PLATINUM

Clinical Decision Making in PSYCHIATRY

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CHAPTER 56

Management of Drug-induced Hyperprolactinemia

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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.

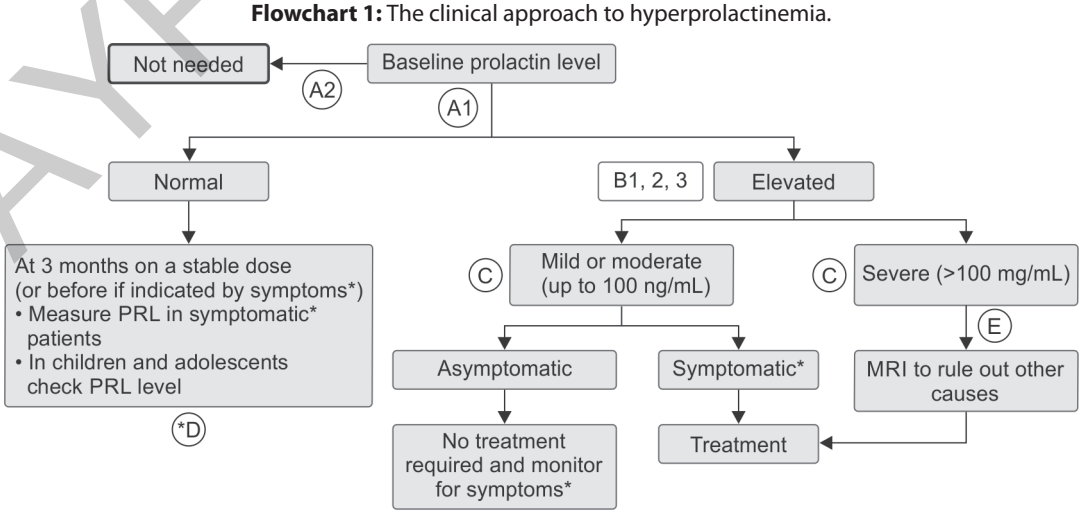
A2: When can we skip baseline prolactin monitoring?

- 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/mL[3]

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]

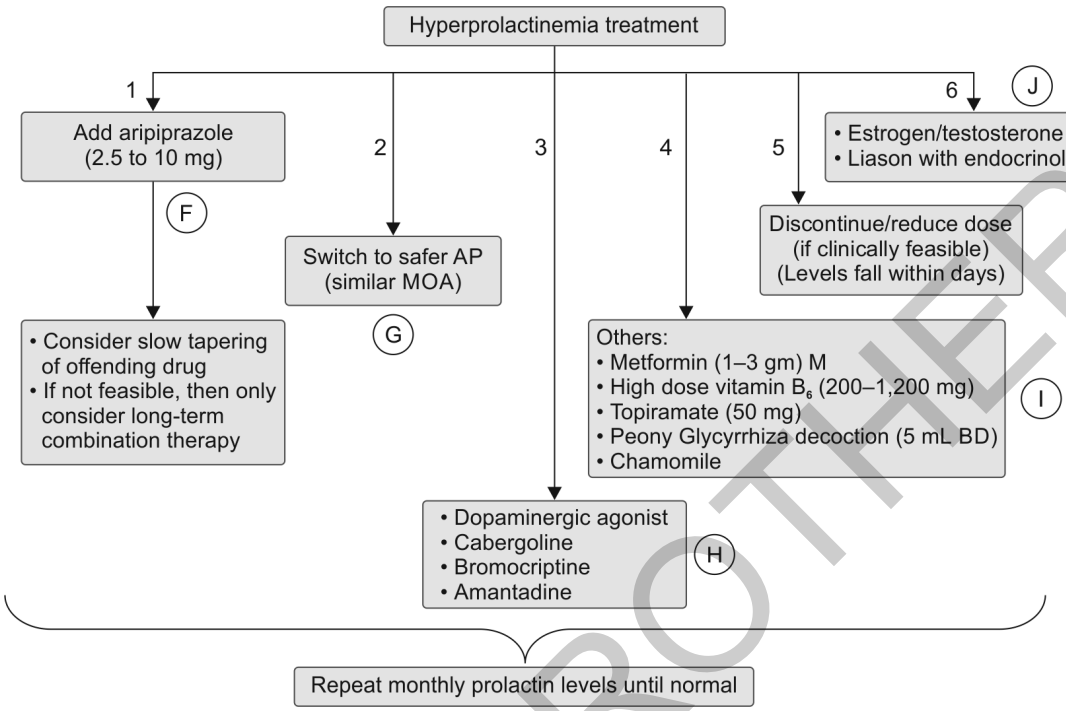
E: When is magnetic resonance imaging (MRI) recommended?

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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