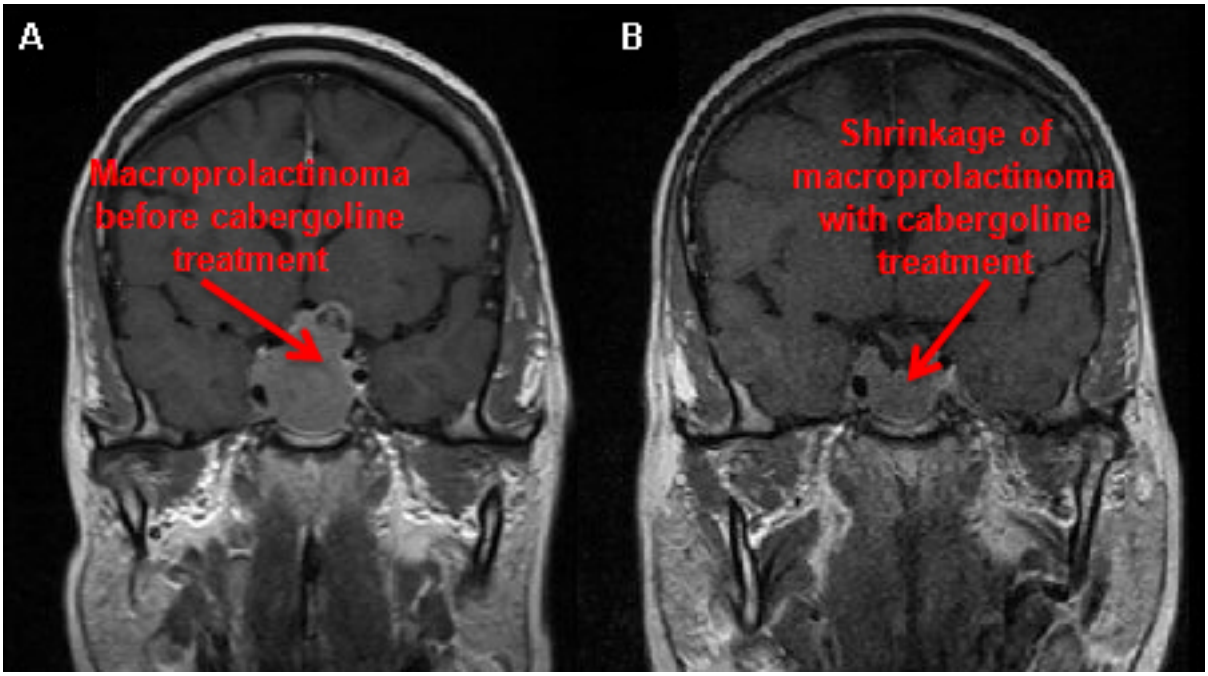


Figure 3: Gadolinium-enhanced magnetic resonance imaging (coronal view) showing a 40 mm pituitary macroprolactinoma in a 41-year-old man before (A) and after (B) 2-month treatment with cabergoline

From the collection of Dr Ilan Shimon

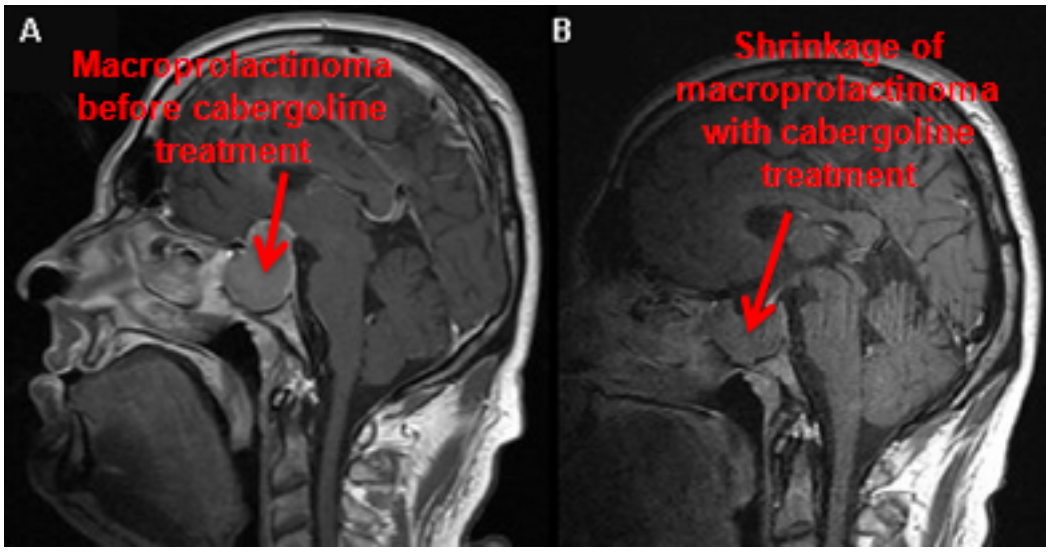


Figure 4: Gadolinium-enhanced magnetic resonance imaging (sagittal view) showing a 40 mm pituitary macroprolactinoma in a 41-year-old man before (A) and after (B) 2-month treatment with cabergoline

