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Consensus statement

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Diagnosis and management of prolactin-secreting pituitary adenomas: a Pituitary Society international Consensus Statement

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Introduction

The Pituitary Society published guidelines on diagnosis and management of prolactin-secreting adenomas (referred to hereafter as prolactinomas) in 2006 (ref. 1) and in conjunction with the Endocrine Society in 2011 (ref. 2).

This updated Consensus Statement considers new evidence that has markedly influenced clinical practice, including long-term adverse effects of dopamine agonist therapy[4], outcomes following dopamine agonist withdrawal[5] and advances in surgical tumour resection[6–9]. In addition, management during pregnancy[10–12], effects of hyperprolactinaemia on bone and fracture risk[13], management of cystic and aggressive prolactinomas[14], and prolactinomas in children and transgender patients are covered.

Background

Epidemiology

- Prolactinomas, which are most commonly benign prolactin secreting adenomas derived from lactotrophs, account for 50% of all pituitary adenomas in both women and men.

- At age 25–44 years, prolactinomas predominantly affect women, with a female to male ratio of 5:1 to 10:1, whereas after menopause the ratio equalizes [18].

- The ratio between macroprolactinomas and microprolactinomas is approximately 1:8 in women and 4:1 in men.

Molecular pathogenetic mechanisms

- Prolactinomas are mostly sporadic monoclonal neoplasms[20,21], implying a somatic genetic event that confers 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 serum levels of prolactin and potentially more aggressive behaviour than prolactinomas without this mutation[22].

- Prolactinomas are very rarely associated with germline mutations and when these are present, onset of disease usually occurs at a younger age than with somatic mutations .

Molecular pathogenetic mechanisms

- Macroprolactinomas in individuals with multiple endocrine neoplasia type 1 (who have germline mutations in MEN1) are more aggressive than in those without these mutations, and prolactinomas with MEN1 mutations could be resistant to therapy[23,24].

- MEN1 germline mutation screening could be considered in patients with a family history of pituitary adenomas and in patients aged <30 years old with macroadenomas (weak).

- Somatic mutation screening should not be routinely performed (strong).

Clinical presentation

Hyperprolactinaemia and hypogonadism

- Increased prolactin secretion during stress, pregnancy and lactation inhibits hypothalamic kisspeptin neuron function, and consequently reduces gonadotrophin-releasing hormone (GnRH) production[26].

- Prolactinoma clinical presentation in part reflects prolactin-induced suppression of the hypothalamic–pituitary–axis that usually reverts after normalization of prolactin serum levels[27], although hypogonadism can persist, especially in men with macroprolactinoma[28,29].

Hyperprolactinaemia and hypogonadism

- Hyperprolactinaemia leads to oligomenorrhoea or amenorrhoea with or without galactorrhoea in women and erectile dysfunction in men, while loss of libido and infertility are observed in both sexes[30].

Hyperprolactinaemia and hypogonadism

Recommendations

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

- Galactorrhoea should trigger investigation for hyperprolactinaemia, except for known physiological reasons (for example, pregnant or lactating women) (strong). Importantly, absence of galactorrhoea does not exclude hyperprolactinaemia (strong).

Hyperprolactinaemia and hypogonadism

Recommendations

- Loss of libido and/or infertility, new-onset menstrual irregularities or amenorrhoea in women, as well as erectile dysfunction and/or hypogonadotrophic hypogonadism in men, should trigger investigation for hyperprolactinaemia (strong).

- Prolactin-secreting adenomas have been associated with increased likelihood of obesity and the metabolic syndrome (weak).

❖ Other pituitary hormone deficiencies before and after treatment

- Macroprolactinomas and, less frequently, microprolactinomas can cause growth hormone (GH), thyroid-stimulating hormone (TSH) and adrenocorticotrophic hormone (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 can resolve hypopituitarism but can also cause new-onset deficiencies. Postoperative retesting is recommended (strong).

❖ Causes of hyperprolactinaemia

Recommendations

- Patients with hyperprolactinaemia but serum levels of prolactin less than five times the upper limit of normal (ULN) should undergo repeat prolactin testing (strong). Cannulated prolactin sampling is recommended if an influence of stress is suspected (strong).

- In general, pituitary adenoma size and serum levels of prolactin correlate; discrepancy should trigger consideration of other possible causes (strong).

- Medication use should be rigorously reviewed to exclude drug induced hyperprolactinaemia (strong).

❖ Causes of hyperprolactinaemia

Recommendations

- Primary hypothyroidism, renal insufficiency and liver failure should be recognized as causes of mild hyperprolactinaemia (strong).

- Pregnancy should not be overlooked as a cause of hyperprolactinaemia (strong).

Causes of hyperprolactinaemia

- The most common pathological cause of hyperprolactinaemia is excess prolactin production by a prolactinoma[21,38]. However, parasellar or intrasellar masses impinging on the pituitary stalk, including non-secreting pituitary adenomas, can compromise dopamine flow and cause hyperprolactinaemia.

- Elevated serum levels of prolactin (up to six times ULN)[39,40] might reflect a hypothalamic–pituitary lesion or evidence of local trauma, surgery, radiation, skull fracture or internal carotid artery aneurysm[41].

