HYPERPROLACTINEMIA

CHI Formulary Indication Review

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Council of Health Insurance

INDICATION UPDATE

ADDENDUM- November 2023

To the CHI Original Hyperprolactinemia Clinical Guidance- Issued April 2020

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Related Documents

Related SOPs

- IDF-FR-P-02-01-IndicationsReview&IDFUpdates
- IDF-FR-P-05-01-UpdatedIndicationReview&IDFUpdates

Related WI:

IDF-FR-WI-01-01SearchMethodologyGuideForNewIndications

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Abbreviations

CHI	Council of Health Insurance
CPG	Clinical Practice Guideline
CT	Computed Tomography
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone
GnRH	Gonadotropin hormone-Releasing Hormone
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
HPrl	Hyperprolactinemia
IDF	Insurance Drug Formulary
LH	Luteinizing Hormone
MGMT	Methylguanine Methyltransferase
MRI	Magnetic Resonance Imaging
PRL	Prolactin
SFDA	Saudi Food and Drug Authority
TMZ	Temozolomide
TRH	Thyrotropin-Releasing Hormone

Executive Summary

Hyperprolactinemia refers to an elevated level of prolactin in the bloodstream. The main function of prolactin is to promote the growth and maintenance of breast epithelial cells, which in turn leads to the initiation and sustenance of milk production. Dopamine plays the primary role in regulating prolactin secretion. Prolactin secretion is subject to continuous suppression by dopamine, which operates through D2-type receptors situated on lactotrophs[1].

This condition is observed in fewer than 1% of the overall population in the United Stated and in 5-14% of individuals who experience secondary amenorrhea. Approximately 75% of patients presenting with galactorrhea and amenorrhea have hyperprolactinemia. Of these patients, approximately 30% have prolactin-secreting tumors[1]. The prevalence of hyperprolactinemia among patients with various psychiatric diagnoses and medications was studied among 997 patients in Saudi Arabia. The average blood prolactin level was 32.6 ± 44.1 ng/mL, with higher levels among females than males (42.9± 61.3 versus 24.4 ± 18.6, p<.001). The prevalence of hyperprolactinemia was 44.3%, with no significant gender difference (41.9% in females versus 46.3% in males=.164) but with huge variability according to individual antipsychotic and other psychotropic medications[2].

The typical physical signs observed in individuals with hyperprolactinemia include the presence of galactorrhea and, in instances of prolactinomas, visual field abnormalities. Typically, hyperprolactinemia is identified during the assessment of a patient's initial complaint, such as amenorrhea, galactorrhea, or erectile dysfunction. In some cases, it may be necessary to take multiple fasting prolactin measurements. Thyroid-stimulating hormone tests have high sensitivity in detecting hypothyroidism. It is crucial to assess blood urea nitrogen and creatinine levels to identify signs of renal failure[1].

The direct treatment approach aims to address hyperprolactinemic symptoms or shrink the tumor. If feasible, patients taking medications that induce hyperprolactinemia should discontinue them. In cases with symptoms, the preferred treatment is medical therapy. Dopamine agonists are the treatment of choice since they can provide long-term management of invasive giant prolactinomas. The dopamine agonists bromocriptine, cabergoline, and quinagolide have comparable effectiveness in treating hyperprolactinemia. However, cabergoline is generally considered the safest among the three. If the objective is solely to address hypogonadism, individuals with idiopathic hyperprolactinemia or microadenoma can receive estrogen replacement therapy, with regular monitoring of prolactin levels[1].

Radiation treatment is another option. However, the risk of hypopituitarism makes this a poor choice. Common reasons for pituitary surgery encompass cases where

patients cannot tolerate medication, tumors do not respond to medical treatment, individuals continue to have visual field abnormalities despite medical therapy, and patients have large cystic or hemorrhagic tumors[1].

CHI issued new guidelines related to the management of Hyperprolactinemia. Updating clinical practice guidelines (CPGs) is a crucial process for maintaining the validity of recommendations. Below is a description of sections that need updates. Below is a description of sections that need updates.

CHI issued Hyperprolactinemia guidance after thorough review of renowned international and national clinical guidelines in April 2020. Updating clinical practice guidelines (CPGs) is a crucial process for maintaining the validity of recommendations.

This report functions as an addendum to the prior CHI Hyperprolactinemia clinical guidance and seeks to offer guidance for the effective management of **Hyperprolactinemia**. It provides an **update on the Hyperprolactinemia Guidelines** for CHI Formulary with the ultimate objective of updating the IDF (CHI Drug Formulary) while addressing **the most updated best available clinical and economic evidence related to drug therapies.**

Main triggers for the update are summarized being **the addition of new guidelines and review articles to the report** such as Clinical guidelines for diagnosis and treatment of prolactinoma and hyperprolactinemia by the NHS Foundation Trust Guidelines for management of hyperprolactinemia in adults on antipsychotic drug therapy (**2022**), Diagnosis and management of prolactin-secreting pituitary adenomas: a Pituitary Society international Consensus Statement (**2023**) and the Review Article: Hyperprolactinemia, Clinical Considerations, and Infertility in Women on Antipsychotic Medications **(2021).**

After carefully examining clinical guidelines and reviewing the SFDA drug list, it is recommended to include the SFDA registered drug **Temozolomide** (TEGOZOL ®), (LAGONA®), (Zolomid®) in the CHI formulary while delisting DROSPIRENONE, ESTRADIOL HEMIHYDRATE and ETHINYLESTRADIOL, NORGESTIMATE as they are no longer registered on the SFDA Drug List of September 2023. There have been no changes or updates made to any of the previously listed drugs in terms of drug information and prescribing edits since April 2020.

All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) in all tables reflecting specific drug classes' role in Hyperprolactinemia management.

Below is a table summarizing the major changes based on the hyperprolactinemia guidelines used to issue this report:

Table 1. General Recommendations for the Management of Hyperprolactinemia

Management of Hyperprolactinemia		
General Recommendations	**Level of Evidence/Grade of Recommendation**	**Reference**
The use of dopamine agonist treatment proves to be extremely successful in lowering serum prolactin levels, enhancing the clinical outcomes of hyperprolactinemia, and reducing the size of adenomas.	Strong	Diagnosis and Management of Prolactin-Secreting Pituitary Adenomas: A Pituitary Society International Consensus Statement (2023)[3]
Cabergoline is the favored dopamine agonist because of its prolonged duration of action, remarkable effectiveness, and well-tolerated nature. Bromocriptine and quinagolide are employed less often, contingent on regional approvals and accessibility.	Strong	Diagnosis and Management of Prolactin-Secreting Pituitary Adenomas: A Pituitary Society International Consensus Statement (2023)[3]
Radiation therapy should be considered for patients with a highly stubborn adenoma that does not respond to dopamine agonist therapy and surgical interventions.	Weak	Diagnosis and Management of Prolactin-Secreting Pituitary Adenomas: A Pituitary Society International Consensus Statement (2023)[3]
Surgical treatment may be proposed to patients who cannot endure or are unresponsive to extended dopamine agonist therapy.	Weak	Diagnosis and Management of Prolactin-Secreting Pituitary Adenomas: A Pituitary Society International Consensus Statement (2023)[3]
For women who have no intention of getting pregnant, it is recommended	Weak	Diagnosis and Management of

to employ barrier methods of contraception when commencing dopamine agonist treatment, as pregnancy can happen before the return of menstruation.		Prolactin-Secreting Pituitary Adenomas: A Pituitary Society International Consensus Statement (2023)[3]
In cases where patients have aggressive prolactinomas that persistently enlarge despite trying all other accessible therapies, the utilization of the chemotherapy drug temozolomide is highly advised.	Strong	Diagnosis and Management of Prolactin-Secreting Pituitary Adenomas: A Pituitary Society International Consensus Statement (2023)[3]
When dealing with antipsychotic-induced hyperprolactinemia, stopping the antipsychotic medication responsible for the condition is one potential approach. However, this could potentially exacerbate the patient's psychiatric symptoms or mood. If discontinuing the antipsychotic is not feasible, an alternative strategy is to consider reducing the dosage.	Not graded	Review Article: Hyperprolactinemia, Clinical Considerations, and Infertility in Women on Antipsychotic Medications (2021)[4]
Another viable option is to switch to an antipsychotic medication with a lower likelihood of causing elevated prolactin levels, such as olanzapine, quetiapine, ziprasidone, aripiprazole, or clozapine.	Not graded	Review Article: Hyperprolactinemia, Clinical Considerations, and Infertility in Women on Antipsychotic Medications (2021)[4]

Section 1.0 Summary of Reviewed Clinical Guidelines & Evidence

This section is divided into two parts: the first includes recommendations from **updated versions of guidelines** mentioned in the previous CHI hyperprolactinemia report, and the second includes **newly added guidelines** that have helped generate this report.

1.1 Revised Guidelines

There are no guidelines that have been updated since April 2020.

Table 2. Guidelines Requiring Revision

Guidelines Requiring Revision	
Old Version	**Updated Version**
Diagnosis and Treatment of Hyperprolactinemia: An **Endocrine Society** Clinical Practice Guideline (**2011**)	Not Available

1.2 Additional Guidelines

This part includes the added guidelines to the previous CHI Hyperprolactinemia report, along with their recommendations.

