



Clinical Decision Making in **PSYCHIATRY**



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Management of Drug-induced Hyperprolactinemia

Shobit Garg, Shaily Mittal, Sai Krishna Tikka

INTRODUCTION

Hyperprolactinemia is the most common pituitary hormone hypersecretion syndrome in both men and women. It is defined as serum prolactin levels >25 ng/mL (>530 mIU/mL) in nonpregnant females and >20 ng/mL (>424 mIU/mL) in males. One of the most common causes of hyperprolactinemia is *drug-induced*.¹

1 ng/mL = 21.2 mIU/mL, $T_{1/2}$ life of prolactin: 25–50 minutes

CLINICAL PEARLS IN APPROACH TO HYPERPROLACTINEMIA (FLOWCHART 1)

A1: Why baseline prolactin levels?

- In the absence of a baseline prolactin value, attributing an elevated prolactin level to the offending drug can be challenging.
- Blood samples should be collected before administering any doses of antipsychotic (AP), as even a single dose can raise prolactin levels.
- If the baseline prolactin level is elevated and no dose of the prolactin-raising drug was taken, stress could be

a plausible explanation. Stress may increase prolactin levels to as high as 42 ng/mL in women and 33 ng/mL in men.¹

Important: If serum prolactin concentration is only slightly elevated (21–40 ng/mL), then the test should be repeated on a fasting sample before considering hyperprolactinemia.

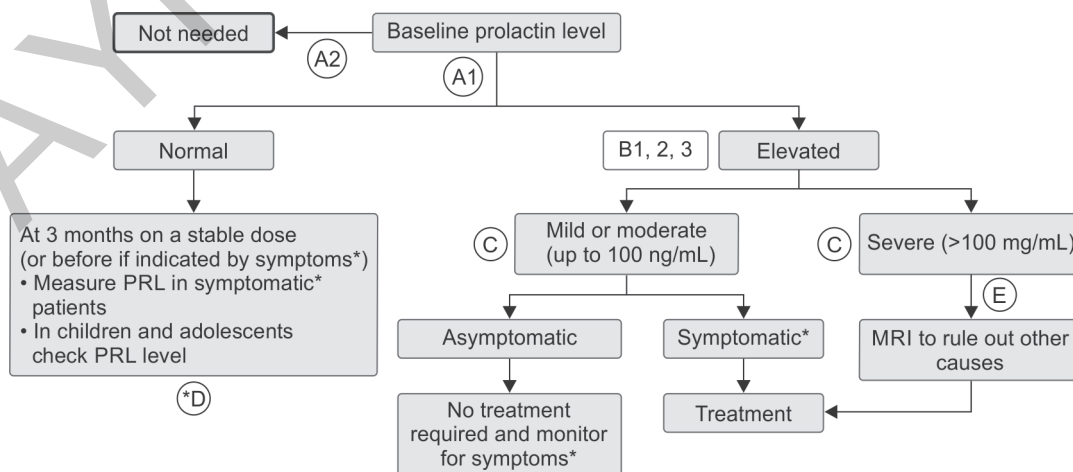
A2: When can we skip baseline prolactin monitoring?

- In women over the age of 50 and men over 65 (elevated prolactin levels have no additional health consequences on bone health beyond these ages)
- *Measuring baseline prolactin levels is mandatory in children and adolescent population before initiating psychotropic medications.*²

B1: What are the causes of prolactin elevation other than drug-induced?

- **Physiological causes:** Stress, venipuncture stress, exercise, coitus, pregnancy (up to 600 ng/mL at term), nipple stimulation and lactation (up to 300 ng/mL), and seizures.

Flowchart 1: The clinical approach to hyperprolactinemia.



- *Pathological causes:* Hypothyroidism, polycystic ovary syndrome, chronic renal failure, liver cirrhosis, prolactinoma (ranging from mild elevation to 50,000 ng/mL), chest wall lesions (e.g., breast surgery, nipple rings, etc.), breast stimulation, macroprolactinoma, etc.
- *Macroprolactinemia:* Also referred to as “big prolactin”, represents large circulating aggregates of prolactin and antibodies, approximately 150 kD in size. It is a benign, asymptomatic condition that does not require treatment but can be misdiagnosed as prolactin hypersecretion. To avoid misdiagnosis, clinicians can use polyethylene glycol (PEG) serum precipitation as a screening method.^{1,3}

B2: What are the causes of prolactin elevation due to drugs other than psychotropics?

