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RECENT ADVANCES IN PROLACTINOMA MANAGEMENT: DIAGNOSIS, TREATMENT, AND CHALLENGES

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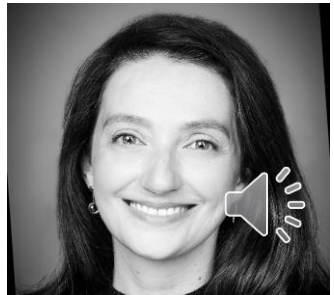

New guidelines from 2023!

nature reviews endocrinology

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Consensus statement

Check for updates

Diagnosis and management of prolactin-secreting pituitary adenomas: a Pituitary Society international Consensus Statement

A list of authors and their affiliations appears at the end of the paper

A new international consensus statement from The Pituitary Society incorporates recent evidence on possible newly recognized adverse events associated with dopamine agonists, efficacy of transsphenoidal surgery and treatment of special populations, such as pregnant women and transgender adults.

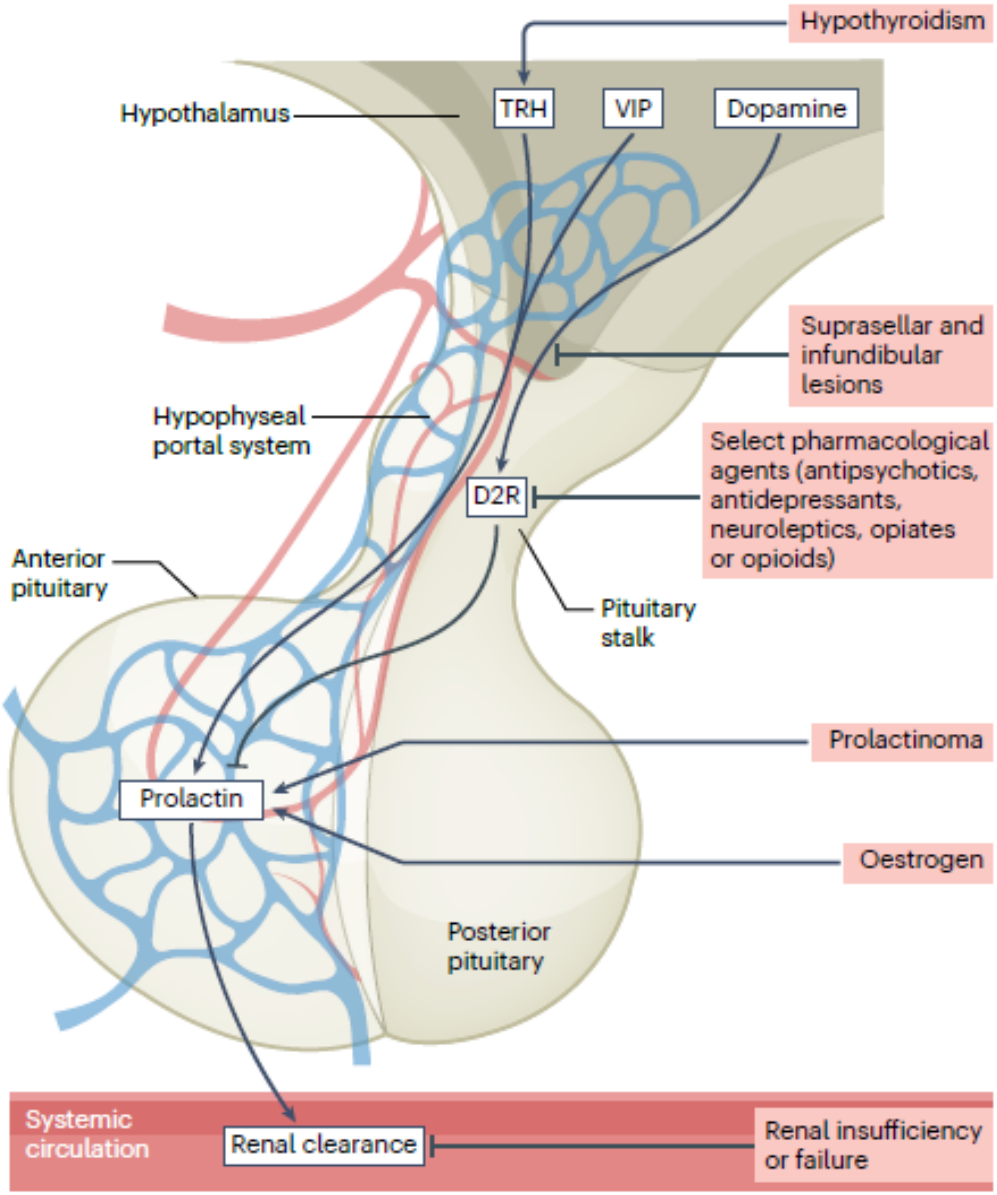

Fig. 1 | Neuroendocrine regulation of prolactin secretion. Dopamine traverses the hypophyseal portal system from the hypothalamus to the anterior pituitary, where it binds the dopamine 2 receptor (D2R) and blocks prolactin secretion. Suprasellar and infundibular lesions involving the stalk and pharmacological agents with antagonist activity at the D2R can result in an increase in prolactin secretion. By contrast, thyrotrophin-releasing hormone (TRH) and vasoactive intestinal peptide (VIP) from the hypothalamus stimulate prolactin secretion in the pituitary, as does oestrogen. Prolactin is systemically cleared by the kidney, so chronic kidney insufficiency can cause elevated serum levels of prolactin.

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Main role of prolactin: to induce and maintain lactation (decreasing reproductive function and libido)