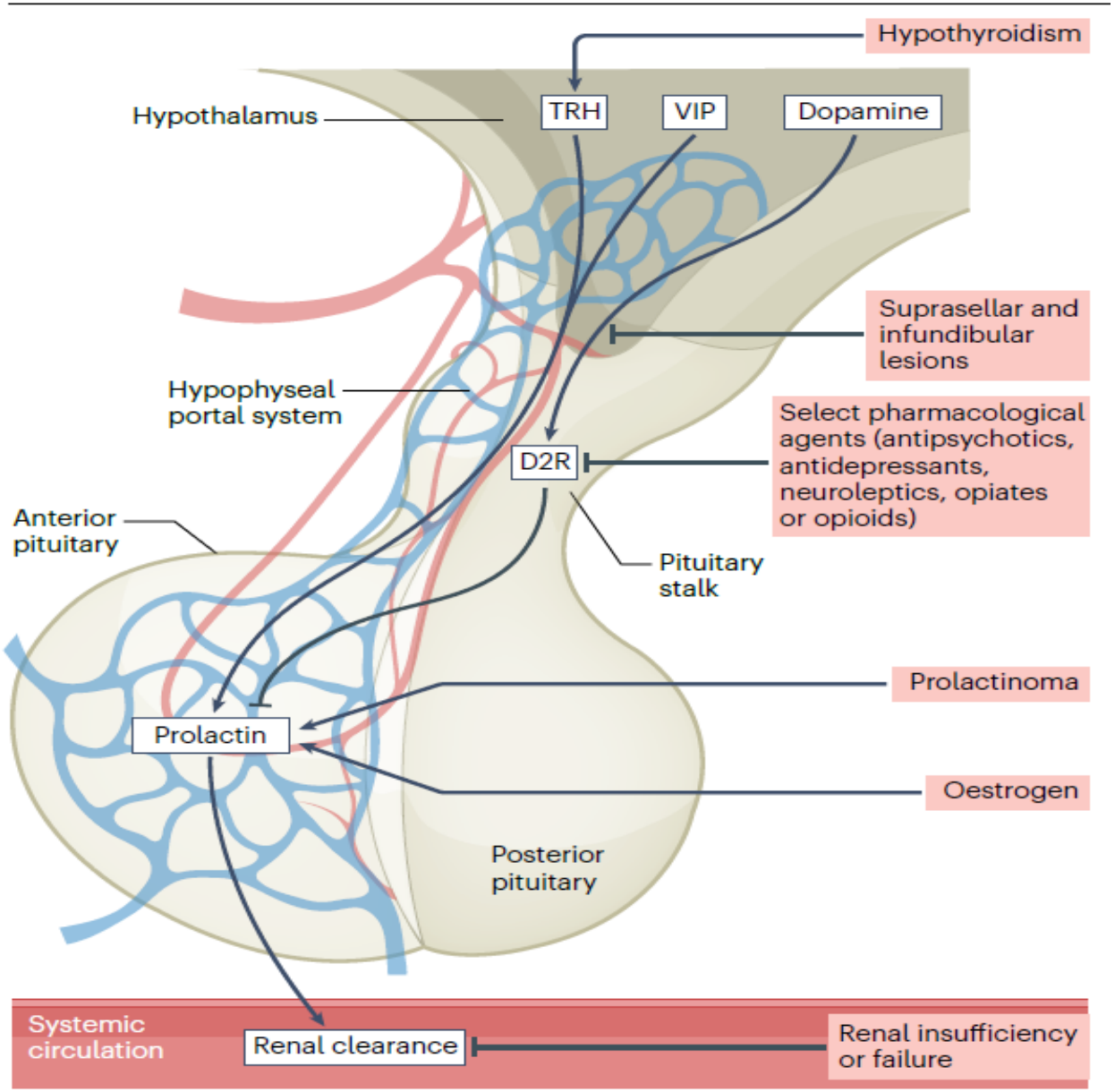
- Oestrogens potently induce hyperprolactinaemia, but the influence of oral contraceptives on prolactinoma development is controversial.

Causes of hyperprolactinaemia

- Physiological prolactin increases can occur after exercise, high-protein meals and alcohol consumption[47,48].
- Patients with polycystic ovary syndrome (PCOS) require further evaluation of elevated serum levels of prolactin, as PCOS per se is rarely associated with hyperprolactinaemia[49].

- High prolactin with lymphocytic hypophysitis could reflect either autoimmune cell actions or a stalk effect[50]

- Prolactin co-secretion with GH in acromegaly or with TSH in thyrotrophinoma is due to either plurihormonal adenoma or a stalk effect[52].


Hypothyroidism
Hypothalamus
TRH
VIP
Dopamine
Suprasellar and infundibular lesions
Hypophyseal portal system
Select pharmacological agents (antipsychotics, antidepressants, neuroleptics, opiates or opioids)
D2R
Anterior pituitary
Pituitary stalk
Prolactinoma
Prolactin
Oestrogen
Posterior pituitary
Systemic circulation
Renal clearance
Renal insufficiency or failure

Box 2

Aetiology of hyperprolactinaemia

Physiological
Pregnancy; breast or nipple stimulation; stress; sleep; coitus; exercise.

Pathological
Hypothalamic–pituitary stalk damage
Adenomas; craniopharyngioma; Rathke's cleft cyst; suprasellar pituitary mass extension; meningioma; dysgerminoma; hypothalamic or 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.

Non-pituitary disorders
Ectopic prolactin secretion; primary hypothyroidism; chronic renal failure; cirrhosis; pseudocyesis; epileptic seizures; malnutrition; anorexia nervosa; chest (neurogenic, chest wall trauma, piercings, surgery, herpes zoster).

Genetic
Inactivating mutation in the gene encoding prolactin receptor (*PRLR*).

Pharmacological
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.

Oestrogens
Oral contraceptives (controversial, see discussion in text).

Anticonvulsants
Phenytoin.

Neuroleptics
Chlorpromazine; risperidone; promazine; promethazine; trifluoperazine; fluphenazine; butaperazine; perphenazine; thiethylperazine; thioridazine; haloperidol; pimozide; thiothixene; molindone.

Opiates and opiate agonists
Heroin; methadone; apomorphine; morphine.

Antidepressants
Tricyclic antidepressants; selective serotonin reuptake inhibitors.

Biochemical evaluation

Recommendations

- In patients with inconsistent symptoms and variable serum levels of prolactin, false-positive or false-negative results should be suspected (strong).

- Serum samples with prolactin levels above the upper detection limit should be diluted to provide an exact value (strong).

- Macroprolactinaemia should be evaluated in patients with moderately increased serum levels of prolactin (<200 ng/ml), at least in those with discordant clinical or imaging findings (strong).

Biochemical evaluation

Recommendations

- With inconsistent symptoms and inconsistent measurement values for prolactin, biotin exposure or heterophilic or human anti-animal antibodies, although rare, should be considered as a cause of erroneous laboratory results (strong).

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

❖ Imaging
MRI

- 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[2,21].

- However, repeat imaging incurs a cost burden and the possible retention of linear gadolinium-based contrast agents has been reported[62,63]; thus, determining the optimal imaging frequency to safely assess treatment response is paramount,but the evidence is sparse.

MRI

- Prolactinomas are typically mildly hyperintense on T2-weighted MRI[68]. Men might exhibit a heterogeneous T2 intensity signal that reflects necrosis and haemorrhage and that might be associated with increased serum levels of prolactin and less effective dopamine agonist response compared with a homogeneous adenoma[69,70]

MRI

Recommendations

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

• Follow-up imaging frequency should be based on clinical, biochemical and histological factors, as well as previous imaging results (strong).