Table 3. List of Additional Guidelines

Additional Guidelines
Diagnosis and Management of Prolactin-Secreting Pituitary Adenomas: A **Pituitary Society** International Consensus Statement (**2023**)
NHS Foundation Trust Guidelines for Management of Hyperprolactinemia in Adults on Antipsychotic Drug Therapy (**2022**)
Review Article: Hyperprolactinemia, Clinical Considerations, and Infertility in Women on Antipsychotic Medications **(2021)**

1.2.1 Diagnosis and Management of Prolactin-Secreting Pituitary Adenomas: A Pituitary Society International Consensus Statement (2023)

This Consensus Statement from an international, multidisciplinary workshop sponsored by the Pituitary Society offers evidence-based graded consensus

recommendations and key summary points for clinical practice on the diagnosis and management of prolactinomas[3]. Consensus recommendations were graded as weak or strong based on the quality of evidence (tables 4 and 5).

Table 4. Quality of Evidence

Quality of evidence	
Very low quality	Expert opinion supported by one or a few small uncontrolled studies
Low quality	Supported by large series of small uncontrolled studies
Moderate quality	Supported by one or a few large uncontrolled studies or meta-analyses
High quality	Supported by controlled studies or large series of large uncontrolled studies with sufficiently long follow-up

Table 5. Strength of Recommendations

Strength of Recommendations	
Weak	Based on very low quality or low-quality evidence
Strong	Based on moderate quality or high-quality evidence

Initial assessment

✓ **Causes of hyperprolactinemia**

- Patients with elevated prolactin levels but with serum prolactin concentrations less than five times the upper limit of normal (ULN) should undergo repeat prolactin testing (strong). If stress is suspected to be influencing the results, cannulated prolactin sampling is advised (strong).
- In most cases, the size of a pituitary adenoma and serum prolactin levels are related. If there is a significant disparity between the two, other potential causes should be considered (strong).
- It is essential to thoroughly review a patient's medication usage to exclude the possibility of drug-induced hyperprolactinemia (strong).
- The presence of mild hyperprolactinemia should prompt consideration of underlying conditions such as primary hypothyroidism, renal insufficiency, and liver failure (strong)
- Pregnancy should not be overlooked as a potential cause of hyperprolactinemia (strong).

✓ **Biochemical evaluation**

- In cases where patients exhibit varying symptoms and inconsistent serum prolactin levels, there should be suspicion of potential false-positive or false-negative results (strong).
- The reference ranges used in standard prolactin assays may not be adequately validated to identify mild hyperprolactinemia (weak).
- For serum samples displaying prolactin levels exceeding the upper limit of detection, it is advisable to dilute the samples to obtain an accurate measurement (strong).
- Patients with moderately elevated serum prolactin levels (< 200 ng/ml) and incongruent clinical or imaging findings should be assessed for macroprolactinemia (strong).
- In cases with inconsistent symptoms and variable measurement values for prolactin, potential factors like biotin exposure or the presence of heterophilic or human anti-animal antibodies, though rare, should be considered as potential causes for inaccurate laboratory results (strong).
- For patients with giant adenomas displaying typical hyperprolactinemia features but with normal or slightly elevated serum prolactin levels, it is recommended to re-measure the samples after a 1:100 dilution to rule out the possibility of a high-dose hook effect (strong).

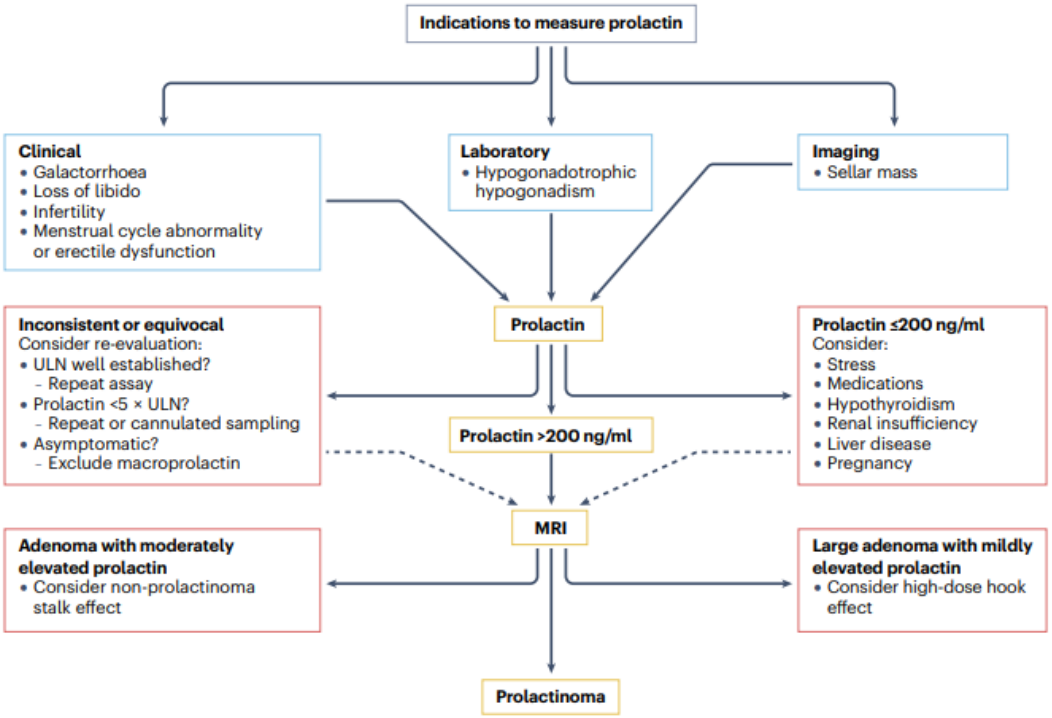

Figure 1. *Diagnostic Algorithm for Prolactinoma*

Retrieved from the Pituitary Society consensus statement for diagnosis and management of prolactin-secreting pituitary adenomas (2023)[3].

✓ Imaging

1- MRI

- Magnetic resonance imaging (MRI) is advised for patients who have confirmed hyperprolactinemia at the time of diagnosis (provided no other non-adenomatous causes for hyperprolactinemia are evident). It is also recommended for demonstrating the response of pituitary adenomas to medical treatment and for establishing a baseline status 3-6 months following surgery (strong). The timing of MRI after initiating medical therapy should be determined based on factors like adenoma size, proximity to the optic chiasm, and the response of prolactin levels to treatment.
- The frequency of follow-up imaging should be determined by taking into account clinical, biochemical, and histological factors, as well as considering previous imaging results (strong).

2- Novel imaging strategies

- Novel imaging strategies have a limited role in standard clinical practice (strong).
- Predicting the response to dopamine agonist therapy may be possible through functional imaging (weak).
- For specific patients, the use of hybrid MRI techniques with functional imaging might enhance the preoperative localization of prolactinomas (weak).

Complications

✓ **Hypogonadism**

- Women with hyperprolactinemia, microprolactinoma, and normal gonadal function can be observed without immediate intervention (weak).
- For premenopausal women with microprolactinoma, unless they intend to become pregnant, their management should involve the possibility of providing sufficient sex hormone replacement without the need for additional treatments (strong).
- The use of combined oral contraceptives can be considered for women with hyperprolactinemia under dopamine agonist therapy, but it may have some limitations and potential side effects (weak).
- Postmenopausal women with microprolactinoma, typically presenting with mild to moderate prolactin elevation, may not require immediate intervention and can be monitored with annual prolactin evaluations (weak).
- Men with persistent hypogonadism while being treated for prolactinoma for over six months should be evaluated for testosterone replacement therapy (weak). However, caution is necessary, especially for large pituitary adenomas, to monitor for potential adenoma growth (weak). The need for testosterone replacement should be reassessed every six months based on serum prolactin levels, as the gonadotrophic axis may recover, eliminating the need for ongoing testosterone replacement (weak)
- Patients experiencing persistent hypogonadotrophic hypogonadism despite dopamine agonist therapy and normal serum prolactin levels who desire fertility may require gonadotropin treatment (strong).
- The use of estrogen and testosterone, likely converted to estradiol through aromatization, can potentially reduce the effectiveness of dopamine agonist therapy. Monitoring the effects of this treatment on serum prolactin levels is important (weak).

✓ **Bone disease**

- Elevated fracture risk is acknowledged as a clinical outcome of prolactinoma (strong).
- Healthcare providers should commence morphological examination through plain radiography for patients with prolactinoma who report back pain or experience a decrease in height (strong).
- Patients ought to undergo assessment of alterations in bone mineral density through dual-energy X-ray absorptiometry (DXA), taking into account factors such as age, duration of hyperprolactinemia and hypogonadism, and other associated risk factors (strong).

Treatment

✓ **Dopamine agonists: efficacy**

- Dopamine agonist therapy is highly effective at reducing serum prolactin levels, improving the clinical effects of hyperprolactinemia, and shrinking adenoma size (strong).
- Cabergoline is the preferred dopamine agonist due to its extended half-life, high efficacy, and good tolerability (strong). Bromocriptine and quinagolide are used less frequently, depending on regional approvals and availability.
- Cabergoline serves as the primary medical treatment for patients with prolactinomas. For microprolactinomas and well-contained macroprolactinomas (Knosp grade 0 and 1), the potential for a cure and the associated risks of surgery should be discussed with patients in a multidisciplinary setting before starting medical treatment (strong).
- Patients with prolactinomas of Knosp grade ≥2 should receive cabergoline treatment (strong).
- Patients who are resistant to or intolerant of other dopamine agonist therapies should switch to cabergoline (strong).
- The necessity of long-term dopamine agonist therapy and the limited likelihood of a permanent cure should be emphasized during patient discussions (strong).
- For women who do not wish to become pregnant, it is advisable to use mechanical contraception when initiating dopamine agonist therapy since pregnancy can occur before the resumption of menstruation (weak).