Further roles of prolactin as stress and metabolic hormone are being discussed

Differential diagnosis

1. Physiological causes of elevated prolactin (normal range up to 25ng/ml or 40-530 mIU/L)

Before diagnosing pathological hyperprolactinemia, consider normal physiological conditions that can increase prolactin levels:

- **Stress-related increases** (anxiety, exercise)
- **Recent food intake** (prolactin secretion can be slightly higher postprandially)
- **Pregnancy and lactation** (physiological hyperprolactinemia)
- **Sleep** (prolactin peaks during sleep, so measure in the morning after waking)
- **Solution**: Measure prolactin **in a fasting, relaxed state**, preferably after 30 minutes of rest.

Differential diagnosis

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2. Macroprolactinemia (falsely high prolactin due to macroprolactin)

• **What it is**: Macroprolactin is a biologically inactive form of prolactin (prolactin bound to IgG antibodies).
• **Problem**: Some immunoassays detect macroprolactin as total prolactin, leading to falsely elevated levels.
• **Clue**: Patients have **high prolactin levels** but **no clinical symptoms** (e.g., no galactorrhea, normal gonadal function).

Solution: Perform **PEG (polyethylene glycol) precipitation** or use a **macroprolactin-specific assay** to confirm true hyperprolactinemia.

Differential diagnosis

3. Hook Effect (falsely low prolactin in macroadenomas)

- **What it is**: When prolactin levels are extremely high (e.g., in large pituitary macroadenomas), the excess antigen saturates the assay antibodies, leading to an **artificially low reading**.
- **Clue**: A patient with a large pituitary tumor on MRI but **normal or mildly elevated prolactin levels**.
- **Solution**: **Dilute the sample** and remeasure to detect true prolactin levels.