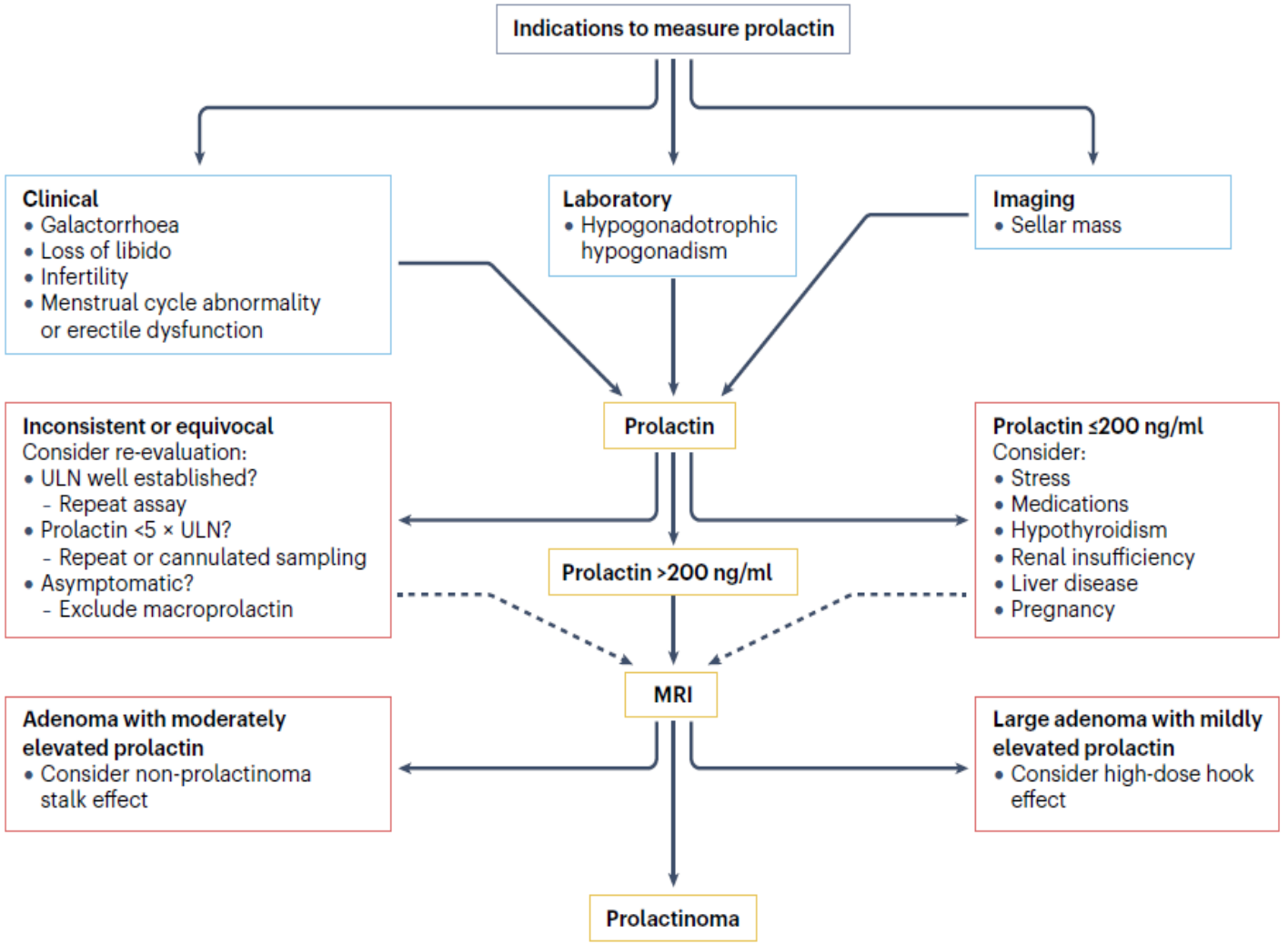
MRI

Recommendations

- Serial imaging should be performed for treatment-resistant prolactinoma; new onset of symptoms, including visual changes, headaches or galactorrhoea; new-onset pituitary dysfunction; and evidence of a new increase in serum levels of prolactin (strong).

- Dynamic gadolinium-based MRI contrast enhancement is important for initial diagnosis of prolactinoma (strong). For follow-up MRIs, gadolinium should be used judiciously; macrocyclic chelates are preferred over linear chelates (strong).

- Gadolinium should be used with caution in patients with chronic kidney disease (CKD) owing to the risk of nephrogenic systemic fibrosis (strong).


Indications to measure prolactin
Clinical
• Galactorrhoea
• Loss of libido
• Infertility
• Menstrual cycle abnormality or erectile dysfunction
Laboratory
• Hypogonadotrophic hypogonadism
Imaging
• Sellar mass
Prolactin
Inconsistent or equivocal
Consider re-evaluation:
• ULN well established?
- Repeat assay
• Prolactin <5 × ULN?
- Repeat or cannulated sampling
• Asymptomatic?
- Exclude macroprolactin
Prolactin ≤200 ng/ml
Consider:
• Stress
• Medications
• Hypothyroidism
• Renal insufficiency
• Liver disease
• Pregnancy
Prolactin >200 ng/ml
MRI
Adenoma with moderately elevated prolactin
• Consider non-prolactinoma stalk effect
Large adenoma with mildly elevated prolactin
• Consider high-dose hook effect
Prolactinoma

❖ Timing after medical therapy.

- For macroprolactinomas, MRI should be repeated at 3–6 months after the start of dopamine agonist treatment,as a reduction in size at 3 months after starting cabergoline could predict further long-term response and/or biochemical control[72]

- For microprolactinomas, re-scanning depends on clinical and biochemical follow-up, but can be repeated after 1 year, or at least when considering withdrawal of dopamine agonists.

- As adenoma growth can occur with biochemically resistant prolactinomas treated with dopamine agonists, follow-up imaging should be considered for persistently elevated or rising serum levels of prolactin.

❖ Timing after medical therapy

- For treatment-responsive microprolactinomas and macroprolactinomas, serial imaging beyond 1 year is not necessary unless serum levels of prolactin persistently increase[65,73].

- However, partially responsive macroprolactinomas or those close to the optic chiasm might require periodic annual imaging for the first 3 years and less frequently thereafter[65].

- MRI should be performed after dopamine agonist withdrawal if serum levels of prolactin 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 might be performed for dopamine agonist-resistant, partially resected adenomas at initial imaging intervals of 6–12 months.
- Completely resected adenomas should be re-imaged only if serum levels of prolactin rise, or if headaches, vision changes or pituitary dysfunction develop[65].
- If surgery is performed as first-line management for microprolactinoma and postoperative normalization of prolactin serum levels is achieved, repeat imaging is required only upon hyperprolactinaemia recurrence.

❖ During pregnancy

- MRI without contrast agent administration should be performed if a pregnant patient with prolactinoma develops headaches of increased severity or different characteristics,or vision changes, typically indicative of adenoma enlargement.

- As apoplexy during pregnancy has been reported even in those with microprolactinoma[78], imaging is required for concerning symptoms.

❖ Complications

Hypogonadism

- Evaluation for restoration of gonadal function should be performed at least 6 months after normalization of prolactin serum levels.

