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Diagnosis and Management of Prolactin-Secreting Pituitary Adenomas: Pituitary Society International Consensus Guidelines

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ABSTRACT

This report 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. Epidemiology and pathogenesis, clinical presentation of disordered pituitary hormone secretion, assessment of hyperprolactinemia and biochemical evaluation, optimal use of imaging strategies and disease-related complications are addressed. In-depth discussions present the latest evidence on treatment of prolactinoma, including efficacy, side effects, and options for withdrawal of dopamine agonist therapy, as well as indications for surgery, preoperative medical therapy, and radiation therapy. Management of prolactinoma in special situations is discussed, including cystic lesions, mixed growth hormone and prolactin-secreting adenomas, and aggressive prolactinomas, considerations for pregnancy and fertility, as well as management of prolactinomas in children and adolescents, patients with underlying psychiatric disorders, menopausal women, transgender individuals, and patients with chronic kidney disease. The workshop concluded that although treatment resistance is rare, there is a need for additional therapeutic options to address clinical challenges in treating these patients and a need to facilitate international registries to enable risk stratification and optimization of therapeutic strategies.

INTRODUCTION

The Pituitary Society published guidelines on diagnosis and management of prolactin (PRL)-secreting adenomas in 2006[1] and in conjunction with the Endocrine Society in 2011.[2] This updated consensus considers new evidence that has markedly influenced clinical practice, including incorporation of transcription factors into pituitary adenoma classification,[3] long-term side effects of dopamine agonist (DA) therapy,[4] outcomes following DA withdrawal,[5] advances in surgical tumor resection,[6-8] management during pregnancy,[9-11] effects of hyperprolactinemia on bone and fracture risk,[12] and management of cystic and aggressive prolactinomas,[13] as well as prolactinomas in children and transgender patients.

METHODS

The Pituitary Society hosted a virtual consensus workshop on the diagnosis and management of prolactinoma in January 2022. Workshop co-chairs (SP, MM, FFC) and Pituitary Society Programs Co-Directors (MF, AG) identified topics related to prolactinoma diagnosis and management to be addressed, and 36 experts in the clinical management of pituitary disease representing 13 countries with different healthcare systems participated in the workshop. Speakers, selected according to their expertise for the specific topic based on their publication record and recognized standing in the field, summarized key data on their assigned topics in 15-minute, fully referenced slide-lecture presentations recorded approximately one month prior to the workshop. Speakers critically reviewed English-language, PubMed-indexed papers published before January 2022. Search terms included “prolactinoma”,

"prolactin-secreting adenoma", and terms associated with topics for discussion, including "epidemiology", "pathogenesis", "clinical symptoms", "assessment", "imaging", "complications", "dopamine agonists", "surgery", and "radiation therapy". Lectures were recorded and précis of key findings prepared, which participants were invited to review and comment on in advance.

During the 2-day meeting, speakers provided 5-minute highlight summaries of their assigned topics, participants were divided into breakout groups for extended discussions, and then reported their conclusions and comments to the entire group. Consensus recommendations were then recorded based on majority opinion. After the meeting, consensus recommendations, slide-lecture presentations, précis, and discussion points were collated, and a draft manuscript was prepared by the lead authors (SP, MF, SM).

Based on principles for grading of evidence for guidelines,[14,15] as well as previously published consensus statements from the Pituitary Society,[16] evidence supporting each consensus recommendation was graded as very low, low, medium, or high quality; consensus recommendations based on very low or low quality were graded as weak, and those based on medium or high quality evidence were graded as strong (**Box 1**). Recommendations and discussion points were circulated to all participants for review, and more recent data identified in literature reviews using the same keywords through January 2023 were added as appropriate. The draft manuscript was circulated to all authors in 3 rounds prior to their final approval. Consensus recommendations and key points are presented and additional background discussion is presented in Supplementary Information.

BACKGROUND

Epidemiology

- Microprolactinomas rarely proliferate and are of low concern for persistent long-term adenoma growth (strong).
- Macroprolactinomas, especially in males, have a different clinical prognosis compared with microadenomas and require closer follow-up (strong).

Prolactinomas, most commonly benign PRL-secreting adenomas derived from lactotrophs, account for 50% of all pituitary adenomas in both females and males. At age 25-44 years, prolactinomas predominantly affect women, with a female:male ratio of 5:1 to 10:1, whereas after menopause the ratio equalizes.[17] The standardized incidence rate in women is 3 times higher than in men. The ratio between macro- and microprolactinomas is approximately 1:8 in women, and 4:1 in men.

Microprolactinomas (<10 mm in maximal diameter) are more frequent, and seldom grow into macroprolactinomas. Giant prolactinomas (macroprolactinomas >40 mm) are rare.[18] Recent studies indicate a higher prevalence for prolactinomas than previously predicted.[17] Incidence and prevalence rates are depicted in **Supplementary Table 1** and described in **Supplementary Box 1**.

Molecular Pathogenetic Mechanisms

- *MEN1* and *AIP* germline mutation screening could be considered in patients with a family history of pituitary adenomas and in patients <30 years old with macroadenomas (weak).
- Somatic mutation screening should not be routinely performed (strong).

Molecular mechanisms for prolactinoma pathogenesis require further elucidation. Prolactinomas are mostly sporadic monoclonal neoplasms,[19,20] implying a somatic genetic event conferring a growth advantage. A hotspot somatic mutation in splicing factor 3 subunit B1 (SF3B1R625H) was identified in 20% of prolactinomas in one series, and was associated with higher PRL levels and potentially more aggressive behavior.[21] Prolactinomas are very rarely associated with germline mutations, and, when present, onset of disease usually occurs at a younger age. With *MEN1* and *AIP* mutations, macroprolactinomas are more aggressive, and with *MEN1* could be resistant to therapy.[22,23] By contrast, microprolactinomas in MEN1 may be less aggressive than previously thought.[24] As pathogenic *AIP* variants are very rarely detected, screening should be considered judiciously to avoid unnecessary testing and cost.

See **Supplementary Box 1** for further discussion.

CLINICAL PRESENTATION

Hyperprolactinemia and Hypogonadism

- The presence of a sellar mass on imaging requires evaluation for hyperprolactinemia (strong).

- Galactorrhea should trigger investigation for hyperprolactinemia, except for known physiological reasons (e.g., pregnant or lactating women) (strong). Importantly, absence of galactorrhea does not exclude hyperprolactinemia (strong).
- Loss of libido and/or infertility, new-onset menstrual irregularities or amenorrhea in women, as well as erectile dysfunction and/or hypogonadotrophic hypogonadism in men, should trigger investigation for hyperprolactinemia (strong).
- PRL-secreting adenomas have been associated with increased obesity and metabolic syndrome (weak).

Increased PRL during stress, pregnancy, and lactation inhibits hypothalamic kisspeptin neuron function, and consequently reduces gonadotrophin-releasing hormone (GnRH) production.[25] Prolactinoma clinical presentation in part reflects PRL-induced suppression of the hypothalamic-pituitary-gonadal axis which usually reverts after PRL normalization,[26] although hypogonadism may persist, especially in male patients with macroprolactinomas.[27,28]

Hyperprolactinemia leads to oligo/amenorrhea with or without galactorrhea in women and erectile dysfunction in men, while loss of libido and infertility are observed in both sexes.[29] Although obesity is reportedly 4-fold more prevalent with prolactinomas vs non-functioning pituitary adenomas,[30] this disorder likely occurs secondary to associated hypogonadism.

See **Supplementary Box 2** for further discussion.

Considerations

Screening for hypogonadotrophic hypogonadism in all male and premenopausal female patients with micro- and macroprolactinomas is recommended.

Other Pituitary Hormone Deficiencies Before and After Treatment

- Macro- and, less frequently, microprolactinomas may cause growth hormone (GH), thyroid-stimulating hormone (TSH), and adrenocorticotrophin (ACTH) axis deficiencies. Patients should be evaluated for associated clinical features, tested for pituitary hormone deficiencies, and appropriately treated per standard guidelines (strong).
- Surgical resection of prolactinomas may resolve hypopituitarism but also cause new-onset deficiencies. Postoperative retesting is warranted (strong).

Prevalence and clinical course of GH/TSH/ACTH deficiencies, derived largely from retrospective studies, are less well delineated compared with hypogonadism. Hormone deficiencies are more frequently encountered with macroprolactinomas.[31-33] In a study of 81 men, prevalence of pretreatment TSH/ACTH deficiency increased from 6.7%/0% for macroprolactinomas 10-19 mm to 17.9%/6.9% for adenomas 20-39 mm and 26.1%/33.3% for giant prolactinomas ≥40 mm.[34]

As surgery and radiation may each induce hypopituitarism, post-treatment evaluation timeline should be individualized.[35]

See **Supplementary Box 2** for further discussion.