Differential diagnosis

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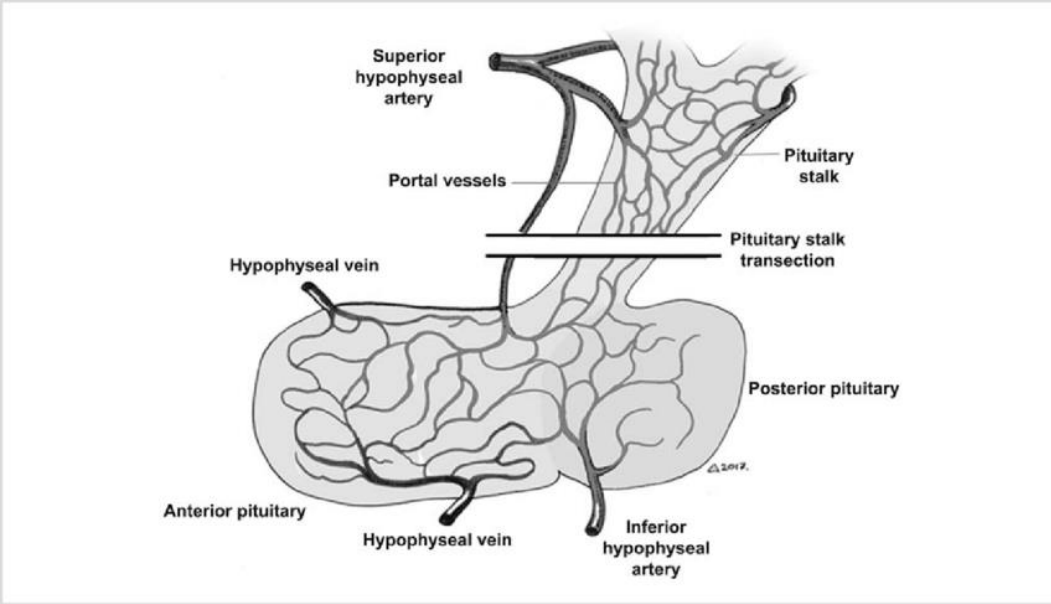
4. Medications that affect prolactin Levels

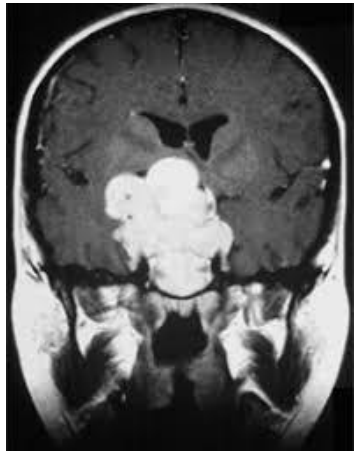
- **Drugs that increase Prolactin**:
  - Antipsychotics (dopamine antagonists, e.g., risperidone, haloperidol)
  - Antidepressants (SSRIs, TCAs)
  - Antiemetics (metoclopramide, domperidone)
  - Estrogens and oral contraceptives
  - Opioids
- **Solution**: **Review medication history** before interpreting prolactin levels.

Differential diagnosis

5. Pituitary stalk compression (Mild hyperprolactinemia in non-prolactinomas)

- **What it is**: Any **mass compressing the pituitary stalk** (e.g., non-functioning pituitary adenoma, meningioma) can block dopamine inhibition, leading to mild hyperprolactinemia (usually <200 ng/mL).
- **Clue**: Moderate prolactin elevation with an MRI showing a pituitary or parasellar mass **not** typical of a prolactinoma.
- **Solution**: MRI of the pituitary to differentiate prolactinoma from stalk compression.





Box 2

Aetiology of hyperprolactinaemia

Physiological
Pregnancy; breast or nipple stimulation; stress; sleep; coitus; exercise.

Pathological
Hypothalamic–pituitary stalk damage
Adenomas; craniopharyngioma; Rathke's cleft cyst; suprasellar pituitary mass extension; meningioma; dysgerminoma; hypothalamic or pituitary metastases; granulomatous disorders; infiltrations; pituitary and/or brain irradiation; intracranial hypotension; trauma (pituitary stalk section, sellar surgery, severe head injury).

Pituitary
Prolactinoma; acromegaly; macroadenoma (compressive); idiopathic; plurihormonal adenoma; lymphocytic hypophysitis; parasellar mass.

Non-pituitary disorders
Ectopic prolactin secretion; primary hypothyroidism; chronic renal failure; cirrhosis; pseudocyesis; epileptic seizures; malnutrition; anorexia nervosa; chest (neurogenic, chest wall trauma, piercings, surgery, herpes zoster).

Genetic
Inactivating mutation in the gene encoding prolactin receptor (*PRLR*).