- Recovery usually occurs in about 60% of men[34] but more frequently in women. The presence of complete hypopituitarism reduces the chances of recovery from hypogonadism and could justify earlier hormone supplementation.

- After sex hormone replacement is started, serum levels of prolactin might increase[83]. Use of a short-acting testosterone formulation (for example, testosterone gel) is recommended in patients with a large adenoma, as it leads to rapid reversal of adverse effects of combined dopamine agonists and testosterone (for example, irritability or hypersexuality), should they develop.

Hypogonadism

Recommendations

- Women with hyperprolactinaemia, microprolactinoma and normal gonadal function can be followed by observation (weak).

- Unless pregnancy is desired, management of premenopausal women with microprolactinoma should include the option of adequate sex hormone replacement without other interventions (strong).

- Postmenopausal women with microprolactinoma, who usually present with mild to moderate prolactin elevation, might not require intervention and can be observed by annual prolactin evaluation (weak).

Hypogonadism

- Men with ongoing hypogonadism for more than 6 months while being treated for prolactinoma should be considered for testosterone replacement (weak). Caution is needed for large pituitary adenomas due to the potential for adenoma growth (weak). Indication for testosterone replacement should be re-evaluated at 6-month intervals based on serum levels of prolactin, as the gonadotrophic axis could recover and ongoing testosterone replacement might no longer be needed (weak).

- Patients with persistent hypogonadotrophic hypogonadism despite dopamine agonist therapy and normal serum levels of prolactin who desire fertility require gonadotrophin treatment (strong).

- Replacement of oestrogen and testosterone (probably via aromatization to oestradiol) can reduce dopamine agonist efficacy. It is important to monitor effects of such treatment on serum levels of prolactin (weak).

Bone disease

- Baseline DXA is recommended in all patients with prolactinoma with suspected long-standing (that is, >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[89]

Bone disease

Recommendations

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

- Clinicians should initiate morphometric investigation by plain radiograph in patients with prolactinoma and back pain or decrease in height (strong).

- Patients should be evaluated for changes in bone mineral densityby dual-energy X-ray absorptiometry (DXA), depending on age, duration of hyperprolactinaemia and hypogonadism, and other risk factors (strong).

❖ Treatment

Dopamine agonists

- Dopamine agonists are an effective treatment for prolactinomas, resulting in normalization of prolactin serum levels, adenoma mass reduction and gonadal function restoration[2]
- High dopamine agonist efficacy is maintained in patients with a giantprolactinoma, with improved visual fields reported in 97% of patients, normalized serum levels of prolactin in 60% and reduced adenoma volume in 74%[92–94]
- Frequently employed cabergoline doses range from 0.5 to 3.5 mg per week (maximum FDA approved dose is 2 mg weekly), bromocriptine doses range from 2.5 to 15 mg per day and quinagolide doses range from 75 to 300 μg per day.

Dopamine agonists

- The greatest decreases in adenoma and serum levels of prolactin occurred within 6 months of therapy initiation. Improvement rates diminished considerably during the subsequent 6 months and even further thereafter.

- Normoprolactinaemia and tumour volume reduction of >25% after 3 months of cabergoline predicts long-term response[95]. After 6 months, lower serum levels of prolactin predict long-term normalization of prolactin serum levels.

- Other predictors of long-term (>15 months) dopamine agonist response include low pretreatment prolactin level and small adenoma at diagnosis, as well as normalization of prolactin serum levels with a low dopamine agonist dose (cabergoline, <2 mg per week)[91].

Dopamine agonists

Recommendations

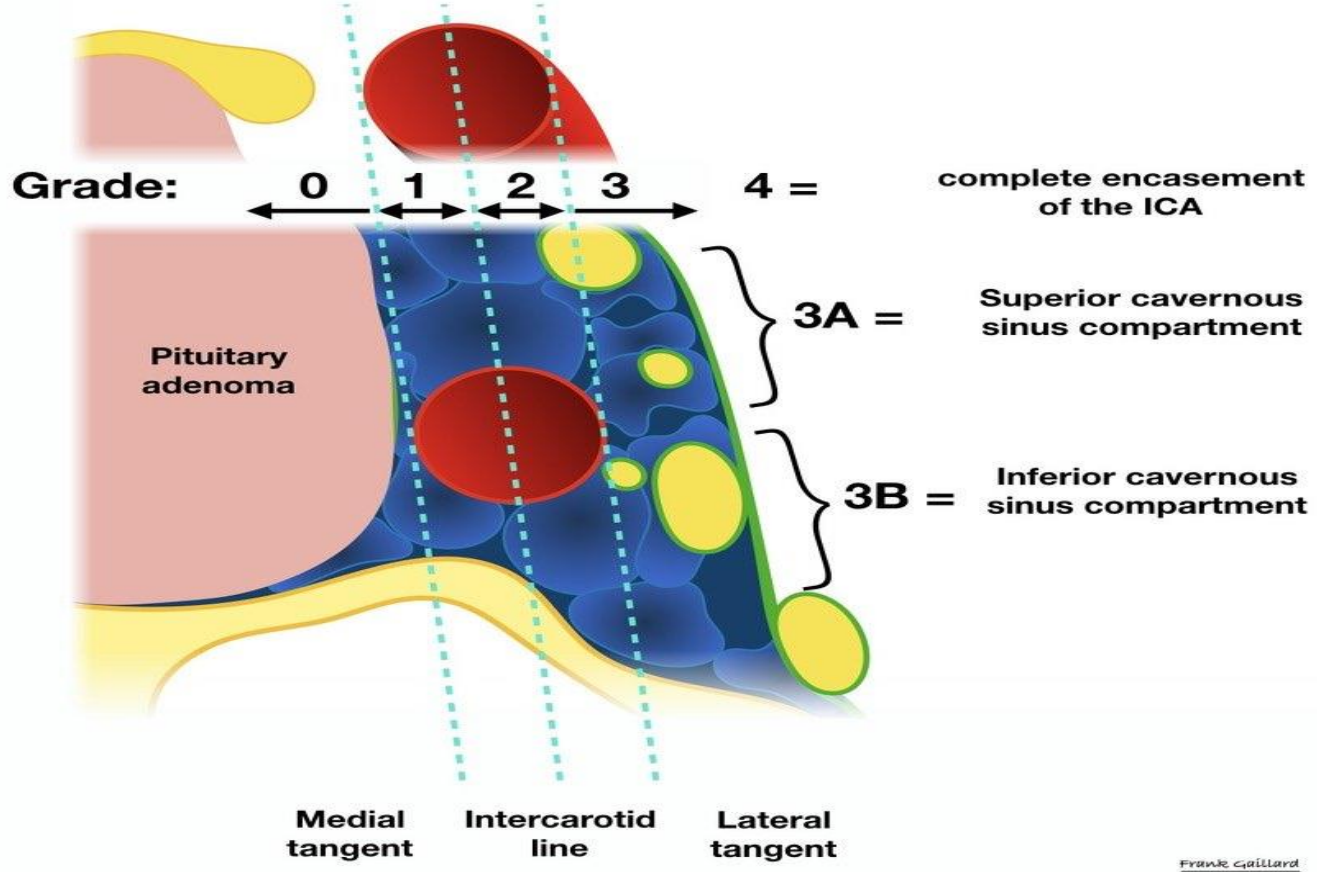
- Cabergoline is the preferred dopamine agonist owing to its long half-life, high efficacy and good tolerability (strong). Bromocriptine and quinagolide are less commonly used, depending on regional approval and availability.