Considerations

Screening for GH/TSH/ACTH deficiencies[35] in all patients with macroadenomas and 6-9 mm microadenomas at diagnosis was recommended; the consensus was to retest pituitary function after effective DA therapy depending on baseline pituitary deficiencies and mass extension, as well as PRL and adenoma response.

Screening for GH/TSH/ACTH deficiencies was recommended for those undergoing surgical resection, and retesting approximately 6-12 weeks after surgery was recommended depending on baseline adenoma size, surgical findings, and postoperative symptoms. Some participants concluded that patients with hormonal deficiencies at diagnosis as well as those with adenomas >6 mm should all be retested after surgery.

INITIAL ASSESSMENT

Causes of Hyperprolactinemia

- Patients with hyperprolactinemia but PRL levels <5×ULN should undergo repeat PRL testing (strong). Cannulated PRL sampling might be useful if an influence of stress is suspected (strong).
- In general, adenoma size and PRL levels correlate; discrepancy should trigger consideration of other possible causes (strong).
- Medication use should be rigorously reviewed to exclude drug-induced hyperprolactinemia (strong).
- Primary hypothyroidism, renal insufficiency, and liver failure should be recognized as causes of mild hyperprolactinemia (strong).
- Pregnancy should not be overlooked as a cause of hyperprolactinemia (strong).

PRL secretion is under chronic inhibitory control by hypothalamic-derived dopamine[36] (**Figure 1**). Dopamine traverses the pituitary stalk and suppresses both PRL production as well as lactotroph proliferation via D2 receptors (D2R). These inhibitory actions are opposed by estrogen.

The most common pathologic cause of hyperprolactinemia is excess PRL production by a prolactinoma.[20] However, parasellar or intrasellar masses impinging on the pituitary stalk, including non-secreting pituitary adenomas, may compromise dopamine flow and lead to hyperprolactinemia (**Table 1**). Hence, elevated PRL levels (up to 6×ULN)[37,38] may reflect a hypothalamic-pituitary lesion, or evidence of local trauma, surgery, radiation, skull fracture, or internal carotid artery aneurysm.[39] Adenoma size-adapted cut-offs for PRL may distinguish true prolactinomas from other pituitary lesions.[40]

Estrogens potently induce hyperprolactinemia, but the influence of oral contraceptives on prolactinoma development is controversial. In a case-control analysis, there was a mildly increased risk with menopausal hormone therapy as well as with oral contraceptives, but risk with oral contraceptives was not present in the prospective cohort analysis.[41] (See **Supplementary Box 3** for discussion on PRL excess in pregnancy.)

Primary hypothyroidism may present with hyperprolactinemia reversible with thyroid hormone replacement. Intracranial hypotension may cause hyperprolactinemia.[42] Stress (e.g., due to venipuncture) may induce a 2- to 4-fold rise in PRL levels that lasts <1 hour. Repeated or cannulated PRL venipuncture sampling for testing is recommended with PRL levels <5×ULN if an influence of stress is suspected.[43,44] Physiologic PRL increases may occur

after exercise, high-protein meals, and alcohol.[45,46] Patients with polycystic ovary syndrome (PCOS) require evaluation for elevated PRL, as PCOS per se is rarely associated with hyperprolactinemia.[47]

High PRL with lymphocytic hypophysitis may reflect either autoimmune cell actions or a stalk effect.[48] Hypophysitis should be considered with apparently idiopathic hyperprolactinemia.[49] PRL co-secretion with GH in acromegaly or with TSH in thyrotrophinoma is due to either plurihormonal adenoma or stalk effect.[50]

An extensive listing of drugs acting as dopamine antagonists or as serotonin agonists may cause hyperprolactinemia and galactorrhea (see **Table 1**).[51-53]

Biochemical Evaluation

- In patients with inconsistent symptoms and variable PRL levels, consider false-positive or false-negative results (strong).
- Standard PRL assay reference ranges may not be sufficiently validated to recognize mild hyperprolactinemia (weak).
- Serum samples with PRL levels above the upper detection limit should be diluted to provide an exact value (strong).
- Macroprolactinemia should be evaluated in patients with moderately increased PRL levels (<200 ng/mL), at least in those with discordant clinical or imaging findings (strong).
- With inconsistent symptoms and discrepancy with PRL levels, biotin exposure or heterophilic or human anti-animal antibodies may rarely cause erroneous laboratory results (strong).

- In patients with giant adenomas and typical features of hyperprolactinemia but normal or slightly elevated PRL levels, samples should be re-measured after 1:100 dilution to exclude a high-dose hook effect (strong).

A correct biochemical diagnosis of hyperprolactinemia is a prerequisite for further investigation but may be hampered by potentially overlapping conditions associated with increased PRL levels.[46,54] Suspicion of an assay artifact should arise in patients whose symptoms and biochemical results are not consistent. Assay errors, macroprolactinemia, and high-dose hook effect are all possible reasons for false-positive or false-negative PRL levels (**Figure 2**).

PRL assays

PRL is usually measured by immunoassays, calibrated against the WHO 84/500 international standard containing exclusively 23 kDa monomeric hPRL. A diagnosis depends on well-established assay- and sex-specific reference intervals. However, published upper limits are lower than those presented by most manufacturers,[55] normal values are higher in women, and different measurement units may be provided (i.e., 1 µg/L = 21.2 mIU/L). Stimulation and suppression tests yield non-specific results and have been largely abandoned.[2]

Macroprolactinemia

The major circulating form of PRL has a molecular weight (MW) of 23 kDa, compared with so-called ‘big’ PRL (MW 40-60 kDa) and ‘big-big’ PRL (MW>150 kDa). In 10-25% of hyperprolactinemic populations, a high proportion of serum

big-PRL and big-big PRL is found.[56] Anti-PRL autoantibodies (mostly IgG) bound to PRL contribute to big-big PRL and therefore to macroprolactinemia. As these variants interfere with PRL assays but are biologically inactive, most patients with macroprolactinemia lack typical clinical symptoms of hyperprolactinemia.[57] PRL recovery after polyethylene glycol precipitation can usually distinguish between macroprolactinemia and true hyperprolactinemia[58] (see **Supplementary Box 3**).

Hook Effect

In two-site immunoradiometric or chemiluminometric assays, incubation with extremely high PRL concentrations saturates both antibodies and prevents sandwich formation, resulting in the so-called 'hook effect.' Thus, patients with very high PRL levels may show only moderately elevated levels. The hook effect is rarely encountered currently, but should be considered when PRL level is only mildly elevated and clinical suspicion for a macroprolactinoma is high.[59]

IMAGING

Magnetic Resonance Imaging

- MRI should be performed in patients with confirmed hyperprolactinemia at diagnosis (if no other non-adenomatous causes for hyperprolactinemia are evident), to demonstrate adenoma response to medical treatment, and to establish baseline status 3-6 months post-surgery (strong). Timing of MRI after medical therapy initiation depends on adenoma size, proximity to the optic chiasm, and PRL response to therapy.

- Follow-up imaging frequency should be based on clinical, biochemical, and histological factors, as well as previous imaging results (strong).
- Serial imaging should be performed for treatment-resistant prolactinoma; new onset of symptoms including visual changes, headaches, or galactorrhea; new-onset pituitary dysfunction; and evidence of new PRL increase (strong).
- Dynamic gadolinium-based MRI contrast enhancement is important for initial diagnosis of prolactinoma. For follow-up MRIs, gadolinium should be used judiciously; macrocyclic chelates are preferred over linear chelates until further studies clarify possible long-term retention risks (strong).
- Gadolinium should be used with caution in patients with chronic kidney disease due to the risk of nephrogenic systemic fibrosis (strong).
- Patients with adenomas at high risk of aggressive behavior require closer surveillance (strong).