✓ **Dopamine agonists: adverse effects**

- Patients should be informed of the common, mild side effects of cabergoline, which include gastrointestinal symptoms, dizziness, and fatigue, before initiating treatment (strong).
- Typically, adverse effects improve over time, although in some individual cases, they may persist and be disabling (strong).
- Even with effective treatment, some patients may still experience impaired quality of life (strong).
- To enhance tolerability, administration before bedtime and/or with food may be considered (weak).
- Commencing therapy with low doses and gradually increasing them may improve tolerability (weak).
- Patients who cannot tolerate cabergoline may try other D2-specific dopamine agonists like quinagolide, which might lead to better tolerance (weak).
- Dopamine agonist therapy can cause neuropsychiatric side effects, such as compulsive buying, gambling, aggression, mood swings, and hypersexuality, particularly in men. Although these effects are rare, if they occur, dopamine agonist therapy should be discontinued or the dose adjusted (strong).
- Patients should be made aware of the rare adverse effect of cardiac valve changes associated with long-term and/or high-dose cabergoline treatment. Screening echocardiography intervals may differ among countries, but baseline and follow-up screening are suggested for patients who may receive long-term or high-dose therapy (weak).
- In patients with invasive macroprolactinoma that shrinks significantly with dopamine agonist therapy, cerebrospinal fluid (CSF) rhinorrhea can rarely occur. If suspected, measurements of β2-transferrin or β-trace protein in nasal fluid are recommended. If confirmed, surgical repair is necessary (strong).
- Dopamine agonist-induced apoplexy, resulting from extensive shrinkage of a macroprolactinoma, can cause visual changes. In such cases, surgical repair is likely to be required (strong).

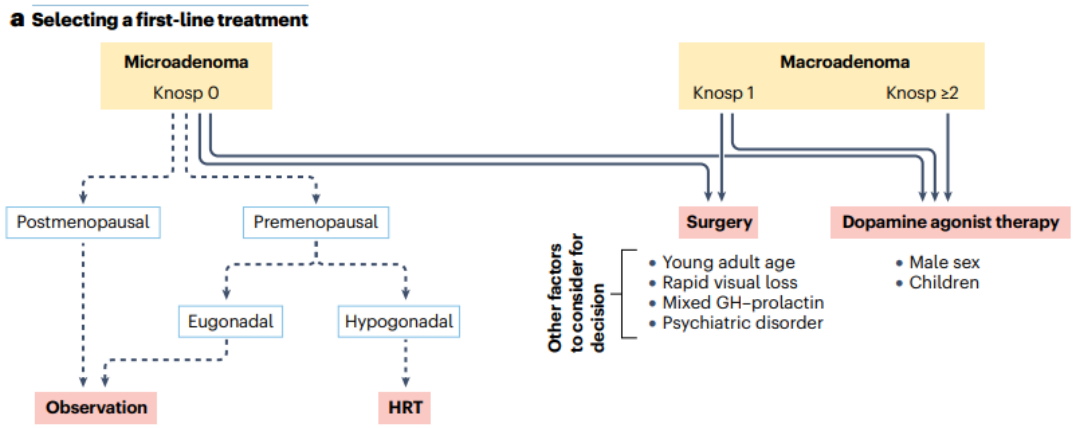

Figure 2. *Selecting a First-Line Treatment*

Retrieved from the Pituitary Society consensus statement for diagnosis and management of prolactin-secreting pituitary adenomas (2023)[3].

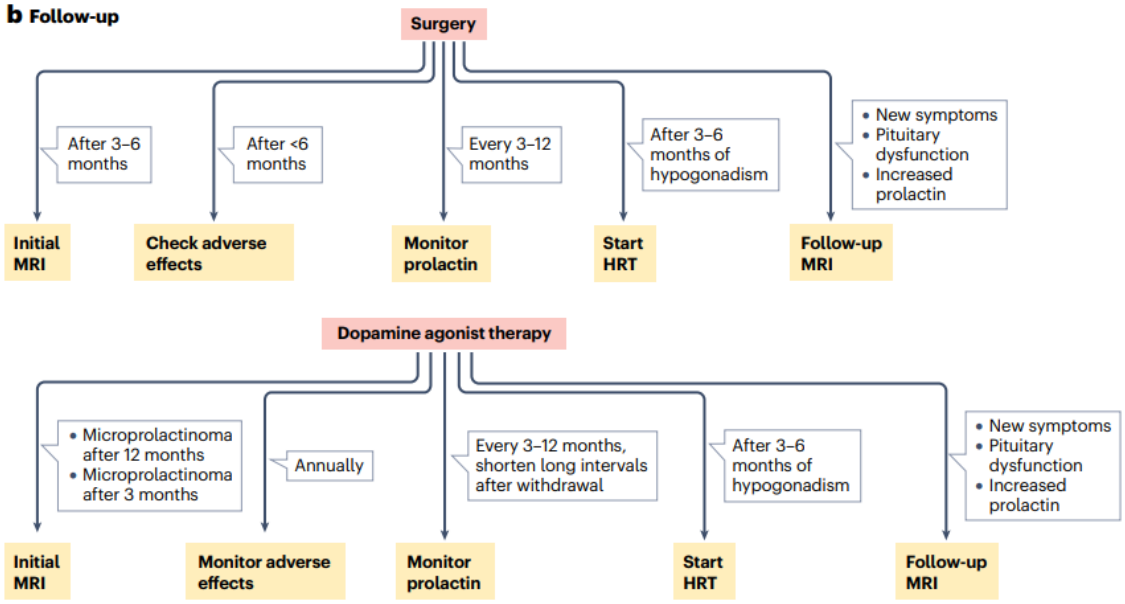

Figure 3. *Follow-Up*

Retrieved from the Pituitary Society consensus statement for diagnosis and management of prolactin-secreting pituitary adenomas (2023)[3].

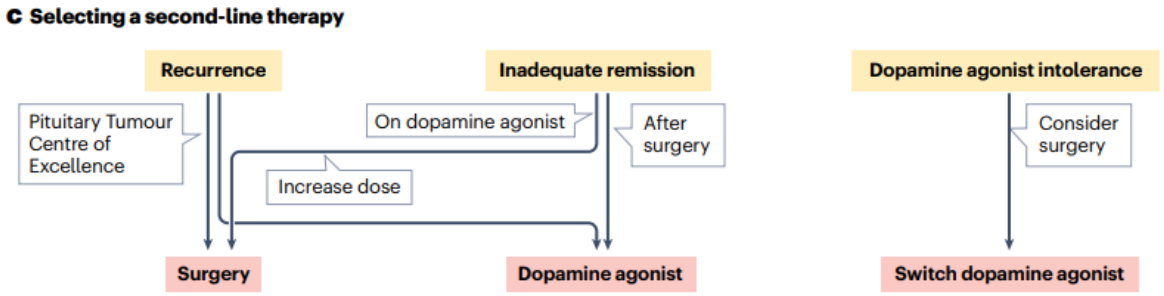

Figure 4. *Selecting a Second-Line Therapy*

Retrieved from the Pituitary Society consensus statement for diagnosis and management of prolactin-secreting pituitary adenomas (2023)[3].

✓ **Dopamine agonists: cardiac valvulopathy**

- If there is an expectation of long-term treatment with high-dose cabergoline (more than 2.0 mg per week), a baseline echocardiography should be conducted to identify any pre-existing valve abnormalities. This evaluation can be conducted either before initiating cabergoline therapy or within the initial months of treatment (weak).

✓ **Dopamine agonists: treatment withdrawal**

- Since approximately one-fifth of patients can achieve remission after discontinuing cabergoline, it is essential to assess patients for favorable indicators, and the consideration of reducing the dosage or discontinuing treatment should be a routine practice (strong).
- Favorable indicators for a successful withdrawal include patients on low maintenance doses of cabergoline, those who have been on treatment for over two years, and individuals with a significant reduction in adenoma size (strong).
- Patients who have successfully withdrawn from cabergoline should undergo lifelong monitoring of their serum prolactin levels, typically on an annual basis or more frequently if symptoms resurface. They should also be educated about potential signs of recurrence (strong).
- In cases where patients experience a recurrence of hyperprolactinemia after withdrawing from cabergoline, they can usually be effectively managed by reintroducing dopamine agonist therapy (strong).
- Patients with long-term maintenance of normalized prolactin levels following cabergoline rechallenge might be re-evaluated for another withdrawal attempt (weak).
- The likelihood of achieving a permanent resolution of autonomous lactotroph cell growth is higher during menopause or after pregnancy. Consequently,

patients in these situations may consider attempting treatment withdrawal (weak).