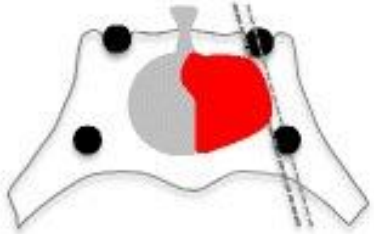
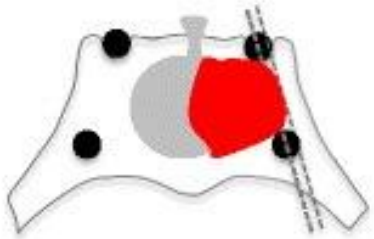
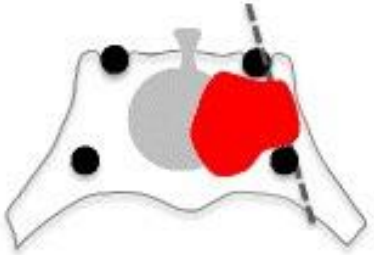
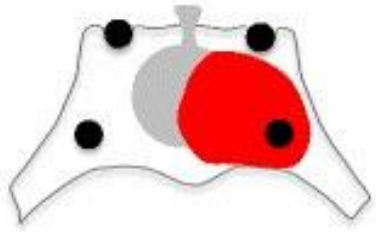
- Cabergoline is used as primary medical therapy in patients with prolactinoma.For microprolactinomas and well-encased macroprolactinomas (Knosp grade 0 and 1), the curative potential and risks of surgery should be discussed with patients in a multidisciplinary setting prior to medical treatment initiation (strong).

Dopamine agonists

- Patients with prolactinoma of Knosp grade ≥2 should be treated with cabergoline (strong).
- Patients with resistance or intolerability to other dopamine agonist therapy should be switched to cabergoline (strong).
- The need for long-term dopamine agonist treatment and the limited chances of permanent cure should be highlighted in patient discussions (strong).
- In women not desiring fertility, mechanical contraception is dvised when starting dopamine agonist therapy as pregnancy can occur prior to menses re-initiation (weak).

Knosp classification



Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
				
Contained within the medial margins of the supra and intracavernous ICA	Extends beyond medial margins but not beyond the midpoint (intercarotid line) of the supra and intracavernous ICA	Extends beyond intercarotid line, but not beyond the lateral margins of the supra and intracavernous ICA	Extends beyond lateral margins of the supra and intracavernous ICA	Total encasement of the intracavernous ICA
			Suggests Cavernous Sinus Invasion	

Dopamine agonists: adverse effects

Recommendations

- Patients should be advised before starting treatment about frequent, mild adverse effects of cabergoline, including gastrointestinal symptoms, dizziness and fatigue (strong).
- Adverse effects usually improve with time, but can be ongoing and disabling in individual patients (strong).
- Quality of life remains impaired in some patients despite effective treatment (strong).
- Administration before bedtime and/or with food might improve tolerability (weak).

Dopamine agonists: adverse effects

Recommendations

- Starting with low doses and escalating slowly might improve tolerability (weak).
- In patients with ongoing intolerance to cabergoline, other D2-specific dopamine agonists, such as quinagolide, could be tried with a chance of improvements intolerance (weak).
- Dopamine agonist therapy can cause neuropsychiatric adverse effects, such as compulsive buying, gambling, aggression, changes in mood and hypersexuality, particularly in men. Although these effects are rarely encountered, if present, dopamine agonist therapy should be discontinued or the dose adjusted (strong).

Dopamine agonists: adverse effects

- Patients should be informed about the potential for the rare adverse 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) rhinorrhoea can rarely occur in patients with an invasive macroprolactinoma that is reduced in size with dopamine agonist therapy. If suspected, β_2-transferrrin or β-trace protein should be measured in nasal fluid; if confirmed, surgical repair is required (strong).

- Dopamine agonist-induced apoplexy due to extensive shrinkage of a macroprolactinoma can lead to visual changes. In such cases, surgical repair is probably warranted (strong).