Pharmacological
Dopamine receptor blockers
Phenothiazines (chlorpromazine, perphenazine); butyrophenones (haloperidol); thioxanthenes; metoclopramide; domperidone; alizapride.

Dopamine synthesis inhibitors
α-Methyldopa.

Catecholamine depleters
Reserpine.

Cholinergic agonists
Physostigmine.

Antihypertensives
Labetalol; reserpine; verapamil.

H_2 antihistamines
Cimetidine; ranitidine.

Oestrogens
Oral contraceptives (controversial, see discussion in text).

Anticonvulsants
Phenytoin.

Neuroleptics
Chlorpromazine; risperidone; promazine; promethazine; trifluoperazine; fluphenazine; butaperazine; perphenazine; thiethylperazine; thioridazine; haloperidol; pimozide; thiothixene; molindone.

Opiates and opiate agonists
Heroin; methadone; apomorphine; morphine.

Antidepressants
Tricyclic antidepressants; selective serotonin reuptake inhibitors.

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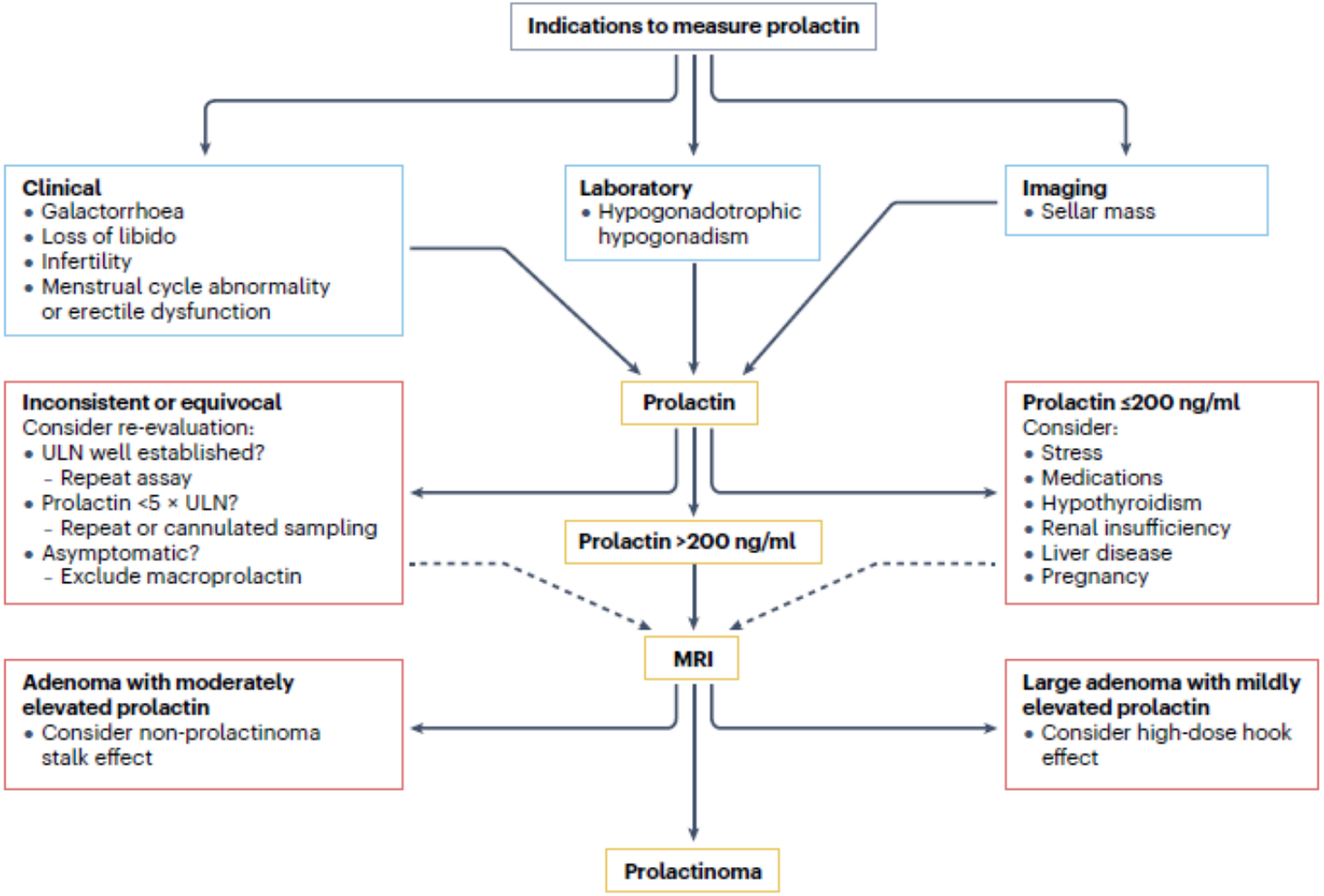