MRI is the recommended imaging modality for diagnosing pituitary and parasellar lesions, as well as for follow-up monitoring of treated or untreated pituitary adenomas.[2,20] However, repeat imaging incurs a cost burden and, coupled with reports on possible retention of linear gadolinium-based contrast agents,[60,61] determining the optimal imaging frequency to safely assess treatment response is paramount. Evidence is sparse. Macroprolactinoma expansion is usually accompanied by biochemical and clinical changes,[62,63] and serum PRL concentrations usually correlate with adenoma size, but exceptions occur.[62,64] As microadenomas not treated with DA rarely increase in size, MRI

(as an adjunct to PRL monitoring) is typically warranted only with suspected adenoma growth or optic chiasm proximity or to evaluate surgical possibilities.[63,65]

Prolactinomas are typically mildly hyperintense on T2-weighted MRI.[66] Men may show a heterogeneous T2 intensity signal reflecting necrosis and hemorrhage associated with higher PRL levels and poorer DA response.[67,68] T2 hypointensity in women has been associated with DA resistance.[69] Increased T2 hyperintensity occurs with DA treatment, although this may not be noticeable in hemorrhagic or highly hyperintense adenomas. T2 echo gradient imaging may be useful for diagnosing hemorrhage.

Timing After Medical Therapy

For macroprolactinomas, MRI should be repeated at 3-6 months after the start of DA treatment as reduction in size at 3 months after starting cabergoline could predict further long-term response and/or biochemical control.[70] For microprolactinomas, re-scanning depends on clinical and biochemical follow-up, but may be repeated after 1 year, or at least when considering withdrawal of DAs. As adenoma growth can occur with biochemically resistant prolactinomas treated with DAs, follow-up imaging should be considered for persistently elevated or rising PRL levels. If shrinkage is not demonstrated with DAs and initial PRL level is not unequivocally indicative of prolactinoma, a stalk effect due to a nonfunctioning adenoma should be reconsidered.

For treatment-responsive microadenomas and macroadenomas, serial imaging beyond 1 year is not necessary unless PRL levels persistently increase.[63,71] However, partially responsive macroadenomas or those close to

the optic chiasm may require periodic annual imaging for the first 3 years and less frequently thereafter.[63] Symptoms suggestive of pituitary apoplexy warrant prompt imaging.

Discordant results showing PRL level normalization without substantial mass shrinkage, or significant shrinkage without complete PRL normalization, may be encountered. Although PRL often normalizes within the first 6 months,[72] and significant shrinkage can also occur early, some prolactinomas only slowly decrease in size over several years of DA therapy.

When DA withdrawal is being considered, absence of residual adenoma on MRI is a favorable prognostic factor for lack of recurrence.[2,73,74] MRI should be performed after DA withdrawal if PRL levels rise progressively or if headaches, vision changes, or pituitary dysfunction develop.

Timing After Surgery

MRI should be performed 3-6 months postoperatively to establish a new baseline. Serial imaging may be performed for resistant, partially resected adenomas at initial imaging intervals of 6-12 months. Completely resected adenomas should be re-imaged only if PRL levels rise, or if headaches, vision changes, or pituitary dysfunction develop.[63] If surgery is performed as first-line management for microprolactinomas, and postoperative PRL normalization is achieved, repeat imaging is required only if recurrence of hyperprolactinemia is observed.

During Pregnancy

Pregnancy is a risk factor for adenoma enlargement, especially for macroadenomas, and risk is increased for patients without prior surgery.[75] MRI without contrast should be performed if a pregnant patient with prolactinoma develops more severe or headaches with different characteristics or vision changes, typically indicative of adenoma enlargement. As apoplexy during pregnancy has been reported even in microprolactinomas,[76] imaging is required for concerning symptoms.

Novel Imaging Strategies

- There is a limited role for novel imaging strategies in routine clinical practice (strong).
- Response to DA therapy may be predicted by functional imaging (weak).
- Functional imaging applied with hybrid MRI techniques may improve pre-operative prolactinoma localization in selected patients (weak).

In patients undergoing surgery, particularly for a microadenoma when the expectation of surgical cure is high,[8,77] as well as in those undergoing stereotactic radiosurgery, accurate adenoma localization could reduce hypopituitarism risk. Although dynamic and volumetric MRI sequences are useful in identifying a previously non-visible mass, molecular (functional) imaging may guide targeted intervention.[78,79] Molecular ^{11}C-methionine PET imaging holds promise as an adjunct to MRI for localization of *de novo* and residual prolactinomas when MRI is indeterminate.[79,80]

See **Supplementary Box 4** for further discussion.

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COMPLICATIONS

Hypogonadism

- Women with hyperprolactinemia, microprolactinoma, and normal gonadal function can be followed by observation (weak).
- Hypogonadal premenopausal women with microprolactinomas can be managed by adequate sex hormone replacement without need for further intervention except when pregnancy is desired (strong).
- Oral contraceptives may be used in women with hyperprolactinemia treated with DA therapy, but they may reduce efficacy of DA therapy and may contribute to persistence of galactorrhea (weak).
- Postmenopausal women with microprolactinomas, who usually present with mild to moderate prolactin elevation, may not require intervention, and can be observed by annual PRL evaluation (weak).
- Males with ongoing hypogonadism for >3-6 months while being treated for prolactinoma should be considered for testosterone replacement (weak). Caution is needed for large pituitary adenomas. Indication for testosterone replacement should be re-evaluated at 6-month intervals based on PRL levels, as the gonadotrophic axis may recover and ongoing testosterone replacement may no longer be needed (weak).
- Patients with persistent hypogonadotrophic hypogonadism despite DA therapy and normal PRL levels who desire fertility may require gonadotrophin treatment (strong).
- Replacement of estrogen and testosterone (probably via aromatization to estradiol) can reduce DA efficacy. It is important to monitor effects of such treatment on PRL levels (weak).

Most participants agreed that evaluation for restoration of gonadal function should be performed at least 6 months after PRL normalization. Recovery usually occurs in about 60% of male patients[33] but more frequently in females. The presence of complete hypopituitarism reduces the chances of recovery from hypogonadism and may justify earlier hormone supplementation.

After sex hormone replacement is started, PRL levels may increase.[81] Use of a short-acting testosterone formulation, e.g., testosterone gel, is recommended in patients with large adenomas. This also allows for faster reversal of adverse effects of combined DA/testosterone (e.g., irritability, hypersexuality) should they develop. Off-label aromatase inhibitor therapy may be considered,[82] although long-term data are limited and there may be additional adverse effects on bone health.[83] Clomiphene has been used as an off-label treatment in men with hypogonadism.[84]

Testosterone should not be started when fertility planning is contemplated. Induction of spermatogenesis by human chorionic gonadotropin and recombinant FSH may be considered.[85] However, a semen analysis should be performed prior to initiating gonadotrophin treatment, as nearly 50% of men with hypopituitarism treated with testosterone had adequate spermatogenesis for fertility in one series.[86]

See **Supplementary Box 5** for further discussion.

Bone Disease

- Increased fracture risk is recognized as a clinical consequence of prolactinoma (strong).

- Clinicians should initiate morphometric investigation by x-ray in prolactinoma patients with back pain or decrease in height (strong).
- Patients should be evaluated for changes in bone density by dual-energy x-ray absorptiometry (DXA), depending on age, duration of hyperprolactinemia and hypogonadism, and other risk factors (weak).

Baseline DXA is recommended for all prolactinoma patients with suspected long-standing (i.e., >6 months) hypogonadism or with other risk factors for osteoporosis, including menopause and previous vertebral fracture. Osteoporosis, particularly if complicated by fractures, should be treated with anti-osteoporotic drugs according to general guidelines.[87] In this context, control of hyperprolactinemia may potentially play a role as suggested by indirect evidence,[88] but specific studies are needed to assess the risk/benefit ratio.

See **Supplementary Box 5** for further discussion.

TREATMENT

Dopamine Agonists

Efficacy

- DA therapy is highly effective at lowering PRL levels, improving clinical consequences of hyperprolactinemia, and reducing adenoma size (strong).
- Cabergoline is the preferred DA due to its long half-life, high efficacy, and good tolerability (strong). Bromocriptine and quinagolide are less commonly used, depending on regional approval and availability.

- Cabergoline is used as primary medical therapy in patients with prolactinoma (**Figure 3**). For microprolactinomas and well-encased macroprolactinomas (Knosp grade 0 and 1), the curative potential and risks of surgery should be discussed with patients in a multidisciplinary setting prior to medical treatment initiation (strong).
- Patients with Knosp grade ≥2 should be treated with cabergoline (strong).
- Patients with resistance or intolerability to other DA therapy should be switched to cabergoline (strong).
- The need for long-term DA treatment and the limited chances of permanent cure should be highlighted in patient discussions (strong).
- In women not desiring fertility, mechanical contraception is advised when starting DA therapy as pregnancy can occur prior to menses re-initiation (weak).