Dopamine agonists: cardiac valvulopathy

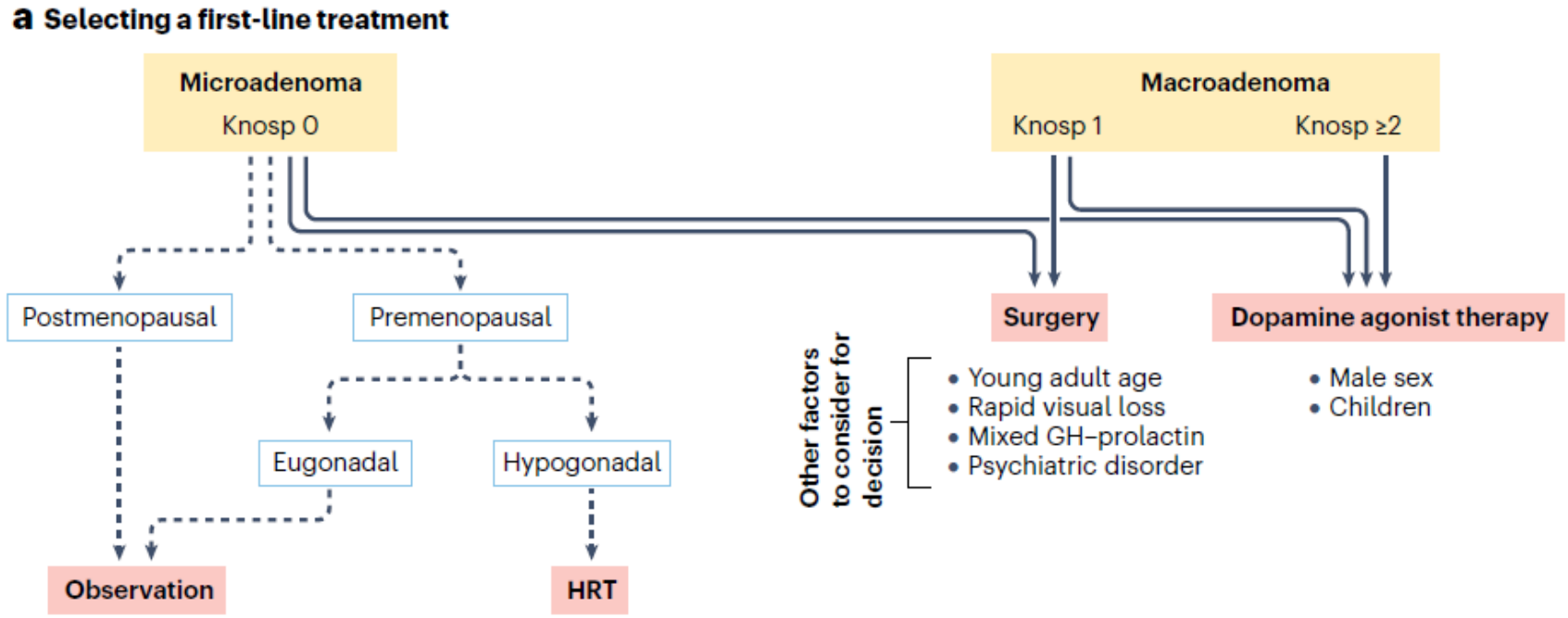
Recommendations

- If long-term treatment with high-dose (>2.0 mg per week) cabergoline is anticipated, perform baseline echocardiography to detect any pre-existing valve alterations. Baseline evaluation can be performed before starting cabergoline therapy or during the first few months of treatment (weak).

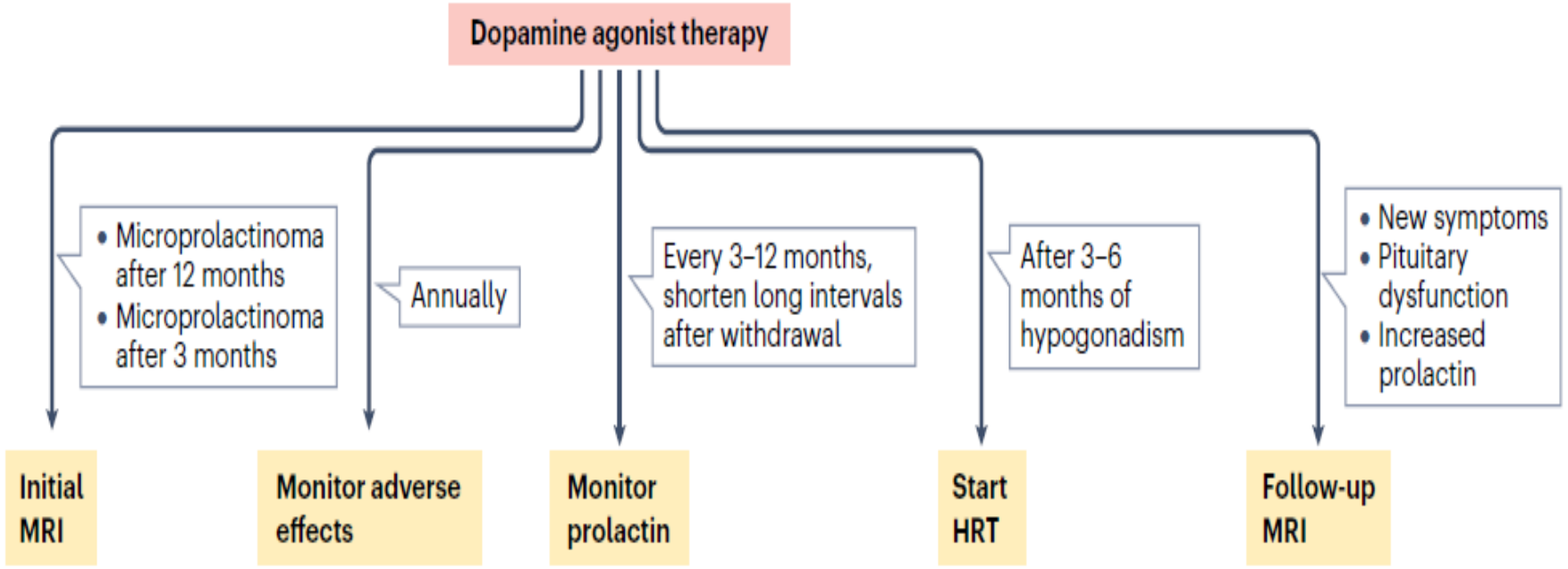
- Repeat echocardiography every 2–3 years in patients treated with >2.0 mg per week of cabergoline (weak). Most workshop participants believed that annual cardiac examination is unnecessary (weak).

Dopamine agonists: cardiac valvulopathy

- Perform echocardiography after 5–6 years in patients treated with ≤2.0 mg per week of cabergoline. Some workshop participants believed that these repeat examinations are not necessary in patients treated with <1.0 mg per week and who have no clinical signs of valvular dysfunction (weak).


a Selecting a first-line treatment
Microadenoma
Knosp 0
Macroadenoma
Knosp 1
Knosp ≥2
Postmenopausal
Premenopausal
Eugonadal
Hypogonadal
Observation
HRT
Surgery
Dopamine agonist therapy
Other factors to consider for decision
• Young adult age
• Rapid visual loss
• Mixed GH–prolactin
• Psychiatric disorder
• Male sex
• Children

Follow-up


Dopamine agonist therapy
• Microprolactinoma after 12 months
• Microprolactinoma after 3 months
Annually
Every 3–12 months, shorten long intervals after withdrawal
After 3–6 months of hypogonadism
• New symptoms
• Pituitary dysfunction
• Increased prolactin
Initial MRI
Monitor adverse effects
Monitor prolactin
Start HRT
Follow-up MRI

Dopamine agonists: treatment withdrawal

Recommendations

- As approximately one-fifth of patients can remain in remission after discontinuing cabergoline, patients should be evaluated for favourable predictors, and dose reduction or treatment withdrawal should be considered at regular intervals (strong). Alternatively, dopamine agonists could be tapered by serial dose decreases and increasing the dosing interval until the minimal effective dose required to maintain a normal serum level of prolactin level is established[107].

- Favourable predictors of successful withdrawal include low maintenance doses of cabergoline, treatment duration >2 years and substantial adenoma size reduction (strong).

Dopamine agonists: treatment withdrawal

- Patients who have recurrence of hyperprolactinaemia after cabergoline withdrawal can usually be successfully treated with dopamine agonist rechallenge (strong).