Fig. 2 | Diagnostic algorithm for prolactinoma. Clinical signs and symptoms of hyperprolactinaemia, laboratory findings of hypogonadotrophic hypogonadism or sellar mass on MRI should all trigger evaluation of prolactin. If moderately elevated blood levels are observed (≤200 ng/ml), diagnoses other than prolactinoma should be considered. Equivocal or questionable results inconsistent with clinical findings should prompt further investigation related to diagnostic procedures. If prolactin levels are >200 ng/ml, prolactinoma is more probable than other diagnoses. Imaging results inconsistent with clinical findings should prompt investigation for non-prolactinoma stalk effect, or high-dose hook effect. ULN, upper limit of normal.

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Signs and symptoms of hyperprolactinemia/prolactinoma

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Annual incidence: 6-10 cases per million population

Microprolactinomas (diameter up to 1 cm): ♀/♂ = 10:1

Macroprolactinomas (diameter more than 1 cm): ♀/♂ = 1:1

1. Symptoms Due to Hyperprolactinemia

- **In Women:**
  - **Menstrual disturbances**: Oligomenorrhea, amenorrhea, or irregular cycles.
  - **Galactorrhea**: Spontaneous or excessive milk production (not always present).
  - **Infertility**: Due to anovulation and disrupted LH/FSH secretion.
  - **Decreased libido and vaginal dryness**: Due to low estrogen levels.
  - **Osteopenia/Osteoporosis**: Due to chronic estrogen deficiency.

- **In Men:**
  - **Hypogonadism**: Low testosterone levels → decreased libido and erectile dysfunction.
  - **Infertility**: Reduced sperm production due to suppressed **LH/FSH**
  - **Gynecomastia (rare)**
  - **Muscle weakness and fatigue/Depression and mood changes**: Due to low testosterone.

- **In both genders:**
  - **Headaches** (due to tumor growth).
  - **Weight gain** (rare, but may be present).

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Signs and symptoms of hyperprolactinemia/prolactinoma

2. Symptoms due to mass effect (Larger tumors - Macroprolactinomas)

- **Visual field defects**: **Bitemporal hemianopia** (due to compression of the optic chiasm).
- **Cranial nerve palsies** causing **diplopia** (double vision)
- **Pituitary insufficiency**: Compression of normal pituitary tissue → secondary **hypothyroidism, adrenal insufficiency, or growth hormone deficiency**.

- **Women** often present **earlier** (due to menstrual irregularities)
- **Men** tend to be diagnosed **later**, when the tumor is larger and causing **mass effects** (e.g., visual symptoms).

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Treatment goals

- Normalization of prolactin levels – elimination of hypogonadism
- Tumor shrinkage up to complete disappearance
- Improvement in visual field and headache symptoms

Dopamine agonistis efficacy

Dopamine agonist therapy is highly effective at lowering serum levels of prolactin, improving clinical consequences of hyperprolactinaemia and reducing adenoma size

- Cabergoline is the **preferred dopamine agonist** owing to its long half-life, high efficacy and good tolerability

Bromocriptine and quinagolide are less commonly used, normalizes PRL levels in ~80–90% of cases and reduces tumor size in >70% of patients