DA is an effective treatment for PRL-secreting adenomas, resulting in PRL normalization, adenoma mass reduction, and gonadal function restoration.[2] Cabergoline, bromocriptine, and quinagolide control most symptoms,[89] but cabergoline has superior efficacy and is the recommended treatment (see **Supplementary Box 6** for further discussion). High DA efficacy is maintained in patients with giant prolactinomas, with improved visual fields reported in 97% of patients, normalized PRL levels in 60%, and reduced adenoma volume in 74%.[90-92] Frequently employed cabergoline doses range from 0.5 to 3.5 mg/week (maximum FDA approved dose is 2 mg weekly), bromocriptine doses

range from 2.5 to 15 mg/day, and quinagolide doses range from 75 to 300 µg/day.

A study on imaging and PRL level regression during DA treatment[72] revealed that the greatest decreases in adenoma size and PRL levels occurred within 6 months of therapy initiation. Improvement rates diminished considerably during the subsequent 6 months and even further thereafter. Thus, if a prolactinoma does not exhibit a favorable response in the first 3-6 months of treatment, it is not likely to respond adequately to DA therapy. Normoprolactinemia and >25% tumor volume reduction after 3 months of cabergoline predicts long-term response.[93] After 6 months, lower PRL levels predict long-term PRL normalization (≤ULN: 100%, ≤3×ULN: 61%, >3×ULN: 39%) and mass shrinkage on MRI correlates with long-term adenoma shrinkage,[94] but results may depend on dose escalation protocols. Other predictors of long-term (>15 month) DA response include lower pretreatment PRL level and smaller adenoma at diagnosis, as well as normalization of PRL with lower DA dose.[89]

Side Effects

- Frequent, mild side effects of cabergoline include gastrointestinal symptoms, dizziness, and fatigue (strong).
- Side effects usually improve with time, but may be ongoing and disabling in individual patients (strong).
- Quality of life may remain impaired in some patients despite effective treatment (strong).

- Administration before bedtime and/or with food may improve tolerability (weak).
- Starting with low doses and escalating slowly may improve tolerability (weak).
- In patients with ongoing intolerance to cabergoline, other D2-specific dopamine agonists such as quinagolide may be tried with a chance of better tolerance (weak).
- DA therapy can cause neuropsychiatric side effects such as compulsive buying, gambling, aggression, changes in mood, and hypersexuality, particularly in men, which rarely may necessitate discontinuation of DA therapy (strong).
- Patients should be informed about the potential for the rare side effect of cardiac valve changes with long-term and/or high-dose cabergoline treatment (strong). Intervals for screening echocardiography vary in different countries. Baseline and follow-up screening is suggested in patients considered for long-term or high-dose therapy (weak).
- Cerebrospinal fluid (CSF) rhinorrhea may rarely occur in patients with invasive macroadenomas that are reduced in size with DA therapy. If suspected, β2-transferrrin or β-trace protein should be measured in nasal fluid; if confirmed, surgical repair is required (strong).
- DA-induced apoplexy due to extensive shrinkage of a macroadenoma may lead to visual changes. In such cases, surgical repair is likely warranted (strong).

The most frequent side effects of cabergoline are gastric discomfort, nausea, and vomiting, as well as mild dizziness.[95,96] Intensity of these symptoms depends on individual tolerability, but they are generally mild and rarely impair drug adherence. They mostly appear at treatment initiation and can typically be reduced or eliminated by starting treatment at a low dose and escalating slowly. If intolerance to oral cabergoline persists, patients can switch to a different DA such as quinagolide (a more specific D2R agonist), if available; intolerance may also be an indication for reevaluation for other treatments, including surgical resection.[97]

Mood changes or impulse control disorders can occur in patients with no previous psychiatric disorder.[98] Changes in impulsivity are more common in men but occur in both males and females and are not dose related; it may lead to gambling, aggressiveness, compulsive spending of money, depression, or mania.[99] Hypersexuality is more frequent in men with prior PRL-mediated hypogonadism, possibly because of the brisk rebound testosterone surge that occurs with restoration of gonadal function upon starting DA therapy.[98] In general, these effects are reversible when DA is discontinued and often ameliorated with dose reduction. Screening for mood changes and impulse control disorders with the Patient Health Questionnaire-9 and Barratt Impulsiveness Scale is useful.[100] It is important to discuss these symptoms with the patient's partner and family members, as they may "hide" behaviors such as impulsive gambling with ruinous outcomes.

CSF rhinorrhea due to medication-induced adenoma mass shrinkage should be managed surgically.[101] The diagnosis is made by finding elevated nasal fluid levels of β2-transferrrin or β-trace protein. Dose reduction and observation

could be considered if CSF leakage flow is modest. However, operative repair is eventually required in 90% of patients with a CSF leak.[102]

The association between high-dose cabergoline and cardiac valvulopathy is discussed below and in **Supplementary Box 6**.

Considerations. Discussion of valvular disease screening was based on guidelines jointly developed by the British Society of Echocardiography, the British Heart Valve Society, and the Society for Endocrinology.[103] Importantly, they diverge somewhat from previously published recommendations:

- If long-term treatment with high-dose (>2.0 mg/week) cabergoline is anticipated, perform baseline echocardiography to detect any pre-existing valve alterations. Baseline evaluation may be performed before starting cabergoline therapy or during the first few months of treatment.
- Repeat echocardiography every 2-3 years in patients treated with >2.0 mg/week of cabergoline. Most participants believe that annual cardiac examination is unnecessary.
- Perform echocardiography after 5-6 years in patients treated with ≤2.0 mg/week of cabergoline. Some participants believe these repeat examinations are not necessary in patients treated with <1.0 mg/week and who have no clinical signs of valvular dysfunction.
- Detection of a heart murmur should prompt echocardiography

Treatment Withdrawal

- As approximately one fifth of patients may remain in remission after discontinuing cabergoline, patients should be evaluated for favorable

predictors and dose reduction/treatment withdrawal be considered at regular intervals (strong).

- Favorable predictors of successful withdrawal include low maintenance doses of cabergoline, treatment duration >2 years, and significant adenoma size reduction (strong).
- Patients successfully withdrawn from cabergoline should have life-long PRL level evaluations (annually or more frequently if symptoms recur) (strong) and be informed about potential symptoms of recurrence.
- Patients who recur after cabergoline withdrawal can usually be successfully treated with DA rechallenge (strong).
- Patients with long-term normalized PRL levels after cabergoline rechallenge may be re-evaluated for another withdrawal trial (weak).
- As chances of permanent resolution of autonomous lactotroph cell growth increase with menopause or after pregnancy, these patients could undergo a trial of withdrawal (weak).

Because of potential long-term side effects with chronic use of DA, cost of long-term medical treatment, and poor compliance in some patients, withdrawal of therapy may be considered under well-defined conditions in patients with a reasonable chance of persistent remission of hyperprolactinemia (see **Supplementary Box 6**).

However, careful selection of patients is critical (**Supplementary Table 2**). The highest likelihood of persistent remission after withdrawal occurs in patients with a non-invasive and smaller adenoma with a normal PRL concentration and a significant reduction in tumor size after at least two years of low-dose

cabergoline (0.25-0.50 mg/week).[74,104] Although only one-third of treated patients are likely to meet these criteria,[5] in this subgroup, nearly 55% of those with microprolactinoma and 43% with macroprolactinoma will achieve ongoing remission after treatment withdrawal.[17] Thus, in such conditions, and in the absence of visible mass on MRI, patients should be encouraged to withdraw treatment. Alternatively, DA could be tapered by serial dose decreases and increasing the dosing interval until the minimal effective dose required to maintain a normal PRL level is established.[105]

If DA therapy withdrawal is attempted, PRL should be measured every 3 months in the first year and annually thereafter. Pituitary MRI may be repeated when hyperprolactinemia reoccurs. In those who recur after withdrawal requiring treatment reinstatement, a second attempt at cabergoline withdrawal may be successful after 2-3 additional years of therapy, particularly in patients with low PRL levels while on treatment who have no visible mass on pituitary MRI.[106,107]

Studies of DA withdrawal in limited series of menopausal women with prolactinomas showed a favorable outcome, with remission rates higher than those observed in premenopausal women.[108]

Surgery

- Surgical resection of microprolactinomas and well-circumscribed macroprolactinomas (Knosp grade 0 and 1) by an experienced neurosurgeon offers a high chance of cure, is cost-effective, and avoids long-term DA treatment. Surgery by an expert pituitary neurosurgeon

should therefore be discussed alongside DA treatment as a first-line option in this subgroup of patients (strong).