- The chances of permanent resolution of autonomous lactotroph cell growth increase with menopause or after pregnancy; therefore, these patients could undergo a trial of withdrawal (weak).

Dopamine agonists: treatment withdrawal

- If dopamine agonist therapy withdrawal is attempted, serum levels of prolactin should be measured every 3 months in the first year and annually thereafter.
- Pituitary MRI can be repeated if hyperprolactinaemia reoccurs.
- In those who have recurrence of hyperprolactinaemia after withdrawal that requires treatment reinstatement, a second attempt at cabergoline withdrawal can be successful after an additional 2–3 years of therapy.

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 dopamine agonist treatment. Surgery by an expert pituitary neurosurgeon should therefore be discussed alongside dopamine agonist 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 could be recommended over medical treatment in patients with rapidly progressive vision loss due to a sellar mass effect or apoplexy (weak).

Surgery

- Surgery could be offered to patients who have intolerance or resistance to long-term dopamine agonist therapy (weak).
- Young age in women could favour a choice of surgical treatment to avoid the need for dopamine agonist therapy over many decades (weak).
- Debulking surgery of a macroprolactinoma is an alternative to dopamine agonist 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 case of spontaneous CSF rhinorrhoea (strong).

Remission rate after surgery

Microprolactinoma

- Preoperative serum levels of prolactin correlate negatively with,microprolactinoma remission rates[115], such that a remission rate of 92% was seen with a preoperative prolactin serum level of ≤200 ng/ml versus only 40% with preoperative prolactin serum level of >200 ng/ml[8].

- Furthermore, remission of fully centrally encased small microprolactinomas was 87% versus 45% for those that were lateral and adjacent to the cavernous sinus wall[116].

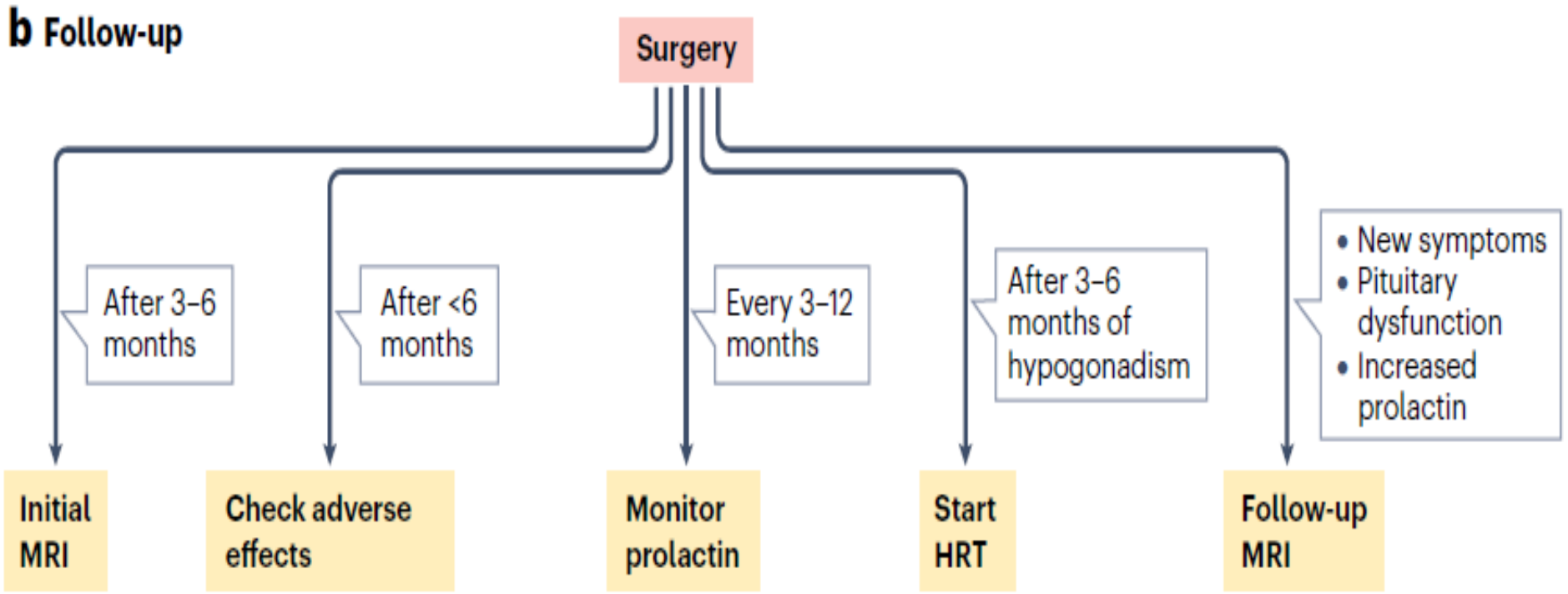
- Early postoperative serum levels of prolactin in the low–normal range predicts long-term remission with low recurrence rates.

Macroprolactinoma

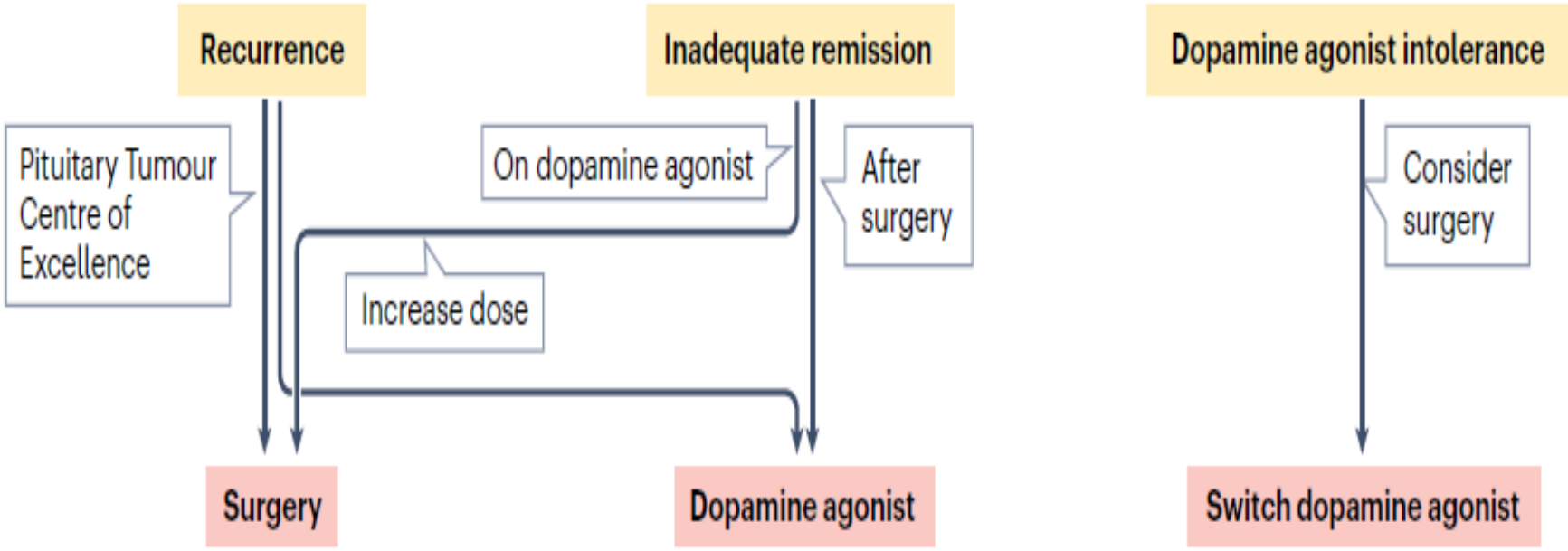
- Not surprisingly, surgical remission rates in patients with macroprolactinoma are inferior to remission rates in those with microprolactinoma[117,118], and decrease considerably with invasiveness, increased adenoma size and notably high preoperative serum levels of prolactin[6,92,113,118–]