- *Prokinetics:* Metoclopramide and domperidone
- *Estrogen-containing oral contraceptives*
- *Antihypertensives:* Verapamil and α -methyldopa
- *Opiates:* Morphine and heroin (transient rise in prolactin levels for a few hours following the dose)
- *H2-receptor blocker agents:* Cimetidine (?) and ranitidine (?)^{1,3}

B3: “3-day” Protocol

This approach is applicable when prolactin is elevated due to AP but no baseline prolactin values are available. If clinically feasible, withholding the current AP for a minimum of 3 days can help determine whether hyperprolactinemia is drug-induced, as prolactin levels should decrease in such cases.²

C: Severity of Hyperprolactinemia

- *Mild:* Up to 50 ng/mL
- *Moderate:* 50–100 ng/mL
- *Severe:* >100 ng/mL³

Drugs-induced hyperprolactinemia is largely *dose-dependent*. Most drugs do not typically elevate prolactin levels beyond 100 ng/mL; however, risperidone can cause elevations as high as 300–400 ng/mL.³

D: Symptoms of Hyperprolactinemia

- *Premenopausal women:*
 - *Mild hyperprolactinemia:* Infertility
 - *Moderate hyperprolactinemia:* Either amenorrhea or oligomenorrhea
 - *Severe hyperprolactinemia:* Amenorrhea, hypogonadism, gynecomastia, galactorrhea

Females with amenorrhea due to hyperprolactinemia have lower bone mineral density compared to those with normal menses and hyperprolactinemia.¹⁻³

- *Postmenopausal women* are already hypogonadal (hypoestrogenic); therefore, hyperprolactinemia does not significantly alter their hormonal status. Also, galactorrhea is very rare in this population.¹⁻³

■ *Men:*

- *Hypogonadotropic hypogonadism:* Hyperprolactinemia causes decreased testosterone levels, resulting in short-term symptoms such as reduced energy and libido. Long-term effects include decreased muscle mass, reduced body hair, and osteoporosis.
- *Erectile dysfunction:* This is caused by mechanisms unrelated to hypogonadism.
- *Infertility:* Although uncommon, infertility due to hyperprolactinemia can occur in males, accounting for approximately 4% of cases.
- *Galactorrhea:* This condition may develop in males but is less common compared to females.¹⁻³

- *Children:* Hyperprolactinemia can delay puberty in children and adolescents.

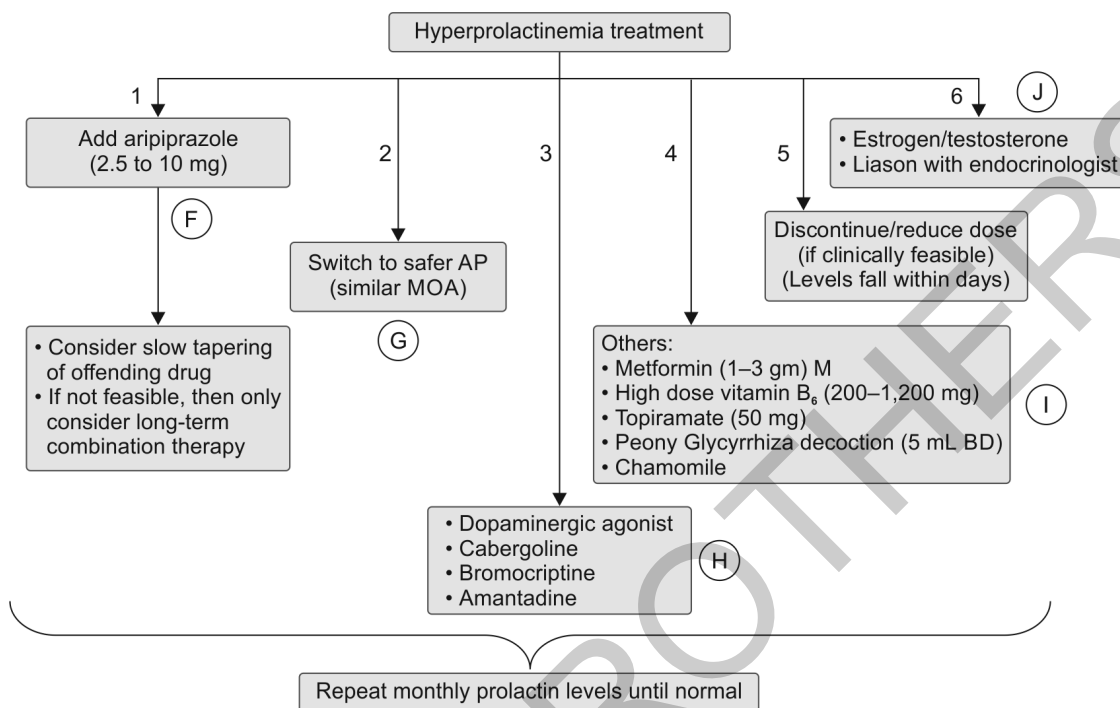
- *Long-term complications:* Osteoporosis—amenorrhoeic women and men with low testosterone are at a higher risk of osteoporosis. While normalization of prolactin prevents further bone loss, bone mineral density typically *never returns to normal*.¹⁻³

E: When is magnetic resonance imaging (MRI) recommended?

