

Investigating Hyperprolactinaemia

Step	Investigation	Clinical reasoning
1. Confirm the result	Repeat fasting morning prolactin (if mild elevation <5× ULN)	Stress, venepuncture, exercise, intercourse and sleep can transiently elevate prolactin. <i>A single mildly elevated result should be confirmed.</i>
2. Exclude physiological causes	Pregnancy test (β-hCG), breastfeeding history	Most common physiological causes in women.
3. Medication review	Dopamine antagonists (antipsychotics, metoclopramide, domperidone), SSRIs, TCAs, opioids, verapamil, oestrogens, methyldopa, etc.	Drug-induced hyperprolactinaemia is common. Consider whether withdrawal/substitution is feasible.
4. Screen for secondary causes	• TSH ± free T4 • U&E/eGFR • LFTs • Consider HbA1c if clinically indicated	Primary hypothyroidism (↑TRH), CKD and chronic liver disease commonly cause moderate elevations.
5. Consider macroprolactin	Polyethylene glycol (PEG) precipitation (macroprolactin assay)	Particularly if prolactin is elevated but symptoms are absent or discordant. Macroprolactin has little biological activity.
6. Assess pituitary function	Depending on clinical context: cortisol, ACTH, IGF-1, LH/FSH, oestradiol or testosterone	Evaluates associated pituitary hormone deficiency or co-secretion.
7. Assess consequences of hypogonadism	Sex hormones; consider DEXA if prolonged hypogonadism	Chronic hyperprolactinaemia causes hypogonadism and bone loss.

Interpretation of prolactin level

Prolactin level*	Likely causes
Mild (<50–100 ng/mL; <1000–2000 mIU/L, assay dependent)	Stress, drugs, hypothyroidism, CKD, macroprolactin
Moderate (100–250 ng/mL; ~2000–5000 mIU/L)	Microprolactinoma, stalk effect, drugs
Marked (>250 ng/mL; >5000 mIU/L)	Macroprolactinoma highly likely
Very high (>500 ng/mL; >10,000 mIU/L)	Usually macroprolactinoma

*Reference ranges vary by assay and units.

When to perform pituitary MRI

MRI pituitary with gadolinium is indicated if:

- Persistent hyperprolactinaemia after exclusion of physiological and pharmacological causes.
- Prolactin level strongly suggests prolactinoma (particularly >200–250 ng/mL or >4000–5000 mIU/L, assay dependent).
- Symptoms/signs of pituitary mass:
 - Visual symptoms
 - Persistent headache
 - Cranial nerve deficits
- Evidence of hypopituitarism.
- Hyperprolactinaemia without an identifiable secondary cause.

Important pitfall: Hook effect

Consider the **high-dose hook effect** when:

- MRI demonstrates a **large pituitary macroadenoma (>3 cm)** but prolactin is only mildly elevated.
- Request **serial dilution of the prolactin sample** to avoid falsely low results.

Additional investigations when indicated

Clinical scenario	Additional tests
Visual symptoms or macroadenoma	Formal visual field testing
Men	Testosterone, LH/FSH; semen/fertility assessment if relevant
Women	Oestradiol, LH/FSH; assessment of menstrual status
Long-standing hypogonadism	Bone mineral density (DEXA)
Large adenoma	Full pituitary hormone profile before treatment

Practical investigation algorithm

1. Confirm elevated prolactin (repeat fasting morning sample if mild).
2. Exclude pregnancy and physiological causes.
3. Review medications.
4. Check TSH, renal and liver function.
5. Test for macroprolactin if clinically appropriate.
6. Assess pituitary hormones and gonadal function.
7. Arrange pituitary MRI if elevation persists without explanation or if prolactin is markedly elevated or there are neurological features.
8. Consider visual fields and full endocrine assessment if a pituitary lesion is identified.

Drug causes for Hyperprolactinaemia

Drug class	Examples	Mechanism	Typical effect on prolactin
Typical (first-generation) antipsychotics	Haloperidol, Chlorpromazine, Fluphenazine, Perphenazine	Dopamine D2 receptor blockade in the tuberoinfundibular pathway	Marked increase (common)
Atypical (second-generation) antipsychotics	Risperidone, Paliperidone, Amisulpride	Potent D2 receptor blockade	Marked increase
	Olanzapine, Ziprasidone	Moderate D2 blockade	Mild–moderate increase
	Quetiapine, Clozapine, Aripiprazole	Minimal or partial D2 agonism	Little or no increase (aripiprazole may lower prolactin)
Antiemetics / Prokinetics	Metoclopramide, Domperidone, Prochlorperazine	Dopamine receptor antagonism	Common; often marked
Antidepressants (SSRIs)	Fluoxetine, Sertraline, Paroxetine, Citalopram, Escitalopram	Increased serotonergic stimulation of prolactin secretion	Mild increase
Other antidepressants	Venlafaxine, Duloxetine, Clomipramine, Amitriptyline	Serotonergic effects	Mild increase
Opioids	Morphine, Oxycodone, Fentanyl, Methadone, Tramadol	Inhibit hypothalamic dopamine release	Mild–moderate increase
Calcium channel blocker	Verapamil	Reduces hypothalamic dopamine activity	Mild increase
Antihypertensives	Methyldopa, Reserpine	Reduced dopamine synthesis/storage	Mild–moderate increase
Hormonal therapies	Combined oral contraceptives, High-dose oestrogens, Hormone replacement therapy	Oestrogen stimulates lactotroph proliferation and prolactin secretion	Mild increase
GnRH analogues	Leuprolide, Goserelin (occasionally)	Unclear; uncommon	Mild increase
H2 receptor antagonists	Cimetidine (rarely ranitidine)	Uncertain	Mild increase
Anticonvulsants (rare)	Valproate, Phenytoin	Uncertain	Usually mild
Protease inhibitors (rare)	Ritonavir and others	Uncertain	Rare
Cannabinoids	Cannabis (evidence inconsistent)	Variable hypothalamic effects	Usually mild if present

Drugs most commonly implicated in clinical practice

High likelihood	Intermediate likelihood	Low likelihood
Risperidone	SSRIs	Verapamil
Paliperidone	SNRIs	Methyldopa
Amisulpride	TCAs	Cimetidine
Haloperidol	Opioids	Oestrogen therapy
Metoclopramide	Domperidone	Valproate
Prochlorperazine	Olanzapine	Cannabis (variable evidence)

Clinical pearls

- **Antipsychotics** and **dopamine antagonist antiemetics** are the **most common causes** of drug-induced hyperprolactinaemia.
- **Risperidone, paliperidone, and amisulpride** produce the highest prolactin levels among atypical antipsychotics.
- **Metoclopramide** can cause substantial prolactin elevation even after short-term use.
- **Aripiprazole**, a partial dopamine D2 agonist, may **reduce prolactin** and is sometimes used to manage antipsychotic-induced hyperprolactinaemia.
- Drug-induced hyperprolactinaemia usually results in prolactin concentrations **<100 ng/mL (<2,000 mIU/L)**, although **metoclopramide, risperidone, and amisulpride** can occasionally produce higher levels. Levels **>200–250 ng/mL (>4,000–5,000 mIU/L)** should raise suspicion for a prolactinoma, although exceptions occur.