- Medical treatment is the preferred first-line treatment option in patients with a low chance of surgical remission (Knosp grade ≥2) (strong).
- Surgery may be recommended over medical treatment in patients with rapidly progressive vision loss due to sellar mass effect or apoplexy (weak).
- Surgery could also be offered to patients who have intolerance or resistance to long-term DA (weak).
- Younger age in females may favor a choice of surgical treatment to avoid the need for DA therapy over many decades (weak).
- Debulking surgery of a macroprolactinoma is an alternative to DA therapy in patients who desire pregnancy as it reduces the risk of symptomatic mass enlargement during future pregnancy (weak).
- Surgical repair should be performed in cases of spontaneous CSF rhinorrhea (strong).

Indications for Surgery

Transsphenoidal surgery (TSS) performed by experienced neurosurgeons can achieve initial normoprolactinemia in up to 93% of microprolactinomas and 75% of selected macroadenomas[6,8] (**Supplementary Table 3**). It should be recognized, however, that there is about a 20% recurrence rate of hyperprolactinemia following surgical normalization of PRL.[109,110] Improved remission and low complication rates warrant reappraisal of the role of surgery

as a viable alternative to first-line DA treatment of prolactinomas in selected patients.

If they are surgically resected, prolactinomas can be further classified according to their cell lineage and based on the WHO classification[3] requiring assessment of specific pituitary hormones and transcription factors (PIT-1 and ERα for PRL-expressing adenomas). Pure lactotroph adenomas are subtyped as sparsely or densely granulated. These are distinguished from plurihormonal mammosomatotroph adenomas, mature plurihormonal PIT1-lineage adenomas, and mixed somatotroph-lactotroph adenomas, as well as from two precursor entities, acidophil stem cell and immature PIT1-lineage adenomas.[75]

In centers with experienced multidisciplinary teams and expert pituitary surgeons, the possibility of surgical remission versus long-term DA therapy should be discussed with patients with mass morphology favoring surgical success, while also acknowledging patient preference.[111,112] The classical indication of “resistance and intolerance to DA” for surgical treatment of prolactinomas remains valid, and is the prevailing indication for surgery in macroprolactinomas[6] (see **Supplementary Box 6**).

In a recent single-center study, patient preference was the main indication for TSS for microprolactinoma in 42% of patients, followed by intolerance of DA (27%), resistance to DA (20%), and combined intolerance and resistance (12%).[6] In another study, remission rates were 71-93% for microscopic TSS and 81-100% for endoscopic surgery.[112] Perioperative and postoperative complication rates were low, i.e., neurosurgical complications were <2% and mortality 0%.[112]

Preoperative PRL levels correlate negatively with microprolactinoma remission rates,[113] such that a remission rate of 92% was seen with preoperative PRL ≤200 ng/mL versus only 40% with preoperative PRL >200 ng/mL.[8] Furthermore, remission of fully centrally encased small microprolactinomas was 87% versus 45% in those that were lateral and adjacent to the cavernous sinus wall.[114] Early postoperative PRL levels in the low-normal range predicts long-term remission with low recurrence rates. New-onset anterior and posterior pituitary hormone deficiencies are rarely encountered with microprolactinomas resected by experienced neurosurgeons.[6,111,112]

Not surprisingly, surgical remission rates in macroprolactinomas are inferior to remission rates in microprolactinomas[115,116] and decrease significantly with invasiveness, larger adenoma size, and significantly higher pre-operative PRL levels[6,90,111,116-118] such that the surgical remission rate in one study was 70.4% in non-invasive macroprolactinomas versus 23.5% in invasive macroprolactinomas,[6] while a second study limited to females found a surgical remission rate of 95% for enclosed macroprolactinoma and only 25% for invasive macroprolactinomas.[119] Remission is less likely with suprasellar extension[111,116] or with PRL >282 ng/mL (>346 ng/ml, if Knosp grade <3);[118] male sex is also a negative predictor for postoperative remission.[116]

Staging according to the Knosp classification seems to offer a better discrimination for surgical success than does dividing micro- from macroprolactinomas only (**Supplementary Table 3**). Whereas some studies suggest better outcome for Knosp 0-1 compared to Knosp 2-4,[6,120] others suggest higher remission rates for Knosp 0-2 compared to Knosp 3-4.[121,122]

Invasive macroprolactinomas or giant prolactinomas are usually treated with first-line DA therapy,[90] and surgery is reserved for spontaneous or DA-induced CSF rhinorrhea.[90,101,102] However, surgery may be preferred in the context of rapid or progressive vision loss with large prolactinomas, or for those with large cystic or hemorrhagic components to ensure immediate decompression of visual pathways.[123] Furthermore, debulking surgery may be considered for DA-resistant patients to improve the outcome of subsequent medical treatment.[110,124]

Women desiring pregnancy may also prefer immediate surgery, as fertility is usually restored following adenoma resection.[6,117] In those with macroadenomas, pre-pregnancy adenoma debulking may avoid symptoms from enlargement during pregnancy. If TSS is performed prior to pregnancy, the risk of symptomatic macroadenoma enlargement is reduced from 21% to 4.7%.[11]

Preoperative Medical Therapy

Whether to use preoperative medical therapy remains controversial. A recent meta-analysis showed higher remission rates in surgical series with less frequent preoperative DA use (although the difference was insignificant in sensitivity analyses),[116] potentially supporting the use of first-line surgery with no preoperative medical therapy in appropriate patients. Adenoma fibrosis was found in most patients undergoing surgery after preoperative bromocriptine treatment for >1 month, but the effect was much less pronounced for cabergoline.[125]

Radiation Therapy

- Radiation therapy is usually reserved for patients who show poor mass shrinkage in response to DA, and have either nonresectable residual adenoma tissue after surgery or contraindications for surgery (strong).
- Stereotactic radiotherapy techniques yield improved outcomes and have now become standard of care where available (strong).
- Response to radiotherapy may take several years (strong).
- Patients should be informed about potential side effects occurring even many years after treatment, and should be followed life-long to detect hypopituitarism, optic neuropathy, cranial nerve palsy, or second brain tumors (strong).

Radiation therapy is the least used management approach and is mainly offered when medical and surgical treatments have not been successful, usually in patients with size-progressing, aggressive prolactinomas or PRL-secreting malignancies. Expected outcomes are described in **Supplementary Box 6**.

SPECIAL SITUATIONS

Cystic Prolactinomas

- Cystic prolactinomas may respond to DA therapy and should be considered a viable option, particularly in patients without urgent need of optic chiasm decompression (strong).
- The diagnostic evaluation should exclude pituitary cystic lesions with hyperprolactinemia caused by stalk compression unlikely to respond to DA therapy (weak).

- In the absence of visual deficits, an MRI follow-up interval of 6 months is likely appropriate (weak).

The presence of a cystic component is not uncommon in pituitary adenomas, and should be distinguished from predominantly cystic prolactinomas in which more than 50% of the volume is fluid-filled.[126] This distinction also does not include prolactinomas that undergo cystic degeneration as a result of DA therapy.[127] Cystic macroprolactinomas can pose a diagnostic challenge, as PRL levels are lower than in similarly sized solid adenomas (50-150 ng/mL), making it difficult to differentiate between a cystic prolactinoma and a non-functioning cystic lesion causing hyperprolactinemia by stalk compression. The rate at which PRL declines after DA therapy initiation is not always helpful in differentiating the two scenarios.[128] DA therapy demonstrated high efficacy in cyst reduction[129] and should therefore be considered, particularly in patients with no urgent need of chiasmatic decompression.[123] However, it is important to also consider other pituitary cystic lesions with hyperprolactinemia that would not shrink with DA.

Prolactinomas in Men

- Males with hypogonadotrophic hypogonadism presenting with gynecomastia, loss of libido, erectile dysfunction, and infertility or with galactorrhea should be evaluated for hyperprolactinemia and a PRL-secreting adenoma (strong).
- Macroprolactinomas in men are more aggressive and show lower response rates to DA therapy (strong). Multimodal treatment with DA

therapy, surgery, and/or radiation therapy may frequently be required for management, with a need for close follow-up (strong).

- DA side effects of impulse control disorders are more frequently observed in men and an informative discussion with patients and their partners and families is needed pre-treatment (strong).