An MRI of the pituitary with contrast is indicated in cases of severe elevation of serum prolactin levels (>100 mg/mL), in those presenting with symptoms suggestive of raised intracranial pressure effects (e.g., visual field disturbances and headaches), and when high prolactin levels cannot be easily attributed to AP medication.³

CLINICAL PEARLS IN APPROACH TO HYPERPROLACTINEMIA TREATMENT (FLOWCHART 2)

F: *Adjunctive aripiprazole:* Aripiprazole is typically started at 2.5 mg and titrated over 4–8 weekly intervals until reaching a maximum dose of 10 mg. Poor response to adjunctive aripiprazole has been specifically observed with amisulpride-induced hyperprolactinemia. Importantly, the goal of adjunctive aripiprazole is not to

Flowchart 2: Algorithm of the clinical approach to hyperprolactinemia treatment.

Note: Numbers 1 to 6 is a preferred sequence of approach to treatment.
(AP: antipsychotics, MOA: mechanism of action)

normalize prolactin levels, but to reduce them sufficiently to restore normal menses and sexual function. A decrease in prolactin could result in the return of fertility even before menses resume, so contraceptive advice may be needed. Better responses are seen with prolactin levels >50 ng/mL. Headache and somnolence are the most common side effects reported in the trials. Adjunctive aripiprazole received an A-grade recommendation in a consensus paper by Montejo et al.⁴

G: Hyperprolactinemia sparing and nonsparing antipsychotics are described in **Table 1**.

High-risk prolactin elevating APs are to be avoided in the following situations.

- Age before 25 years, i.e., before peak bone mass
- Young women
- Patients with osteoporosis
- Patients with hormone-dependent breast cancer

Switching to AP with a lower risk of hyperprolactinemia were assigned grade A, B, or C recommendations (depending on the specific agent) in a consensus paper by Montejo et al.⁴

TABLE 1: Describing antipsychotics based on their effects on prolactin levels.⁵⁻⁷

Prolactin sparing	Prolactin elevating (low risk)	Prolactin elevating (high risk)
Quetiapine	Lurasidone*	Amisulpride
Aripiprazole	Ziprasidone	Risperidone
Clozapine	Olanzapine	Paliperidone
Cariprazine	Asenapine®	Sulpiride
Iloperidone		FGA

Note:* Dose related; ®Data limited
(FGA: first-generation antipsychotics)

H: *Dopaminergic agonist (DA)*: They carry a potential risk of inducing psychosis or worsening preexisting psychosis, although this has not been clearly established by studies.

- *Cabergoline*: This is the most common DA used in hyperprolactinemia due to prolactinomas. Dose ranges from 0.125 mg weekly to 1 mg twice weekly, with a maximum dose of 1.5 mg twice weekly. Prolactin levels typically normalize within 3 months. Cardiac valvular

abnormalities are among the more serious adverse events reported.

- **Bromocriptine:** This is preferred in pregnancy. Dose is 2.5 mg twice daily until prolactin normalizes, with a maximum dose of 15–20 mg/day. Nausea and vomiting are the most frequent side effects. Bromocriptine has better cardiac safety profile compared to cabergoline.³

The DAs should be avoided in cases of uncontrolled hypertension. The addition of DA received a B-grade recommendation in a consensus paper by Montejo et al.⁴

I: Other strategies to mitigate long-term risk of reduced bone mineral density or osteoporosis should be addressed, including smoking cessation, reducing sedentary lifestyle, correcting vitamin D deficiency (with supplements of 800–1,000 IU/day), and limiting alcohol intake. Calcium supplementation (500–1,000 mg/day) is recommended for patients with a calcium deficient diet, defined as consuming fewer than 4–5 daily serving of dairy products (equivalent to 1 liter of milk).^{7,8}

J: Use of estrogen or testosterone in patients with long-term hypogonadism or low bone mass due to hyperprolactinemia should be considered in *liaison with an endocrinologist*. Additionally, phosphodiesterase inhibitors can be initiated to treat erectile dysfunction secondary to hyperprolactinemia.^{3,7,8}

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Clinical Decision Making in PSYCHIATRY

Salient Features

- *Clinical Decision Making in Psychiatry* is a practical guide designed to help clinicians navigate complex psychiatric decisions using structured, algorithm-driven frameworks
- The book uniquely blends evidence-based practices with real-world insights from experienced clinicians
- It includes chapters on key challenges in psychiatric diagnosis, treatment planning, and long-term management, including treatment-resistant conditions and comorbidities
- These decision-making algorithms provide easy step-by-step pathways to integrate clinical data with available treatment options
- Intended for a wide range of mental health professionals, the book promotes evidence-informed, flexible, and compassionate psychiatric care.

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