- ✓ **Surgery**
  - Microprolactinomas and well-circumscribed macroprolactinomas (Knosp grade 0 and 1) can be effectively treated with surgical resection by an experienced neurosurgeon. This approach offers a high probability of cure, is cost-effective, and eliminates the need for long-term dopamine agonist therapy. Therefore, for this subgroup of patients, surgical treatment by an expert pituitary neurosurgeon should be considered as a first-line option alongside dopamine agonist treatment (strong).
  - Medical treatment is the preferred initial approach for patients with a lower chance of achieving remission through surgery (Knosp grade ≥2) (strong).
  - Surgery may be recommended over medical treatment for patients with rapidly progressive vision loss caused by a sellar mass effect or apoplexy (weak).
  - Surgery may also be offered to patients who are intolerant of or resistant to long-term dopamine agonist therapy (weak).
  - In women of young age, surgical treatment could be favored to avoid the need for dopamine agonist therapy over many decades (weak).
  - Debulking surgery for a macroprolactinoma can be considered as an option instead of dopamine agonist therapy for patients who wish to become pregnant. This surgical approach helps reduce the risk of experiencing symptomatic tumor enlargement during a future pregnancy (weak).
  - In cases of spontaneous cerebrospinal fluid (CSF) rhinorrhea, surgical repair is recommended (strong).
- ✓ **Radiation therapy**
  - Radiation therapy should be considered for patients who do not experience significant tumor shrinkage in response to dopamine agonists and have either residual adenoma tissue that cannot be surgically removed or are not suitable candidates for surgery (strong).
  - The use of stereotactic radiotherapy techniques has led to improved outcomes and is now considered the standard of care where it is available (strong).
  - Patients need to be aware that the response to radiotherapy can take several years (strong).

- Patients should also be informed about potential adverse effects that can occur even many years after treatment. It is essential to monitor them for life to detect conditions like hypopituitarism, optic neuropathy, cranial nerve palsy, or the development of secondary brain tumors (strong).

Special situations

✓ **Cystic prolactinomas**

- Cystic prolactinomas may react positively to dopamine agonist therapy, making it a viable treatment option, especially for patients who do not urgently require optic chiasm decompression (strong).
- However, it's crucial to conduct a thorough diagnostic evaluation to differentiate pituitary cystic lesions with hyperprolactinemia caused by stalk compression (strong) as they are unlikely to respond well to dopamine agonist therapy (weak).
- In cases where there are no visual deficits, an MRI follow-up interval of 6 months is likely to be suitable (weak).

✓ **Prolactinomas in men**

- Men with hypogonadotrophic hypogonadism who exhibit symptoms like gynecomastia, loss of libido, erectile dysfunction, infertility, or galactorrhea should undergo an evaluation for hyperprolactinemia and the presence of a prolactin-secreting adenoma (strong).
- In men, macroprolactinomas tend to be more aggressive and have lower response rates to dopamine agonist therapy compared to women (strong). Managing these cases often requires a combination of dopamine agonist therapy, surgery, and/or radiation therapy, with the necessity for close follow-up (strong).
- Men are more prone to experiencing adverse effects related to impulse control disorders from dopamine agonist therapy. Therefore, it is essential to have an informative discussion with patients and involve their partners and families before initiating treatment (strong).

✓ **Mixed GH–prolactin pituitary adenomas**

- Patients with both hyperprolactinemia and excess GH (growth hormone) secretion from pituitary adenomas require a distinct therapeutic approach (strong).
- In cases where patients have acromegaly (excess GH) and hyperprolactinemia, it is crucial to differentiate between the effects on the pituitary stalk and co-production of these hormones by the adenoma. This

assessment should consider factors like the size of the adenoma and be a part of regular follow-up (strong).

- Histological differentiation is needed to distinguish between pure somatotroph adenomas, mammosomatotroph adenomas (secreting both prolactin and GH from a single cell), and somatotroph–lactotroph adenomas (containing both cell types) (strong). An accurate diagnosis is crucial because the outlook or prognosis varies among these different types (weak).
- Aggressive prolactinomas should be evaluated for markers of acidophil stem cell adenomas and co-secretion of GH (weak).
- Patients with hyperprolactinemia should undergo a baseline evaluation for autonomous GH secretion by screening serum levels of insulin-like growth factor 1 (IGF1). This is because clinical features of acromegaly could be either masked or develop over time. If autonomous GH secretion is detected, the treatment strategy should follow the current guidelines for acromegaly (strong).
- If during follow-up, IGF1 levels rise above the upper limit of normal (ULN), and there are no visual changes due to adenoma size, dopamine agonist therapy should be paused for 4 weeks to assess for GH hypersecretion (strong).

✓ **Giant prolactinomas**

- Giant prolactinomas, which are uncommon and mostly found in men, typically show a favorable response to dopamine agonist therapy. Therefore, medical management is the preferred approach (strong).
- However, in cases of giant prolactinomas associated with apoplexy, cerebrospinal fluid (CSF) leakage, or continued tumor growth despite optimal treatment, surgical resection may be considered due to the increased risk of complications and poor outcomes (strong).

✓ **Aggressive prolactinomas and therapy resistance**

- Aggressive prolactinomas are characterized by either an unusually rapid growth rate or clinically relevant growth despite receiving the maximum tolerated doses of dopamine agonists (strong).
- An increase in prolactin levels in a patient who previously had their prolactinoma well controlled with cabergoline might suggest the development of an aggressive adenoma or, very rarely, a carcinoma (weak).
- Patients with prolactinomas who exhibit site-specific symptoms (e.g., neurological deficits or back pain) or significant discordance between serum prolactin levels and pituitary mass should be assessed for potential metastases, which would indicate a carcinoma (strong).

- The combination of imaging signs indicating invasiveness and histological markers of proliferation is likely to provide insights into the behavior of prolactinomas (strong).
- For patients with aggressive prolactinomas that continue to grow despite exhausting all other available treatments, the use of the chemotherapeutic agent temozolomide is strongly recommended (strong).
- Response to temozolomide treatment should be assessed after 3 months, and treatment should be continued for at least 6 months in responsive patients (strong) or for as long as they continue to benefit from the treatment (weak).
- In cases where temozolomide treatment fails, the use of immune checkpoint inhibitors may be considered as an option for managing aggressive prolactinomas (weak).

✓ **Pregnancy and fertility**

- Patients with prolactinomas who are considering pregnancy should be informed about both medical and surgical treatment options (strong).
- Performing a comprehensive examination shortly before pregnancy is advisable as it provides baseline information on serum prolactin levels, visual field status, and adenoma size (weak).
- Patients desiring fertility and planning pituitary surgery before pregnancy should be aware of the potential risk of developing hypopituitarism and its potential impact on fertility (strong).
- Mechanical contraception is recommended instead of hormonal forms of contraception to confirm treatment efficacy before pregnancy and establish the menstrual interval (weak).
- To minimize fetal exposure to dopamine agonist therapy, these medications should be discontinued as soon as pregnancy is confirmed (strong).
- In cases of large macroprolactinomas, it is also an option to maintain dopamine agonist therapy during pregnancy (strong). Although bromocriptine might reduce fetal exposure due to its shorter half-life, cabergoline is now preferred by most medical centers due to increasing safety data (weak).
- For patients with macroprolactinomas, it is essential to confirm the adenoma's response to dopamine agonist therapy before conception (strong). If there is no reduction in adenoma size, surgical intervention should be considered before conception (strong).

- Resuming dopamine agonist therapy that was halted during pregnancy should be contemplated in patients experiencing significant adenoma growth (strong).
- In cases where patients have a significantly enlarged adenoma that does not respond to the re-initiation of dopamine agonist therapy, it may be necessary to consider either pituitary surgery or, if the pregnancy is sufficiently advanced, delivery (strong).

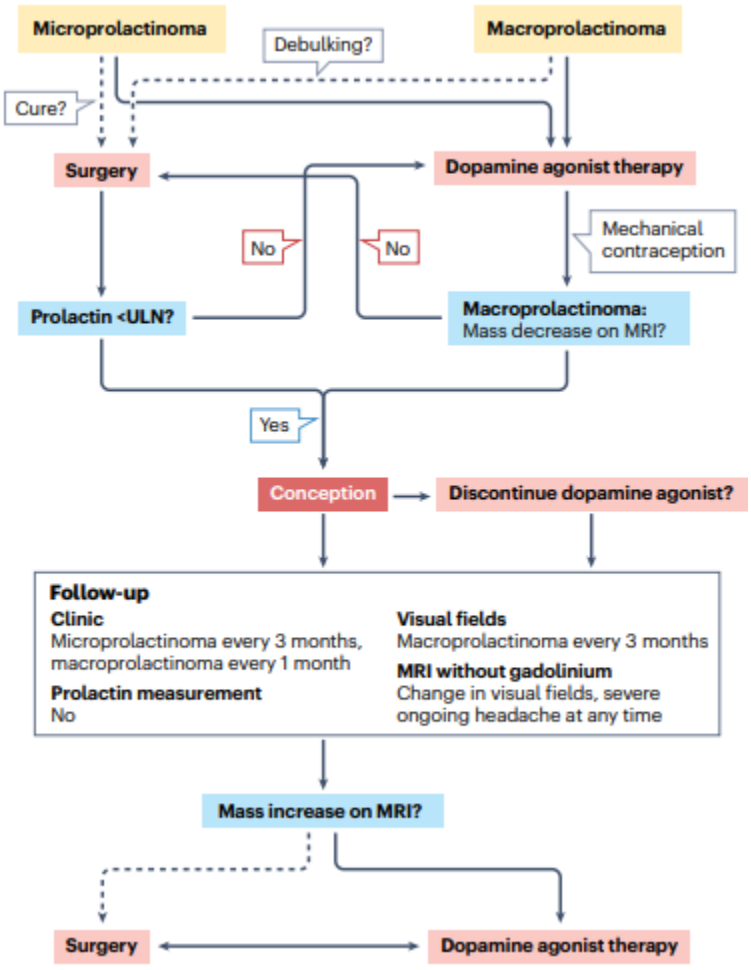

Figure 5. *Prolactinoma Management Considerations for Pregnancy and Fertility*

Retrieved from the Pituitary Society consensus statement for diagnosis and management of prolactin-secreting pituitary adenomas (2023)[3].