- Cabergoline is used as primary medical therapy in patients with prolactinoma. For microprolactinomas and well-encased macroprolactinomas (Knosp grade 0 and 1), the curative potential and risks of surgery should be discussed with patients in a multidisciplinary setting prior to medical treatment initiation.
- Patients with prolactinoma of Knosp grade ≥2 should be treated with cabergoline
- Patients with resistance or intolerability to other dopamine agonist therapy should be switched to cabergoline
- The need for long-term dopamine agonist treatment and the limited chances of permanent cure should be highlighted in patient discussions
- In women not desiring fertility, **mechanical contraception** is advised when starting dopamine agonist therapy as pregnancy can occur prior to menses re-initiation

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Side effects of dopamine agonists

"Classic" side effects

Nausea, vomiting

Dizziness, fatigue

Orthostatic hypotension

- Rare under cabergoline
- Adverse effects usually improve with time, but can be ongoing and disabling in individual patients
- Administration before bedtime and/or with food might improve tolerability
- Starting with low doses and escalating slowly might improve tolerability

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Side effects of dopamine agonists-cardiac valvulopathy

- If long-term treatment with high-dose (>2.0 mg per week) cabergoline is anticipated, perform **baseline echocardiography** to detect any pre-existing valve alterations. Baseline evaluation can be performed before starting cabergoline therapy or during the first few months of treatment
- Repeat echocardiography **every 2–3 years** in patients treated **with >2.0 mg per week** of cabergoline.
- Perform echocardiography after **5–6 years** in patients treated with **≤2.0 mg** per week of cabergoline.
- Detection of a heart murmur in patients treated with cabergoline should prompt echocardiography

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Side effects of dopamine agonists- neuropsychiatric adverse events

Dopamine agonist therapy can cause neuropsychiatric adverse effects, such as compulsive buying, gambling, aggression, changes in mood and hypersexuality, particularly in men. Although these effects are rarely encountered, if present, dopamine agonist therapy should be discontinued or the dose adjusted.

Endocrinologists should ask about these behaviors at each subsequent visit in dopamine agonist-treated patients.

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Cessation of treatment

- Favourable predictors of successful withdrawal include low maintenance doses of cabergoline, treatment duration >2 years and substantial adenoma size reduction (strong).
- Although only one-third of treated patients are likely to meet these criteria, in this subgroup, nearly 55% of those with microprolactinoma and 43% of those with macroprolactinoma will achieve ongoing remission after treatment withdrawal
- Thus, under such conditions and in the absence of a visible mass on MRI, patients should be encouraged to withdraw treatment.
- If dopamine agonist therapy withdrawal is attempted, serum levels of prolactin should be measured every 3 months in the first year and annually thereafter.
- Pituitary MRI can be repeated if hyperprolactinaemia reoccurs.

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Surgical treatment

- Surgical resection of microprolactinomas and well-circumscribed macroprolactinomas (Knosp grade 0 and 1) by an experienced neurosurgeon offers a high chance of cure, is cost-effective and avoids long-term dopamine agonist treatment and should be discussed as a first-line option in this subgroup of patients
- Medical treatment is the preferred first-line treatment option in patients with a low chance of surgical remission (Knosp grade ≥2)
- Surgery could be recommended over medical treatment in patients with rapidly progressive vision loss due to a sellar mass effect or apoplexy
- Surgery could be offered to patients who have intolerance or resistance to long-term dopamine agonist therapy
- Young age in women could favour a choice of surgical treatment to avoid the need for dopamine agonist therapy over many decades
- Debulking surgery of a macroprolactinoma is an alternative to dopamine agonist therapy in patients who desire pregnancy, as it reduces the risk of symptomatic mass enlargement during future pregnancy

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Radiation Therapy

- Radiation therapy should be reserved for patients who show poor mass shrinkage in response to dopamine agonists and have either non-resectable residual adenoma tissue after surgery or contraindications for surgery
- Stereotactic radiotherapy techniques yield improved outcomes and have now become standard of care where available
- Patients should be advised that response to radiotherapy can take several years
- Patients should be informed about potential adverse effects occurring even many years after treatment and should be followed lifelong to detect hypopituitarism, optic neuropathy, cranial nerve palsy or second brain tumours
- Radiation therapy is the least used management approach for prolactinoma and is mainly offered when medical and surgical treatments have not been successful, usually in patients with size-progressing, aggressive prolactinoma or prolactin-secreting malignancies.