From the collection of Dr Ilan Shimon

Disclaimer

BMJ Best Practice is intended for licensed medical professionals. BMJ Publishing Group Ltd (BMJ) does not advocate or endorse the use of any drug or therapy contained within this publication nor does it diagnose patients. As a medical professional you retain full responsibility for the care and treatment of your patients and you should use your own clinical judgement and expertise when using this product.

This content is not intended to cover all possible diagnosis methods, treatments, follow up, drugs and any contraindications or side effects. In addition, since such standards and practices in medicine change as new data become available, you should consult a variety of sources. We strongly recommend that you independently verify specified diagnosis, treatments and follow-up and ensure it is appropriate for your patient within your region. In addition, with respect to prescription medication, you are advised to check the product information sheet accompanying each drug to verify conditions of use and identify any changes in dosage schedule or contraindications, particularly if the drug to be administered is new, infrequently used, or has a narrow therapeutic range. You must always check that drugs referenced are licensed for the specified use and at the specified doses in your region.

Information included in BMJ Best Practice is provided on an “as is” basis without any representations, conditions or warranties that it is accurate and up to date. BMJ and its licensors and licensees assume no responsibility for any aspect of treatment administered to any patients with the aid of this information. To the fullest extent permitted by law, BMJ and its licensors and licensees shall not incur any liability, including without limitation, liability for damages, arising from the content. All conditions, warranties and other terms which might otherwise be implied by the law including, without limitation, the warranties of satisfactory quality, fitness for a particular purpose, use of reasonable care and skill and non-infringement of proprietary rights are excluded.

Where BMJ Best Practice has been translated into a language other than English, BMJ does not warrant the accuracy and reliability of the translations or the content provided by third parties (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages). BMJ is not responsible for any errors and omissions arising from translation and adaptation or otherwise.Where BMJ Best Practice lists drug names, it does so by recommended International Nonproprietary Names (rINNs) only. It is possible that certain drug formularies might refer to the same drugs using different names.

Please note that recommended formulations and doses may differ between drug databases drug names and brands, drug formularies, or locations. A local drug formulary should always be consulted for full prescribing information.

Treatment recommendations in BMJ Best Practice are specific to patient groups. Care is advised when selecting the integrated drug formulary as some treatment recommendations are for adults only, and external links to a paediatric formulary do not necessarily advocate use in children (and vice-versa). Always check that you have selected the correct drug formulary for your patient.

Where your version of BMJ Best Practice does not integrate with a local drug formulary, you should consult a local pharmaceutical database for comprehensive drug information including contraindications, drug interactions, and alternative dosing before prescribing.

Interpretation of numbers

Regardless of the language in which the content is displayed, numerals are displayed according to the original English-language numerical separator standard. For example 4 digit numbers shall not include a comma nor a decimal point; numbers of 5 or more digits shall include commas; and numbers stated to be less than 1 shall be depicted using decimal points. See Figure 1 below for an explanatory table.

BMJ accepts no responsibility for misinterpretation of numbers which comply with this stated numerical separator standard.

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

Our full website and application terms and conditions can be found here: Website Terms and Conditions.

Contact us

+ 44 (0) 207 111 1105
support@bmj.com

BMJ
BMA House
Tavistock Square
London
WC1H 9JR
UK

DISCLAIMER

Contributors:

// Authors:

Niamh Martin, MB ChB, PhD, FRCP

Reader in Endocrinology
Imperial Centre for Endocrinology, Department of Metabolism, Digestion and Reproduction, Imperial College London, London, UK
DISCLOSURES: NM declares that she has no competing interests.

// Acknowledgements:

Dr Niamh Martin would like to gratefully acknowledge Dr Ilan Shimon, the previous contributor to this topic.
DISCLOSURES: IS receives consultancy and lecturing fees from Pfizer, Israel, and is an author of a number of references cited in this topic.

// Peer Reviewers:

Mark Molitch, MD

Professor
Division of Endocrinology, Northwestern University Feinberg School of Medicine, Chicago, IL
DISCLOSURES: MM is an author of a number of references cited in this topic.