- Breastfeeding is generally not forbidden and may be permitted for a specific duration, depending on whether treatment needs to be resumed for tumor size management (strong).

✓ **Prolactinomas in children and adolescents**

- In children, the presence of delayed puberty due to hypogonadotrophic hypogonadism should prompt an evaluation for hyperprolactinemia, along with the clinical signs and symptoms typically observed in adults, such as secondary amenorrhea and galactorrhoea (strong).
- Due to the higher incidence of apoplexy and aggressive prolactinoma behavior in children compared to adults, a high degree of clinical suspicion justifies prompt investigation (strong).
- Children with macroprolactinoma should undergo genetic testing for MEN1 and AIP germline mutations (strong).
- Initiating dopamine agonist therapy in children should begin with low doses (e.g., 0.25 mg per week of cabergoline) and involve slow dose increases due to the increased risk of adverse effects in children (strong).
- Surgery should be considered in cases where vision is threatened, severe neurological symptoms are present, or there is CSF leakage, or if the adenoma is unresponsive to dopamine agonist therapy (strong).
- Surgery might be considered in children with microprolactinoma to avoid the need for long-term medical treatment (weak).
- Radiation therapy should be reserved for patients with an aggressive adenoma unresponsive to dopamine agonist therapy and surgery (weak).

✓ **Patients with an underlying psychiatric disorder**

- The management of prolactinoma in patients with an underlying psychiatric disorder necessitates close collaboration between the endocrinologist, neurosurgeon, and psychiatrist (strong).
- Initiating dopamine agonist treatment in patients with a preexisting psychiatric illness is likely safe but should be approached with caution and involve consultation with a psychiatrist (weak).
- Prior to the initiation of an antipsychotic drug, prolactin levels should be measured (strong).
- Serum prolactin levels exceeding ten times the upper limit of normal (ULN) are uncommon in cases of antipsychotic-induced hyperprolactinemia and should raise suspicion of a prolactinoma (strong).
- To distinguish between prolactinoma and drug-induced hyperprolactinemia in most patients, considerations may include dose reduction or switching to a second-generation antipsychotic that does not induce hyperprolactinemia,

such as aripiprazole. Additionally, an MRI may be used to rule out the presence of a large lesion with a stalk effect (weak).

- Patients treated with antipsychotics might experience reduced efficacy of dopamine agonist therapy, potentially requiring higher doses (weak).
- The use of prolactin-sparing antipsychotics, either alone or in combination with conventional antipsychotic therapy, could facilitate a reduction in dopamine agonist doses (weak).
- In cases where patients require treatment with antipsychotics, alternative treatment modalities for prolactinomas, such as sex hormone replacement in patients with microprolactinoma or surgery, might need to be considered (weak).

✓ **Prolactinomas and menopause**

- Women with microprolactinoma that is effectively managed and who are entering menopause should consider discontinuing dopamine agonist treatment (strong).
- For postmenopausal women with macroprolactinoma, the treatment approach should prioritize the control of adenoma growth (strong).
- There is no indication to normalize serum prolactin levels in postmenopausal women with microprolactinoma for the purpose of enhancing metabolic parameters, reducing the risk of breast cancer, or improving bone density (weak).

✓ **Transgender individuals**

- Transgender women typically experience mild and symptom-free hyperprolactinemia when treated with a combination of estradiol and cyproterone acetate (strong).
- If prolactin levels significantly rise or if symptoms associated with mass effect or galactorrhea develop, the possibility of a prolactinoma should be taken into consideration (weak).
- There is no supporting evidence for an increased occurrence of prolactinomas in transgender women undergoing gender-affirming hormone therapy (weak).

✓ **Hyperprolactinemia and renal failure**

- The evaluation for hyperprolactinemia in individuals with chronic kidney disease (CKD) should be customized based on the presence of symptoms and hypogonadism (weak).

- In patients with CKD, treatment for hypogonadism and the underlying hyperprolactinemia can be contemplated, either through dopamine agonist therapy or sex hormone replacement, depending on clinical symptoms (weak).

1.2.2 NHS Foundation Trust Guidelines for Management of Hyperprolactinemia in Adults on Antipsychotic Drug Therapy (2022)

The following recommendations are retrieved from the NHS Foundation Trust Guidelines for management of hyperprolactinemia in adults on antipsychotic drug therapy (2022)[5].

Introduction, Background and Purpose

- Hyperprolactinemia can result from various causes, some of which are outlined below. This guideline primarily focuses on hyperprolactinemia induced by antipsychotic medications.

Table 6. Causes of Hyperprolactinemia

Physiological causes (non-exhaustive list)	Pharmacological causes (non-exhaustive list)	Pathological causes (non-exhaustive list)
Pregnancy	Antipsychotics	Microprolactinoma
Lactation	Dopamine-receptor blockers: • Metoclopramide • Domperidone • Cimetidine	Macroprolactinoma
Stress (including venipuncture)	Antidepressants • Imipramine • Amitriptyline • Clomipramine	“Blocking” pituitary tumor
Macroprolactin (larger molecular forms of prolactin with no biological significance which may be detected in some assays)	Antihypertensives • α-methyldopa	Acromegaly
	Estrogens	Idiopathic

	Opioids	Sarcoidosis
	Calcium channel blockers • Verapamil	Tuberculosis
		Cushing's disease
		Primary hypothyroidism
		Chronic renal failure
		Cirrhosis
		Untreated Parkinson's disease

Adapted from the NHS Foundation Trust guidelines for management of hyperprolactinemia in adults on antipsychotic drug therapy (2022)[5]

- Antipsychotic medications represent the second most frequent cause of hyperprolactinemia, following pregnancy. All antipsychotic drugs have the capacity to elevate prolactin levels.
- Among typical antipsychotics, hyperprolactinemia is linked to varying degrees of prolactin increase.
- The highest rates of hyperprolactinemia are associated with risperidone, amisulpride, and paliperidone.
- The effect appears to be dose related.

Table 7. Antipsychotic Effect on Prolactin Concentration

<table>
<tr><th>Prolactin-sparing (prolactin increase very rare)</th><th>Prolactin-elevating (low risk - minor changes only)</th><th>Prolactin-elevating (high risk- major changes)</th></tr>
<tr><td>Aripiprazole</td><td>Lurasidone</td><td>Amisulpride</td></tr>
<tr><td>Asenapine</td><td>Olanzapine</td><td>Paliperidone</td></tr>
<tr><td>Clozapine</td><td></td><td></td></tr>
<tr><td>Quetiapine</td><td></td><td>Risperidone</td></tr>
<tr><td></td><td></td><td>Sulpiride</td></tr>
<tr><td></td><td></td><td><u>First Generation Antipsychotics</u>
<table>
<tr><td>Thioxanthenes (Flupentixol, Zuclopenthixol)</td><td>Increase in prolactin 2-3 fold during the 1st month with reduction and normalisation after 6 months</td></tr>
<tr><td>Phenothiazines (Chlorpromazine, Fluphenazine, Pipotiazine, Trifluoperazine)</td><td>2-3 fold increase occurs within hours of treatment initiation with further 2 fold elevation in the following weeks</td></tr>
<tr><td>Butyrophenones (Haloperidol)</td><td>Similar to phenothiazines</td></tr>
</table></td></tr>
</table>

Retrieved from the NHS Foundation Trust guidelines for management of hyperprolactinemia in adults on antipsychotic drug therapy (2022)[5].

Contraindications

Drugs with a high-risk of elevating prolactin should, if possible, be avoided in the following patient groups:

- Patients under 25 years of age (i.e., before peak bone mass)
- Patients with osteoporosis
- Patients with a history of hormone-dependent breast cancer
- Young women (e.g., women of childbearing age where fertility required/desired)
- Antidepressants are considered to have less effect on prolactin concentration.

Table 8. Reported Associations Between Antidepressants and Changes in Prolactin Concentrations

Drug/ group	Prospective studies	Case reports/ series
Agomelatine	No mention of prolactin changes in clinical trials.	None
Monoamine Oxidase inhibitors	Small mean prolactin changes observed with phenelzine and tranylcypromine	Very occasional reports of increased prolactin
Selective serotonin reuptake inhibitor (SSRI's)	Prospective studies generally show no change in prolactin. Some evidence from prescription event monitoring that SSRI's are associated with high risk of non-puerperal lactation. In a French study, 1.6% of adverse effect reports for SSRI were of hyperprolactinaemia.	Galactorrhoea reported with fluoxetine and paroxetine. Euprolactinaemic galactorrhoea and amenorrhoea reported with escitalopram and fluvoxamine Hyperprolactinaemia reported with sertraline
Serotonin-noradrenaline reuptake inhibitors (SNRI's)	Clear association observed between venlafaxine and duloxetine and prolactin elevation	Galactorrhoea reported with venlafaxine and duloxetine
Tricyclic antidepressants	Small mean changes in prolactin seen in some studies but no change in others	Symptomatic hyperprolactinaemia reported with imipramine, dosulepin and clomipramine Galactorrhoea reported with nortriptyline and when trazodone was added to citalopram Raised prolactin may be linked to response to amitriptyline
Mirtazapine	Strong evidence that mirtazapine has no effect on prolactin	Occasional reports of galactorrhoea and gynaecomastia
Vortioxetine	No mention of prolactin changes in clinical trials	None, although clinical experience is limited.