Prolactinomas in men can be large and invasive, sometimes giant, and present with hypogonadism and mass effects, including vision damage and hypopituitarism.[130] PRL levels are typically high, associated with low testosterone and osteoporosis if left untreated.[131,132]

Diagnosis of hyperprolactinemia is often delayed in elderly men, as decreased libido and erectile dysfunction develop gradually, are not specific, and may be attributed to aging or are underreported.[133]

Prolactinomas are more aggressive in males, with higher Ki-67, cellular atypia, angiogenic and proliferative features, and invasion.[134-137]

Treatment with DA is preferred regardless of size or invasion. Men with macroprolactinomas demonstrate PRL normalization in 80-85% of cases and significant mass shrinkage in 90%.[33] Improvement of visual fields occurs in 85-95% of men harboring macroprolactinomas and vision damage.

Mixed GH-PRL Pituitary Adenomas

- Hyperprolactinemia in patients with pituitary adenomas may occur in combination with excess GH secretion and warrants a different therapeutic approach (strong).

- In patients with acromegaly and hyperprolactinemia, stalk effect should be distinguished from adenoma co-production considering adenoma size and follow-up (strong).
- Pure somatotroph adenomas should be distinguished histologically from mammosomatotroph adenomas (combined secretion of PRL and GH from the same single cell) and somatotroph-lactotroph adenomas (presence of both cell types) (strong; see **Supplementary Box 7**). A correct diagnosis is important, as prognosis differs between these types (weak).
- Aggressive prolactinomas should be evaluated for markers of acidophil stem cell adenomas and co-secretion of GH (weak).
- Patients with hyperprolactinemia should be evaluated at baseline for autonomous GH secretion by screening IGF-1 levels, as clinical features of acromegaly may be masked or occur over time. Demonstration of autonomous GH secretion will alter treatment strategy, which should follow current guidelines on acromegaly (strong).
- If IGF-1 levels increase above ULN during follow-up and there are no vision changes due to adenoma mass, DA therapy should be stopped for 4 weeks to assess for GH hypersecretion (strong).

Giant Prolactinomas

- Giant prolactinomas are rare and are predominantly observed in males; as they usually respond well to DA therapy, they should be managed medically (strong).

- Due to higher morbidity and mortality, surgical resection of these large prolactinomas should be restricted to those with apoplexy or CSF leakage or to patients with progressive mass growth despite optimal treatment (strong).

Giant prolactinomas are defined as those with diameter >40 mm with significant extrasellar extension, very high PRL concentrations, usually >1000 µg/L, and no concomitant GH or ACTH secretion.[91] They have a male-to-female ratio of approximately 9:1. The diagnosis is usually delayed until neurologic complications arise from massive extension into surrounding structures, leading to cranial nerve palsies, hydrocephalus, temporal epilepsy, or exophthalmos. Despite their aggressive appearance, these adenomas are mostly benign and respond well to cabergoline.[18,90-92] Neurologic symptoms improve in most patients with a significant mass size reduction, and PRL normalizes in up to 70% of patients.[91] These lesions are usually not completely resectable.

Aggressive Prolactinomas

- Aggressive prolactinomas are defined as invasive adenomas with an unusually rapid growth rate or adenomas with clinically relevant growth despite maximal tolerated DA doses (strong).
- Increasing PRL levels in a prolactinoma previously well controlled by cabergoline may indicate development of an aggressive adenoma and, very rarely, a carcinoma (weak).
- Rarely encountered patients with prolactinoma complaining of site-specific symptoms, including neurological deficits or back pain, as well as

patients with obvious discordance between PRL levels and pituitary mass, should be evaluated for metastases, which would define a carcinoma (strong).

- Imaging signs of invasiveness coupled with histological markers of proliferation may predict behavior (strong).
- In patients with aggressive prolactinomas and documented persistent adenoma growth despite exhausting all treatment modalities (strong), the chemotherapeutic agent temozolomide (TMZ) is recommended.
- Response to TMZ should be evaluated after 3 months, and treatment continued for at least 6 months in responsive patients (strong), or for as long as responses are observed (weak).
- The use of immune-checkpoint inhibitors could be a viable option after TMZ failure (weak).

Definition

Most patients with PRL-secreting adenomas respond well to DA, showing both PRL normalization and mass shrinkage. However, variable degrees of resistance are encountered, and may indicate specific underlying pathophysiology. The consensus was to define ‘resistance’ as lack of PRL normalization or lack of relevant mass shrinkage of ≥30% reduction in maximum diameter when treated with standard DA doses (7.5-10 mg/day of bromocriptine or 2.0 mg/week of cabergoline) for at least 6 months. Importantly, not all patients with resistance require a change in treatment; DA continuation is a good option, for example, in patients without mass effects, where tumor shrinkage is not required due to location, or in patients with

macroprolactinomas, where the adenoma is controlled, but due to persistent hyperprolactinemia, hypogonadism persists and needs continuous replacement.

If PRL is not controlled even by dose escalation to maximally tolerated doses of DA and surgery is considered for debulking, the term suggested is 'refractory' prolactinoma. Furthermore, refractoriness should be distinguished from 'aggressiveness,' which should be reserved for patients with ongoing adenoma proliferation despite treatment with maximally tolerated doses of DA.

Distant metastases can occur, defining these as carcinomas.[138] Although extremely rare overall, carcinomas of lactotroph origin represent 30% of all pituitary carcinomas and are the most common type.[75,139]

Prognosis

Most studies of prognostic markers focus on predictive markers of DA resistance and do not specifically focus on aggressiveness or malignancy. Male sex, younger age, and invasiveness are associated with higher risk of DA resistance. A combined clinicopathological classification taking into account both invasion (based on MRI, surgical, and histological findings) and proliferation (Ki-67 index ≥3%, mitotic count >2/10 high power fields, and positive p53 staining) may predict potential aggressive behavior of pituitary adenomas.[139]

Treatment

Escalation to maximally tolerated cabergoline dose is the first step for large residual or growing adenomas that do not respond to lower doses; surgical debulking may improve postoperative medical control, and adjuvant

radiotherapy could also be considered.[140] When these therapies fail, the alkylating chemotherapeutic agent TMZ is currently the best option,[141] with approximately 40% of treated pituitary adenomas showing at least partial remission.[13,142] Longer duration of TMZ treatment and its early use, may, in addition to radiation therapy, improve outcomes.[139,142-145] When TMZ treatment fails, immunotherapy with the checkpoint inhibitors ipilimumab and nivolumab also demonstrate responses in PRL-secreting carcinomas.[146-148] Other options that have been studied in patients with aggressive prolactinomas include targeted oncological agents such as everolimus, bevacizumab, and lapatinib,[149,150] as well as the estrogen receptor modulator tamoxifen[151] and peptide receptor radionuclide treatment.[152]

Management is discussed in detail in the current European Society of Endocrinology Clinical Practice Guideline.[141] Patients should be followed in multidisciplinary Pituitary Tumor Centers of Excellence.[153]

Pregnancy and Fertility

- Patients with prolactinoma considering pregnancy should be informed about both medical and surgical options (strong) (**Figure 4**).
- A comprehensive examination performed shortly before pregnancy provides baseline information on PRL level, visual fields, and adenoma size (weak).
- Patients desiring fertility and undergoing pituitary surgery pre-pregnancy should be informed of the potential risk of hypopituitarism and its impact on fertility (strong).

- Mechanical contraception should be used to confirm treatment efficacy prior to pregnancy and establish the menstrual interval (weak).
- To reduce exposure of the developing fetus to DA therapy, DAs should be discontinued as soon as pregnancy is confirmed (strong).
- In patients with large macroprolactinomas, maintenance of DA therapy during pregnancy is also an option (strong).
- Although bromocriptine might reduce fetal exposure due to its shorter half-life, cabergoline is now preferred by the majority of centers relying on increasing safety data (weak).
- In patients with macroprolactinoma, adenoma response to DA therapy should be confirmed prior to conception (strong). In those without mass response, surgery should be considered prior to conception (strong).
- Pregnancy in patients with microprolactinomas is usually uneventful, and patients should be followed clinically every 3 months (strong).
- Patients with macroprolactinomas have a risk of clinically relevant adenoma expansion and apoplexy during pregnancy. Patients should be seen monthly during pregnancy and questioned about local mass effects, and should undergo visual field evaluation every 3 months (strong).
- Patients with suspicion of clinically relevant adenoma growth should undergo MRI without gadolinium (strong).
- DA therapy that was discontinued at conception may be re-initiated in patients with clinically relevant adenoma growth (strong).
- In patients whose enlarged adenomas do not respond to re-initiation of DA therapy, consideration should be given to surgery or delivery if the pregnancy is sufficiently advanced (strong).