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Pregnancy and prolactinoma

- Pregnancy in patients with microprolactinomas is usually uneventful, and patients should be followed clinically every 3 months
- Patients with macroprolactinoma have a risk of clinically relevant adenoma expansion and apoplexy during pregnancy- monthly control during pregnancy and questioned about local mass effects, and should undergo visual field evaluation every 3 months
- Patients with suspicion of clinically relevant adenoma growth during pregnancy should undergo MRI without gadolinium
- Re-initiation of dopamine agonist therapy that was discontinued at conception should be considered in patients with clinically relevant adenoma growth
- **Serum levels of prolactin should not be used to assess** for adenoma growth during pregnancy
- **Breastfeeding is usually not contraindicated** and could be allowed for a period depending on whether treatment reintroduction is needed for mass control

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Pregnancy and prolactinoma

- Patients with prolactinoma considering pregnancy should be informed about both medical and surgical options
- A comprehensive examination performed shortly **before pregnancy** provides baseline information on serum levels of prolactin, visual fields and adenoma size
- Mechanical contraception should be used instead of hormonal forms of contraception to confirm treatment efficacy before pregnancy and establish the menstrual interval
- To reduce exposure of the developing fetus to dopamine agonist therapy, dopamine agonists should be discontinued as soon as pregnancy is confirmed
- Exception -> patients with large macroprolactinomas, **maintenance of dopamine agonist** therapy during pregnancy should be considered
- Although bromocriptine might reduce fetal exposure due to its shorter half-life, **cabergoline** is now preferred by the majority of centres owing to increasing safety data
- In patients with macroprolactinoma, adenoma response to dopamine agonist therapy should be confirmed prior to conception. In those without mass response, surgery should be considered prior to conception

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Prolactinomas and menopause

- Women with well-controlled microprolactinoma entering menopause should undergo a trial of dopamine agonist withdrawal
- In postmenopausal women with macroprolactinoma, treatment should be targeted to controlling adenoma growth
- Normalization of serum levels of prolactin in postmenopausal women with microprolactinoma is not indicated to improve metabolic parameters, decrease breast cancer risk or improve bone density
- Normalization of serum prolactin levels occurs in 45% of untreated women with microprolactinoma entering menopause
- Current evidence does not support microprolactinoma treatment in asymptomatic postmenopausal women. Macroprolactinomas should be treated according to standard practice. Breast cancer risk was not increased in postmenopausal women with prolactinoma

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Prolactinomas in transgender individuals

- In transgender women, combined treatment with oestradiol and cyproterone acetate usually causes mild and asymptomatic hyperprolactinaemia
- A diagnosis of prolactinoma should be considered when prolactin increases markedly or with symptoms of mass effect or galactorrhoea
- There is no evidence for increased incidence of prolactinomas in transgender women receiving gender-affirming hormone therapy

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Additional Bibliography / original publications in the filed of prolactinoma by Dr. Athanasoulia-Kaspar!

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European Journal of Endocrinology (2012) 167 1–10

Polymorphisms of the drug transporter gene *ABCB1* predict side effects of treatment with cabergoline in patients with PRL adenomas

A P Athanasoulia[1,*], C Sievers[1,*], M Ising[2], A C Brockhaus[3], A Yassouridis[3], G K Stalla[1,†] and M Uhr[4,†]

Departments of [1]Internal Medicine, Endocrinology and Clinical Chemistry and [2]Molecular Psychology, Max Planck Institute of Psychiatry, Kraepelinstrasse 2-10, 80804 Munich, Germany, [3]Division of Biostatistics, Kraepelinstrasse 2-10, 80804 Munich, Germany and [4]Division of Pharmacokinetics and CSF Analysis, Kraepelinstrasse 2-10, 80804 Munich, Germany

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