Retrieved from the NHS Foundation Trust guidelines for management of hyperprolactinemia in adults on antipsychotic drug therapy (2022)[5]

Monitoring and baseline prolactin concentration

- Before starting antipsychotic medications known to cause hyperprolactinemia, it is advisable to measure the baseline blood prolactin levels. In some cases, even a single dose of the medication can lead to an increase in prolactin levels.
- Conducting a baseline prolactin measurement, especially if it falls within the normal range, can often prevent the need for a pituitary MRI later on if hyperprolactinemia develops as a result of antipsychotic therapy.
- Check thyroid function before initiating antipsychotic treatment and reevaluate it if symptoms suggestive of hyperprolactinemia emerge, as prolactin levels are influenced by thyroid-stimulating hormone (TSH). Poorly controlled hypothyroidism can contribute to hyperprolactinemia.

- Assess renal function, as patients with kidney disease may experience moderate hyperprolactinemia due to impaired renal clearance of prolactin and changes in central prolactin regulation.
- Confirm mild hyperprolactinemia on at least one occasion before considering a referral, assuming it is not medication-induced. If prolactin levels remain persistently elevated without an identifiable cause and are only mildly elevated, consider pituitary imaging.
- For prolactin concentrations exceeding 1000 mIU/L, measured before starting any antipsychotic, consider a review by an endocrinologist.
- For concentrations exceeding 2000 mIU/L at any point, the patient should be referred to an endocrinologist, as such elevated concentrations may indicate the presence of underlying structural pituitary issues.
- After three months, it is important to inquire about symptoms associated with elevated prolactin levels, which may include sexual side effects, absence of menstruation, headaches, and visual disturbances, among other things.
- If these symptoms are reported or if there is evidence of hormonal imbalances, a prolactin level assessment is recommended. For individuals with hyperprolactinemia, routine monitoring of prolactin concentrations should be performed every 3 to 6 months.

Management of Hyperprolactinemia

When a patient exhibits elevated prolactin levels attributed to antipsychotic treatment and after ruling out physiological causes, it is advisable to proceed with the recommended management steps outlined below:

- If the patient's prolactin levels are elevated but they are not experiencing any symptoms, it is advisable to maintain antipsychotic treatment and closely observe for any signs of symptoms. Keep the patient informed and remain vigilant regarding potential long-term complications.
- However, if the patient's prolactin levels are elevated, and they are experiencing symptoms, further action should be taken:
    1. A dose reduction or withdrawal of the antipsychotic after consideration of the risk/benefit ratio
    2. Consider switching from the current antipsychotic to one with a lower likelihood of increasing prolactin levels. However, carefully evaluate the overall profile of the replacement drug to ensure that the benefits of the change outweigh any potential new risks. Antipsychotics known to have a lower risk of causing hyperprolactinemia include aripiprazole,

olanzapine, clozapine, and quetiapine. Mirtazapine is an example of an antidepressant that does not induce prolactin elevation.

3. If the options above are not feasible, contemplate adding a low dose of aripiprazole to address hyperprolactinemia. A dose of 2.5 mg to 5 mg of aripiprazole may be adequate, although some patients might require higher doses. Monitor prolactin levels on a weekly basis to determine its effectiveness. If prolactin levels do not return to normal after 4 weeks of treatment, discontinue aripiprazole. Keep in mind that using aripiprazole in this manner is an off-label application.
4. For patients who must remain on an antipsychotic known to increase prolactin levels, dopamine agonists like amantadine, cabergoline, and bromocriptine may be considered. However, each of these options carries the potential risk of exacerbating psychosis, so it's crucial to carefully assess the risk-to-benefit ratio. Patients who need to stay on a prolactin-increasing antipsychotic should be offered measures to protect their bone health.

1.2.3 Review Article: Hyperprolactinemia, Clinical Considerations, and Infertility in Women on Antipsychotic Medications (2021)

The review article included in this section was published by Edinoff et al. in Psychopharmacology Bulletin in 2021 and describes clinical considerations in women on antipsychotic medications. Only the part related to hyperprolactinemia will be detailed below[4]:

Hyperprolactinemia causes and risk factors

- ✓ **Physiological Causes of Hyperprolactinemia:**
    1. Pregnancy
    2. Lactation
    3. Nipple stimulation
    4. Orgasm
    5. Stress
- ✓ **Pathological Causes of Hyperprolactinemia:**
    1. Hypothalamic and pituitary diseases
    2. Drug use
    3. Systemic diseases

✓ **Disease States Associated with Hyperprolactinemia:**

1. Prolactin-secreting pituitary adenomas
2. Hypothyroidism
3. Chronic renal failure
4. Cushing's disease
5. Cirrhosis

✓ **Medications Linked to Hyperprolactinemia:**

1. Antipsychotics
2. Antidepressants
3. Antihypertensives
4. Serotonergic medications
5. Antiandrogens
6. Estrogens
7. Opiates
8. Cocaine

Antipsychotics and Hyperprolactinemia:

- First-generation antipsychotics are notably associated with hyperprolactinemia.
- Some second-generation antipsychotics also lead to elevated prolactin levels.
- Specifically, risperidone and paliperidone, among second-generation antipsychotics, have demonstrated evidence of inducing hyperprolactinemia.

Hyperprolactinemia-Associated Infertility

- Hyperprolactinemia leads to infertility by suppressing the release of GnRH (Gonadotropin-Releasing Hormone) from the hypothalamus. This inhibition of GnRH secretion, in turn, prevents the release of FSH (Follicle-Stimulating Hormone) and LH (Luteinizing Hormone) from the anterior pituitary gland.
- Consequently, Due to reduced FSH, there is a lack of ovarian follicular development during the follicular phase of the menstrual cycle. This also results in decreased production of estrogen by the developing follicles.
- In the absence of an LH surge, the ovarian follicle does not rupture to release a mature ovum, leading to anovulation, where ovulation does not occur.

Antipsychotic-induced Hyperprolactinemia

- Antipsychotic medications function through blockade of D2 receptors, including those located in the mesolimbic and mesocortical areas, the striatum, and tuberoinfundibular pathway.
- Blockade of D2 receptors of the tuberoinfundibular pathway, especially lactotroph cells, results in the disinhibition of dopamine on prolactin secretion, which results in the increased release of prolactin from the anterior pituitary.
- The occurrence of hyperprolactinemia in females who use first-generation antipsychotics has been documented at 47.6%. In comparison, females taking risperidone, a second-generation antipsychotic, have a notably higher prevalence, reaching 88%.
- It is worth noting that hyperprolactinemia has been linked to the potency of antipsychotic drugs in relation to the extent of D2 receptor blockade they achieve.

Evaluation of Antipsychotic-induced Hyperprolactinemia

- The assessment of hyperprolactinemia starts with measuring prolactin levels using a fasting blood sample taken two hours after waking. If a single prolactin level exceeds the upper limit of normal, which is 25 mg/L in women, it confirms the diagnosis of hyperprolactinemia.
- Other causes of hyperprolactinemia must be excluded from the differential, including prolactinomas, hypothyroidism, chronic renal failure, and other medication use.
- To exclude the presence of a pituitary or hypothalamic mass, it is recommended to undergo a brain MRI. Additionally, thyroid function tests should be conducted to evaluate for hypothyroidism since thyrotropin-releasing hormone (TRH) can trigger the release of prolactin. Furthermore, renal function panels should be obtained because impaired kidney function can result in reduced degradation and clearance of prolactin.
- Research has shown that hyperprolactinemia induced by antipsychotic drugs is linked to serum prolactin levels within the range of 25 mg/L to 100 mg/L, and notably, levels exceeding 200 mg/L have been observed with the use of risperidone. If feasible, measuring prolactin levels before starting antipsychotic treatment can establish a baseline level and serve as a reference point for assessing changes during therapy.

Management of Antipsychotic-induced Hyperprolactinemia and Infertility

- The treatment of hyperprolactinemia induced by antipsychotic medications and the associated infertility requires an evaluation of multiple factors. These factors include assessing the severity of hyperprolactinemia symptoms, the duration of secondary amenorrhea in premenopausal patients, the length of time the patient has been on the antipsychotic treatment, the level of therapeutic benefit obtained from the antipsychotic, and the risk of relapse if the antipsychotic is either discontinued, reduced in dosage, or replaced.
- Stopping the antipsychotic medication that causes hyperprolactinemia is a possible choice, but it may exacerbate the patient's psychosis or mood. If discontinuing the antipsychotic is not possible, an alternative approach is to attempt a reduction in the dosage.
- Another option is to switch to an antipsychotic medication that has a lower likelihood of causing prolactin elevation, such as olanzapine, quetiapine, ziprasidone, aripiprazole, or clozapine.
- To address the absence of estrogen, regulate menstrual cycles, and prevent osteoporosis, hormonal contraceptives can be incorporated. However, it's essential to be aware of the associated risks, such as thromboembolism and breast cancer. Certain contraindications exist for the use of hormonal contraceptives, including cigarette smoking in women older than 35, a history of thromboembolic events, and experiencing migraines with aura. Nevertheless, these risks should be carefully considered in light of the anticipated benefits.
- To lower the prolactin levels directly, the introduction of a dopamine agonist like cabergoline or bromocriptine can be considered. However, it is crucial to carefully evaluate the use of dopamine agonists in these patients, considering the potential risk of exacerbating their psychosis. This worsening of psychosis is associated with the rise in dopamine levels. During the transition to alternative treatment options, it is essential to consistently monitor the prolactin levels to gauge improvement.