- PRL levels should not be used to assess for adenoma growth during pregnancy (strong).
- Breastfeeding is usually not contraindicated and may be allowed for a period depending on whether treatment reintroduction is needed for mass control (strong).

Considerations

Most workshop participants recommend medical treatment with DA as the first choice of therapy for females with prolactinoma desiring pregnancy (see **Supplementary Box 7**). However, surgery for noninvasive microprolactinomas by an experienced pituitary surgeon was also considered reasonable. Risk of postoperative hypopituitarism in microprolactinomas is very low if surgery is performed by an experienced pituitary surgeon.[6,112] By contrast, for patients with macroprolactinoma, most recommend surgery only if the adenoma is not responsive to DAs and/or if it is close to optic structures. In such cases, management by a multidisciplinary team comprising expert neurosurgeons, obstetricians, ophthalmologists, and endocrinologists is recommended.[154] Patients who had prior surgery have very little risk of adenoma growth during pregnancy.[11]

Rather than routinely switching all patients from cabergoline to bromocriptine in women desiring pregnancy, the majority of workshop participants favored using cabergoline at the lowest effective dose, particularly for patients already well controlled on cabergoline, as there were concerns that switching to bromocriptine may result in loss of PRL level control and negatively impact fertility. In addition, the potential for increased side effects after switching to

bromocriptine may impact compliance and the need for dose adjustments, and thereby also adversely affect fertility. Continued use of cabergoline during pregnancy was associated with a higher miscarriage rate in one retrospective study, with little additional data available.[155]

There was strong consensus against recommending measurement of PRL during pregnancy. Rather, evaluation of clinically relevant pituitary mass expansion during pregnancy should be based on symptoms, and imaging should be performed if symptoms or signs of mass effects/adenoma expansion occur.[10]

Prolactinomas in Children and Adolescents

- In addition to the clinical signs and symptoms present in adults, delayed puberty due to hypogonadotrophic hypogonadism should trigger evaluation for hyperprolactinemia in children (weak).
- As apoplexy and aggressive prolactinoma behavior are more common in children than adults, high clinical suspicion warrants prompt investigation (weak).
- Children with macroprolactinomas should undergo genetic testing for *MEN1* and *AIP* mutations (strong).
- DA therapy is initiated at low doses (e.g., 0.25 mg/week of cabergoline) (weak), with slow dose increases due to increased probability of side effects in children (strong).
- Surgery should be considered in cases where vision is threatened, if severe neurological symptoms or CSF leakage is present, or if the mass is resistant to DA therapy (strong).

- Surgery may be considered in children with microprolactinoma to avoid long-term medical treatment (weak).
- Radiation therapy should be limited to patients with aggressive adenomas unresponsive to DA therapy and surgery (weak).

Prolactinoma in a pediatric patient should raise suspicion for the presence of germline *MEN1* and *AIP* mutations.[156] Adenomas with these mutations may have a more aggressive behavior.[157] (See **Supplementary Box 7** for further discussion.)

DA is recommended as first-line therapy, starting at a low dose and individualizing dose adjustments due to the potentially increased susceptibility to side effects in children.[158,159] Surgery should be considered in cases of threatened vision.[160]

Pituitary hemorrhage resulting in apoplexy may be more common within prolactinomas in children. The level of suspicion for potential apoplexy in children with prolactinomas and new headache, visual loss, or other sudden symptoms should be high.[161,162] In microprolactinomas, pediatric surgical series report remission rates around 80%.[163]

Patients with Underlying Psychiatric Disorders

- Management of prolactinoma with underlying psychiatric disorders requires collaboration between the endocrinologist, neurosurgeon, and psychiatrist (strong).
- Initiation of DA treatment in patients with underlying psychiatric illness is likely safe, but requires caution and psychiatric consultation (weak).

- PRL should be measured prior to initiation of an antipsychotic drug (strong).
- PRL levels >10×ULN are uncommon in antipsychotic-mediated hyperprolactinemia and should trigger suspicion for a prolactinoma (strong).
- Dose reduction or switching to a second-generation antipsychotic that does not cause hyperprolactinemia, such as aripiprazole, may distinguish prolactinoma from drug-induced hyperprolactinemia (strong). MRI may exclude a large lesion with stalk effect (weak).
- DA therapy efficacy may be reduced in patients treated with antipsychotics, requiring higher doses (weak).
- PRL-sparing antipsychotics alone or in combination with established antipsychotic therapy, may allow DA dose reduction (weak).
- Alternative treatment modalities for prolactinomas, including sex hormone replacement in microprolactinomas or surgery, may be considered in patients requiring treatment with antipsychotics (weak).

Management of prolactinoma in patients with psychiatric disorders is challenging and requires collaboration between the endocrinologist, neurosurgeon, and psychiatrist.[164] Hyperprolactinemia resulting from antagonism of D2R occurs in 30-75% of individuals receiving antipsychotics[165] within the first 3 months of treatment, and elevations up to 10×ULN have been described.[166]

PRL measurements prior to initiation of an antipsychotic drug may avoid unnecessary investigation and concern for an underlying prolactinoma. MRI

should be performed in patients on antipsychotic drugs with PRL levels >10×ULN, mass effect symptoms such as headache or visual disturbance, or pituitary hormone deficiencies other than the gonadal axis. Antipsychotic dose reduction or switching to a PRL-sparing antipsychotic with subsequent reduction in PRL levels is useful.[166] When withholding antipsychotics, drug-induced hyperprolactinemia resolves in 48-96 hours.

DA therapy may contribute to exacerbation of underlying psychiatric illness, although this appears to be uncommon and is subject to publication bias.[167] DA treatment is effective in patients receiving antipsychotics, with higher DA doses required to achieve biochemical control and reduce adenoma size, although improvement in visual fields occurs in most patients prescribed first-line DA therapy[168] (see **Supplementary Box 7**). Switching to a PRL-sparing antipsychotic such as aripiprazole may enable lower doses of DA therapy, or even cessation, although this is not consistently evident.[168] Addition of aripiprazole to established antipsychotic therapy is utilized for antipsychotic-mediated hyperprolactinemia.[169] Pituitary surgery should be considered if there is concern for DA intolerance or poor effectiveness.

Prolactinomas and Menopause

- Female patients with well-controlled microprolactinoma entering menopause should undergo a trial of DA withdrawal (strong).
- In postmenopausal women with macroprolactinoma, treatment should be targeted to controlling adenoma growth (strong).

- Normalization of PRL levels in postmenopausal women with microprolactinoma is not indicated to improve metabolic parameters, decrease breast cancer risk, or improve bone density (weak).

Menopause is associated with a physiological decrease in PRL levels.[170] PRL normalization occurs in 45% of untreated women with microprolactinoma entering menopause,[171] and PRL levels remained normal in 52-71% of postmenopausal women with prolactinomas, most of which were microadenomas, after withdrawal of DA treatment, irrespective of PRL level prior to treatment discontinuation.[172,173] The prevalence of newly diagnosed post-menopausal prolactinomas cannot be accurately determined as microadenomas or small macroadenomas not causing mass effects may remain unrecognized in the absence of endocrine manifestations. Three series reported on 37 women diagnosed with prolactinomas after menopause,[174-176] the majority of whom harbored macroadenomas (73%) or giant adenomas (18.9%), and many were discovered incidentally following head imaging.[108] PRL normalization and mass shrinkage were achieved with DA therapy in most patients.

Current evidence does not support microprolactinoma treatment in asymptomatic postmenopausal women. Macroprolactinomas should be treated according to standard practice. Breast cancer risk was not increased with prolactinomas.[177,178]

Transgender Individuals

- In transgender women, combined treatment with estradiol and cyproterone acetate may cause mild and asymptomatic hyperprolactinemia (strong).
- A diagnosis of prolactinoma should be considered when PRL increases markedly, or with symptoms of mass effect or galactorrhea (weak).
- There is no evidence for increased incidence of prolactinomas in transgender women receiving gender-affirming therapy (weak).

Hyperprolactinemia related to feminizing hormone treatment occurs in up to 20% of transwomen, and is usually mild and asymptomatic.[179] PRL levels up to 2×ULN were observed following initiation of estradiol combined with cyproterone acetate, but levels remained within the normal range in most patients.[180] Marked or symptomatic PRL elevations resulting in galactorrhea should prompt further investigations.[181,182]

Prolactinomas have been reported in transgender women receiving feminizing hormone treatment[180,182] (see **Supplementary Box 7**). However, there is no definitive link between gender-affirming hormone treatment and prolactinoma.