Section 2.0 Drug Therapy in Hyperprolactinemia

This section comprises four subsections: the first contains the newly recommended drugs, the second covers drug modifications, the third outlines the drugs that have been withdrawn from the market, and the fourth details other drugs that are not currently SFDA registered.

2.1 Additions

After April 2020, there have been no hyperprolactinemia drugs that have received FDA or EMA approval. However, Temozolomide is registered on the SFDA and is recommended for PRL-Secreting pituitary carcinomas and malignant prolactinomas if other therapeutic options have failed. It was detailed in the previous CHI report, therefore we recommend adding it to the drug summary spreadsheet.

2.2 Modifications

No modifications have been made since April 2020.

2.3 Delisting

The medications below are no longer SFDA registered[6], therefore, it is advisable to delist the following drugs from CHI formulary. *Please refer to* ***Drugs therapy in hyperprolactinemia - section 2*** *of CHI Hyperprolactinemia original clinical guidance*

- DROSPIRENONE, ESTRADIOL HEMIHYDRATE
- ETHINYLESTRADIOL, NORGESTIMATE

Section 3.0 Key Recommendations Synthesis

- Employing dopamine agonist therapy is highly effective in reducing serum prolactin levels, improving the clinical outcomes of hyperprolactinemia, and shrinking adenomas (strong)[3].
- Cabergoline is the preferred dopamine agonist due to its extended duration of action, exceptional efficacy, and good tolerability (strong). Bromocriptine and quinagolide are used less frequently, depending on regional approvals and availability[3].
- Women who do not wish to become pregnant should consider using barrier methods of contraception when starting dopamine agonist treatment, as pregnancy can occur before the resumption of menstruation (weak)[3].
- In situations where patients have aggressive prolactinomas that continue to grow despite exhausting all other available treatments, the use of the chemotherapy drug temozolomide is strongly recommended (strong)[3].
- Radiation therapy should be considered for patients with a highly stubborn and unresponsive adenoma, after both dopamine agonist therapy and surgery have been exhausted (weak)[3].
- Surgery might also be considered for patients who cannot tolerate or do not respond well to extended dopamine agonist treatment (weak).
- Patients with prolactinomas classified as Knosp grade ≥2 should be prescribed cabergoline therapy (strong)[3].
- Individuals who do not respond well to or cannot tolerate alternative dopamine agonist treatments should transition to cabergoline (strong)[3].
- The management of antipsychotic-induced hyperprolactinemia and its impact on fertility necessitates a comprehensive assessment of several factors. These factors encompass evaluating the severity of hyperprolactinemia symptoms, the duration of secondary amenorrhea in premenopausal individuals, the duration of antipsychotic treatment, the effectiveness of the antipsychotic therapy, and the potential risk of relapse if the antipsychotic is discontinued, dose-reduced, or substituted[4].
- Ceasing the antipsychotic medication responsible for hyperprolactinemia is a potential option; however, this could potentially worsen the patient's psychotic symptoms or mood. If discontinuation of the antipsychotic is not feasible, an alternative strategy is to explore dose reduction[4].

- Another viable choice involves transitioning to an antipsychotic medication with a lower propensity to elevate prolactin levels, such as olanzapine, quetiapine, ziprasidone, aripiprazole, or clozapine[4].

Section 4.0 Conclusion

This report serves as **an annex to the previous CHI Hyperprolactinemia report** and aims to provide recommendations to aid in the management of Hyperprolactinemia. It is important to note that these recommendations should be utilized to support clinical decision-making and not replace it in the management of individual patients with Hyperprolactinemia. Health professionals are expected to consider this guidance alongside the specific needs, preferences, and values of their patients when exercising their judgment.

Section 5.0 References

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4. Amber Edinoff BN, Silverblatt NS, Vervaeke HE, et al. *Hyperprolactinemia, Clinical Considerations, and Infertility in Women on Antipsychotic Medications*. Vol 51.
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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

I. Prescribing Edits (ensure consistent use of abbreviations, e.g., CU, ST)

Some covered drugs may have additional requirements, rules, or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses, and sequence of therapy

Appendix B. Hyperprolactinemia Scope

2020	Changes	2023	Rationale
Section 1.0 Hyperprolactinemia Clinical Guidelines			
Diagnosis and Treatment of Hyperprolactinemia: An Endocrine Society Clinical Practice Guideline 2011	N/A		
	Missing	Foundation Trust Guidelines for management of hyperprolactinemia in adults on antipsychotic drug therapy (2022)[5]	**Introduction, Background and Purpose** • Hyperprolactinemia can result from various causes, some of which are outlined below. This guideline primarily focuses on hyperprolactinemia induced by antipsychotic medications. • Antipsychotic medications represent the second most frequent cause of hyperprolactinemia, following pregnancy. All antipsychotic drugs have the capacity to elevate prolactin levels. **Contraindications:** Drugs with a high-risk of elevating prolactin should, if possible, be avoided in specific patient groups: • Antidepressants are considered to have less effect on prolactin concentration. **Monitoring and baseline prolactin concentration** • Before starting antipsychotic medications known to cause hyperprolactinemia, it is advisable to measure the baseline blood prolactin levels. In some cases, even a single dose of the medication can lead to an increase in prolactin levels. **Management of Hyperprolactinaemia** When a patient exhibits elevated prolactin levels attributed to antipsychotic treatment

			and after ruling out physiological causes, it is advisable to proceed with the recommended management steps outlined below: • If the patient's prolactin levels are elevated but they are not experiencing any symptoms, it is advisable to maintain antipsychotic treatment and closely observe for any signs of symptoms. Keep the patient informed and remain vigilant regarding potential long-term complications. • However, if the patient's prolactin levels are elevated, and they are experiencing symptoms, further action should be taken: o A dose reduction or withdrawal of the antipsychotic after consideration of the risk/benefit ratio o Consider switching from the current antipsychotic to one with a lower likelihood of increasing prolactin levels. o If the options above are not feasible, contemplate adding a low dose of aripiprazole to address hyperprolactinemia. A dose of 2.5 mg to 5 mg of aripiprazole may be adequate, although some patients might require higher doses. Monitor prolactin levels on a weekly basis to determine its effectiveness. If prolactin levels do not return to normal after 4 weeks of treatment, discontinue aripiprazole. Keep in mind that using aripiprazole in this manner is an off-label application. o For patients who must remain on an antipsychotic known to increase prolactin levels, dopamine agonists

			like amantadine, cabergoline, and bromocriptine may be considered.
	Missing	Diagnosis and management of prolactin-secreting pituitary adenomas: a Pituitary Society international Consensus Statement (2023)[3]	**Initial assessment** ✓ Causes of hyperprolactinemia ✓ Biochemical evaluation **Imaging** ✓ MRI ✓ Novel imaging strategies **Complications** ✓ Hypogonadism ✓ Bone disease **Treatment** ✓ Dopamine agonists: efficacy ✓ Dopamine agonists: adverse effects ✓ Dopamine agonists: cardiac valvulopathy ✓ Dopamine agonists: treatment withdrawal ✓ Surgery ✓ Radiation therapy **Special situations** ✓ Cystic prolactinomas ✓ Prolactinomas in men ✓ Mixed GH–prolactin pituitary adenomas ✓ Giant prolactinomas ✓ Aggressive prolactinomas and therapy resistance ✓ Pregnancy and fertility ✓ Prolactinomas in children and adolescents ✓ Patients with an underlying psychiatric disorder ✓ Prolactinomas and menopause ✓ Transgender individuals ✓ Hyperprolactinaemia and renal failure

	Missing	Review Article: Hyperprolactinemia, Clinical Considerations, and Infertility in Women on Antipsychotic Medications (2021)[4]	**Hyperprolactinemia causes and risk factors** They can be classified into pathological, physiological, associated with disease states, and medication-induced. **Hyperprolactinemia-associated Infertility** Hyperprolactinemia leads to infertility by suppressing the release of GnRH (Gonadotropin-Releasing Hormone) from the hypothalamus. This inhibition of GnRH secretion, in turn, prevents the release of FSH (Follicle-Stimulating Hormone) and LH (Luteinizing Hormone) from the anterior pituitary gland. **Antipsychotic-induced Hyperprolactinemia** • Antipsychotic medications function through blockade of D2 receptors, including those located in the mesolimbic and mesocortical areas, the striatum, and tuberoinfundibular pathway. • Blockade of D2 receptors of the tuberoinfundibular pathway, especially lactotroph cells, results in the disinhibition of dopamine on prolactin secretion, which results in the increased release of prolactin from the anterior pituitary. **Evaluation of Antipsychotic-induced Hyperprolactinemia** • The assessment of hyperprolactinemia starts with measuring prolactin levels using a fasting blood sample taken two hours after waking. If a single prolactin level exceeds the upper limit of normal, which is 25 mg/L in women, it confirms the diagnosis of hyperprolactinemia.

			• Other tests include MRI and TRH. **Management of Antipsychotic-induced Hyperprolactinemia and Infertility** • Stopping the antipsychotic medication that causes hyperprolactinemia is a possible choice, but it may exacerbate the patient's psychosis or mood. If discontinuing the antipsychotic is not possible, an alternative approach is to attempt a reduction in the dosage. • Another option is to switch to an antipsychotic medication that has a lower likelihood of causing prolactin elevation, such as olanzapine, quetiapine, ziprasidone, aripiprazole, or clozapine. • To address the absence of estrogen, regulate menstrual cycles, and prevent osteoporosis, hormonal contraceptives can be incorporated. • To lower the prolactin levels directly, the introduction of a dopamine agonist like cabergoline or bromocriptine can be considered. However, it is crucial to carefully evaluate the use of dopamine agonists in these patients, considering the potential risk of exacerbating their psychosis.

Appendix C. MeSH Terms PubMed

C.1 Pubmed Search for Hyperprolactinemia

The following is the result of the PubMed search conducted for hyperprolactinemia guideline search:

Query	Filters	Search Details	Results
((((((((((Hyperprolactinemia[MeSH Terms]) OR (Hyperprolactinemias[Title/Abstract])) OR (Prolactin, Inappropriate Secretion[Title/Abstract])) OR (Inappropriate Secretion Prolactin[Title/Abstract])) OR (Secretion Prolactin, Inappropriate[Title/Abstract])) OR (Inappropriate Prolactin Secretion Syndrome[Title/Abstract])) OR (Prolactin Hypersecretion Syndrome[Title/Abstract])) OR (Hypersecretion Syndrome, Prolactin[Title/Abstract])) OR (Syndrome, Prolactin Hypersecretion[Title/Abstract])) OR (Hyperprolactinaemia[Title/Abstract])) OR (Inappropriate Prolactin Secretion[Title/Abstract])) OR (Prolactin Secretion, Inappropriate[Title/Abstract])) OR (Secretion, Inappropriate Prolactin[Title/Abstract])	Guideline, in the last 5 years	("hyperprolactinemia"[MeSH Terms] OR "Hyperprolactinemias"[Title/Abstract] OR (("Prolactin"[MeSH Terms] OR "Prolactin"[All Fields] OR "prolactins"[All Fields] OR "prolactin s"[All Fields] OR "prolactine"[All Fields] OR "prolactinic"[All Fields]) AND "inappropriate secretion"[Title/Abstract]) OR (("Inappropriate"[All Fields] OR "inappropriately"[All Fields] OR "inappropriateness"[All Fields]) AND "secretion prolactin"[Title/Abstract]) OR ((("bodily secretions"[MeSH Terms] OR ("bodily"[All Fields] AND "secretions"[All Fields]) OR "bodily secretions"[All Fields] OR "secretions"[All Fields] OR "metabolism"[MeSH Subheading] OR "metabolism"[All Fields] OR "Secretion"[All Fields] OR "metabolism"[MeSH Terms] OR "secretable"[All Fields] OR "secrete"[All Fields] OR "secreted"[All Fields] OR "secretes"[All Fields] OR "secreting"[All Fields]) AND ("Prolactin"[MeSH Terms] OR "Prolactin"[All Fields]	2

		OR "prolactins"[All Fields] OR "prolactin s"[All Fields] OR "prolactine"[All Fields] OR "prolactinic"[All Fields])) AND "Inappropriate"[Title/Abstract]) OR ((("Inappropriate"[All Fields] OR "inappropriately"[All Fields] OR "inappropriateness"[All Fields]) AND ("Prolactin"[MeSH Terms] OR "Prolactin"[All Fields] OR "prolactins"[All Fields] OR "prolactin s"[All Fields] OR "prolactine"[All Fields] OR "prolactinic"[All Fields])) AND "secretion syndrome"[Title/Abstract]) OR (("Prolactin"[MeSH Terms] OR "Prolactin"[All Fields] OR "prolactins"[All Fields] OR "prolactin s"[All Fields] OR "prolactine"[All Fields] OR "prolactinic"[All Fields]) AND "hypersecretion syndrome"[Title/Abstract]) OR (("hypersecrete"[All Fields] OR "hypersecreted"[All Fields] OR "hypersecretes"[All Fields] OR "hypersecreting"[All Fields] OR "Hypersecretion"[All Fields] OR "hypersecretions"[All Fields]) AND "syndrome prolactin"[Title/Abstract]) OR (("syndrom"[All Fields] OR "syndromal"[All Fields] OR "syndromally"[All Fields] OR "Syndrome"[MeSH Terms] OR "Syndrome"[All Fields]	

		OR "syndromes"[All Fields] OR "syndrome s"[All Fields] OR "syndromic"[All Fields] OR "syndroms"[All Fields]) AND "prolactin hypersecretion"[Title/Abstract]) OR "Hyperprolactinaemia"[Title/Abstract] OR (("Inappropriate"[All Fields] OR "inappropriately"[All Fields] OR "inappropriateness"[All Fields]) AND "prolactin secretion"[Title/Abstract]) OR (("Prolactin"[MeSH Terms] OR "Prolactin"[All Fields] OR "prolactins"[All Fields] OR "prolactin s"[All Fields] OR "prolactine"[All Fields] OR "prolactinic"[All Fields]) AND "secretion inappropriate"[Title/Abstract]) OR ((("bodily secretions"[MeSH Terms] OR ("bodily"[All Fields] AND "secretions"[All Fields]) OR "bodily secretions"[All Fields] OR "secretions"[All Fields] OR "metabolism"[MeSH Subheading] OR "metabolism"[All Fields] OR "Secretion"[All Fields] OR "metabolism"[MeSH Terms] OR "secretable"[All Fields] OR "secrete"[All Fields] OR "secreted"[All Fields] OR "secretes"[All Fields] OR "secreting"[All Fields]) AND ("Inappropriate"[All Fields] OR "inappropriately"[All Fields] OR "inappropriateness"[All Fields])) AND "Prolactin"[Title/Abstract]))	

		AND ((y_5[Filter]) AND (guideline[Filter]))	

Appendix D. Treatment Algorithm

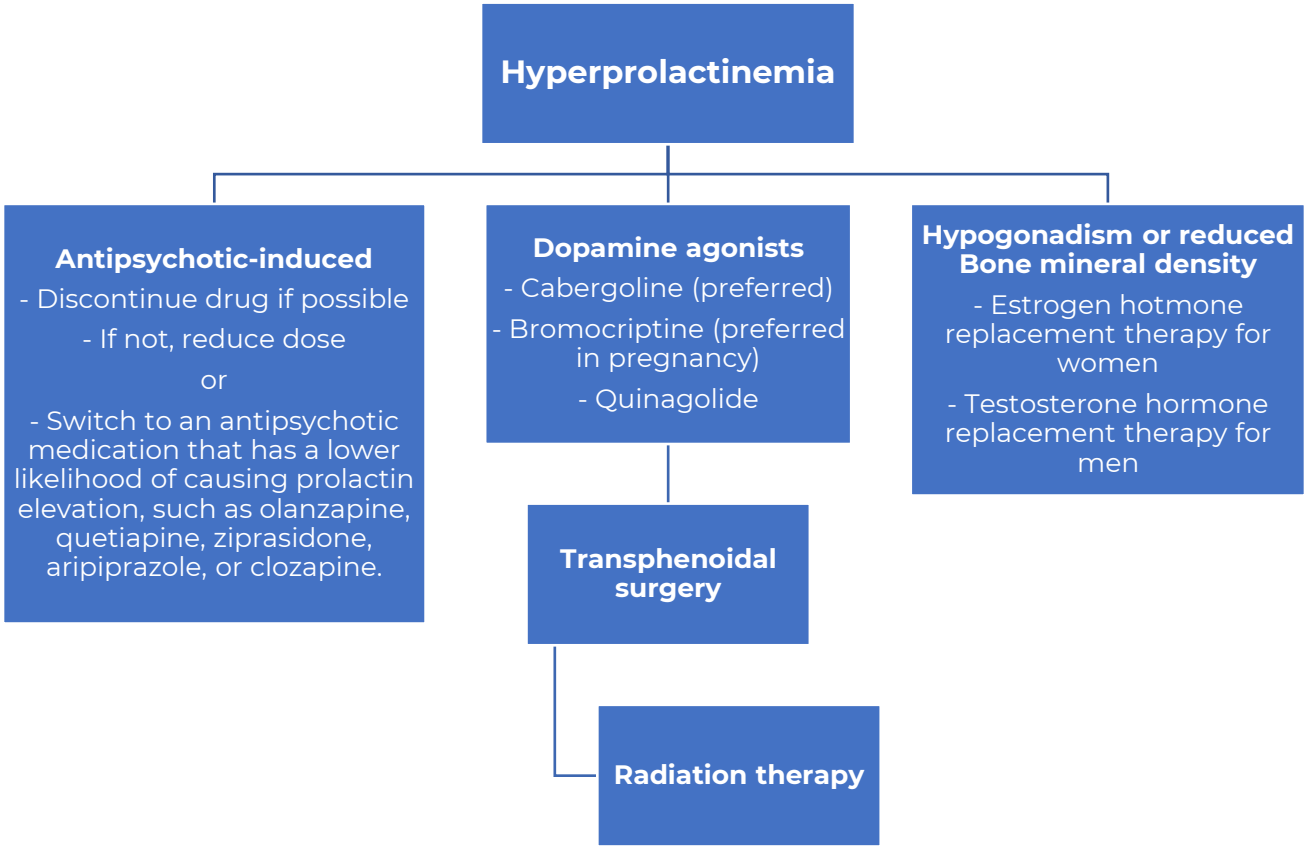

Figure 6. *Treatment Algorithm for Hyperprolactinemia*[3,4,5]