Hyperprolactinemia and Renal Failure

- Assessment for hyperprolactinemia in patients with chronic kidney disease (CKD) should be individualized depending on symptoms and hypogonadism (weak).

- Treatment of hypogonadism and underlying hyperprolactinemia by DA therapy or sex hormone replacement may be considered with CKD, depending on clinical symptoms (weak).

PRL levels are elevated in patients with CKD. In one study, 23% of CKD patients and creatinine levels <6.8 mg/dL had hyperprolactinemia; the proportion increased to 77% of those with creatinine levels >6.8 mg/dL and 78% of those on hemodialysis.[183] Elevated PRL levels were reported in patients with creatinine levels as low as 2.0 mg/dL.[184] Most of the PRL is monomeric and not due to accumulated macroprolactin.[185] Hyperprolactinemia is caused by delayed circulating PRL clearance as well as increased PRL production.[186] Hyperprolactinemia is not influenced by intensification of dialysis,[187] but is reversed by renal transplantation.

Bromocriptine effectively lowers PRL levels, increases testosterone levels, and restores sexual potency in men with CKD and hyperprolactinemia.[188] Interestingly, treatment of CKD patients on hemodialysis with recombinant erythropoietin may result in PRL normalization.[189]

FUTURE DIRECTIONS

Cabergoline is highly effective at normalizing PRL levels and shrinking prolactinomas in most patients, and DA resistance rarely occurs. Nevertheless, exploration of alternative strategies for medical therapy is warranted, and there is an unmet need for additional treatments to address clinical challenges in treating patients with refractory prolactinomas.

There is a need to facilitate international registries to allow risk stratification and optimization of therapeutic strategies. Standardizing treatment response may enable comparison of results across series, critically important for a rare disease such as prolactinoma.

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COMPETING INTERESTS

The authors declare that they have no competing interests or other interests that might be perceived to influence the interpretation of the article.

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Table 1: Etiology of Hyperprolactinemia.

Physiologic
Pregnancy
Breast/nipple stimulation
Stress
Sleep
Coitus
Exercise
Pathologic
Hypothalamic-Pituitary Stalk Damage
Adenomas
Craniopharyngioma
Rathke's cleft cyst
Suprasellar pituitary mass extension
Meningioma
Dysgerminoma
Hypothalamic/pituitary metastases
Granulomatous disorders
Infiltrations
Pituitary and/or brain irradiation
Intracranial hypotension
Trauma: pituitary stalk section, sellar surgery, severe head injury
Pituitary
Prolactinoma
Acromegaly

Macroadenoma (compressive) Idiopathic Plurihormonal adenoma Lymphocytic hypophysitis Parasellar mass
Systemic Disorders Ectopic PRL secretion Primary hypothyroidism Chronic renal failure Polycystic ovary syndrome Cirrhosis Pseudocyesis Epileptic seizures Malnutrition Anorexia nervosa Chest: neurogenic, chest wall trauma, piercings, surgery, herpes zoster
Genetic Inactivating PRL receptor mutation
Pharmacologic
Dopamine Receptor Blockers Phenothiazines: chlorpromazine, perphenazine Butyrophenones: haloperidol Thioxanthenes Metoclopramide, domperidone, alizapride
Dopamine Synthesis Inhibitors

α-Methyldopa
Catecholamine Depleters
Reserpine
Cholinergic Agonists
Physostigmine
Antihypertensives
Labetalol
Reserpine
Verapamil
H_2 Antihistamines
Cimetidine
Ranitidine
Estrogens
Oral contraceptives*
Anticonvulsants
Phenytoin
Neuroleptics
Chlorpromazine
Risperidone
Promazine
Promethazine
Trifluoperazine
Fluphenazine
Butaperazine
Perphenazine

Thiethylperazine Thioridazine Haloperidol Pimozide Thiothixene Molindone
Opiates and Opiate Antagonists Heroin Methadone Apomorphine Morphine
Antidepressants Tricyclic antidepressants Selective serotonin reuptake inhibitors

*Controversial; see discussion in text.

Modified from Kaiser U, Ho K. Pituitary physiology and diagnostic evaluation. In: Melmed S, Koenig R, Rosen C, Auchus R, Goldfine A, eds. *Williams Textbook of Endocrinology*, 14th ed. Elsevier; 2019.

Figure Legends

Figure 1. Neuroendocrine regulation of PRL secretion.

Dopamine traverses the hypophyseal portal system from the hypothalamus to the anterior pituitary, where it binds the D2R and blocks PRL secretion. Suprasellar and infundibular lesions involving the stalk and pharmacologic agents with antagonist activity at the D2R can result in an increase of PRL secretion. By contrast, hypothalamic TRH and VIP stimulate PRL secretion in the pituitary, as does estrogen. PRL is systemically cleared by the kidney so chronic kidney insufficiency can cause elevated levels.

D2R, dopamine 2 receptor; GH, growth hormone; PRL, prolactin; TRH, thyrotrophin-releasing hormone; VIP, vasoactive intestinal peptide. Modified from Huang W, Molitch ME. Evaluation and management of galactorrhea. *Am Fam Physician*. 2012;85:1073-1080.

Figure 2. Diagnostic algorithm for prolactinoma.

Clinical signs and symptoms of hyperprolactinemia, laboratory findings of hypogonadotrophic hypogonadism or sellar mass on MRI should all trigger evaluation of PRL. If moderately elevated (≤200 ng/mL), diagnoses other than prolactinoma may be more likely and should be considered. Equivocal or questionable results inconsistent with clinical findings should prompt further investigation related to diagnostic procedures. If PRL >200 ng/mL, prolactinoma is more likely. Imaging results inconsistent with clinical findings should prompt investigation for nonpituitary mass and stalk effect, or high-dose hook effect.

MRI, magnetic resonance imaging; PRL, prolactin; ULN, upper limit of normal.

Figure 3. Treatment algorithm for prolactinoma.

Prolactinomas are treated with surgery or DA depending on adenoma size, clinical factors, and patient preference. In microadenomas, patient preference for observation or HRT may also be considered depending on menopausal and gonadal status (dashed line). Follow-up should consider PRL levels, changes on MRI, need for HRT, complications/side effects, and potential for DA withdrawal. Recurrence or lack of remission should prompt DA dose increase or consideration for surgery; intolerability may be addressed by switching to a different DA or surgery. In all of these cases, management at PTCOE is recommended.

DA, dopamine agonist; HRT, hormone replacement therapy; macro, macroadenoma; micro, microadenoma; mo, month; MRI, magnetic resonance imaging; PRL, prolactin; PTCOE, Pituitary Tumors Centers of Excellence.

Figure 4. Prolactinoma management considerations for pregnancy and fertility.

For patients desiring pregnancy, surgery by an experienced surgeon may be considered if cure is likely (dashed line). In patients treated with DA, mechanical contraception should be used until mass shrinkage is observed on MRI. During pregnancy, patients should be closely followed for signs of mass increase; MRI should be used without gadolinium contrast. PRL levels should not be tested. If the mass increases, restart DA if previously discontinued and/or consider surgery in second trimester if absolutely necessary.

DA, dopamine agonist; Gd, gadolinium; MRI, magnetic resonance imaging; PRL, prolactin; ULN, upper limit of normal.

Box 1: Grading of Evidence and Recommendations.

Evidence	• Very low quality (VLQ): expert opinion supported by one or few small uncontrolled studies • Low quality (LQ): supported by large series of small uncontrolled studies • Moderate quality (MQ): supported by one or few large uncontrolled studies or meta-analyses • High quality (HQ): supported by controlled studies or large series of large uncontrolled studies with sufficiently long follow-up
Recommendations	• Weak: based on VLQ or LQ evidence • Strong: based on MQ or HQ evidence

Based on principles for grading of evidence for guidelines (Guyatt GH, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924-926 and Swiglo BA, et al. A case for clarity, consistency, and helpfulness: state-of-the-art clinical practice guidelines in endocrinology using the grading of recommendations, assessment, development, and evaluation system. *J Clin Endocrinol Metab* 2008;93:666-673) as well as on previously published consensus statements from the Pituitary Society (Fleseriu M, et al. Consensus on diagnosis and management of Cushing's disease: a guideline update. *Lancet Diabetes Endocrinol* 2021;9:847-875).