- Invasive macroprolactinomas or giant prolactinomas are usually treated with first-line dopamine agonist therapy[92] and surgery is reserved for spontaneous or dopamine agonist-induced CSF rhinorrhoea[92,103,104].

Preoperative medical therapy : 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[127]. These findings potentially support the use of first-line surgery with no preoperative medical therapy in appropriate patients.


b Follow-up
Surgery
After 3–6 months
After <6 months
Every 3–12 months
After 3–6 months of hypogonadism
• New symptoms
• Pituitary dysfunction
• Increased prolactin
Initial MRI
Check adverse effects
Monitor prolactin
Start HRT
Follow-up MRI

C Selecting a second-line therapy



Radiation therapy

- Radiation therapy should be reserved for patients who show poor mass shrinkage in response to dopamine agonists and have either non-resectable residual adenoma tissue after surgery or contraindications for surgery (strong).

- Patients should be advised that response to radiotherapy can take several years (strong).

- Patients should be informed about potential adverse effects occurring even many years after treatment and should be followed lifelong to detect hypopituitarism, optic neuropathy, cranial nerve palsy or second brain tumours (strong).

❖ Special situations

Cystic prolactinomas

- The presence of a cystic component is not uncommon in all pituitary adenomas and should be distinguished from predominantly cystic prolactinomas, in which usually more than 50% of the volume is fluid-filled[128].

- This distinction also does not include prolactinomas that undergo cystic degeneration as a result of dopamine agonist therapy[129].

- Cystic macroprolactinomas can pose a diagnostic challenge, as serum levels of prolactin in cystic prolactinomas (50–150 ng/ml) are lower than in similarly sized solid prolactinomas. This peculiarity makes it difficult to differentiate between a cystic prolactinoma and a non-functioning cystic lesion causing hyperprolactinaemia by stalk compression.

Cystic prolactinomas

Recommendations

- Cystic prolactinomas respond to dopamine agonist therapy, which 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 hyperprolactinaemia caused by stalk compression (strong), which are unlikely to respond to dopamine agonist therapy (weak).

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

Prolactinomas in men

- Prolactinomas in men can be large and invasive, sometimes giant, and present with hypogonadism and mass effects, including vision damage and hypopituitarism[132].

- Serum levels of prolactin are typically high, and are associated with low testosterone and osteoporosis if left untreated[133,134].

- Diagnosis of hyperprolactinaemia is often delayed in older men, as decreased libido and erectile dysfunction develop gradually, are not specific, and might be attributed to ageing or are under-reported[135].

- Prolactinomas are generally more aggressive in men than in women, with higher proliferation (assessed by Ki-67), cellular atypia, angiogenic and proliferative features, and greater invasiveness[136–139].

Prolactinomas in men

Recommendations

- Men with hypogonadotrophic hypogonadism presenting with gynaecomastia, loss of libido, erectile dysfunction and infertility or with galactorrhoea should be evaluated for hyperprolactinaemia and a prolactin-secreting adenoma (strong).

- Macroprolactinomas in men are more aggressive and show lower response rates to dopamine agonist therapy than in women (strong). Multimodal treatment with dopamine agonist therapy ,surgery and/or radiation therapy is frequently required for management, with a need for close follow-up (strong).

- Dopamine agonist adverse effects of impulse control disorders are more frequently observed in men than in women and an informative discussion with patients and their partners and families is needed before initiating treatment (strong).

Mixed GH–prolactin pituitary adenomas

- Hyperprolactinaemia in patients with pituitary adenoma that occurs in combination with excess GH secretion warrants a different therapeutic approach (strong).

- In patients with acromegaly and hyperprolactinaemia, 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 prolactin and GH from the same single cell) and somatotroph– lactotroph adenomas (presence of both cell types) (strong). A correct diagnosis is important, as prognosis differs between these types (weak).

Mixed GH–prolactin pituitary adenomas

- Aggressive prolactinomas should be evaluated for markers of acidophil stem cell adenomas and co-secretion of GH (weak).

- Patients with hyperprolactinaemia should be evaluated at baseline for autonomous GH secretion by screening serum levels of insulin-like growth factor 1 (IGF1), as clinical features of acromegaly could be masked or occur over time. Demonstration of autonomous GH secretion will alter treatment strategy, which should follow current guidelines on acromegaly (strong).

- If IGF1 levels increase above ULN during follow-up and there are no vision changes due to adenoma mass, dopamine agonist therapy should be stopped for 4 weeks to assess for GH hypersecretion (strong).

Giant prolactinomas

Giant prolactinomas are defined as those with a diameter >40 mm with notable extrasellar extension, very high serum levels of prolactin (usually >1,000 µg/l) and no concomitant GH or ACTH secretion[93].

Recommendations

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

- Due to increased risk of 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).

❖ Aggressive prolactinomas and therapy resistance

Definitions

‘**Resistance’** : lack of normalization of prolactin serum levels or lack of relevant mass shrinkage (≥30% reduction in maximum diameter) when treated with standard dopamine agonist doses (7.5–10 mg per day of bromocriptine or 2.0 mg per week of cabergoline) for at least 6 months.

‘**Refractory’ prolactinoma**:If prolactin is not controlled even by dose escalation to maximally doses of dopamine agonists and surgery is considered for debulking, the term suggested is ‘refractory’ prolactinoma.

Aggressive prolactinoma’:patients with ongoing adenoma proliferation despite treatment with maximally tolerated doses of dopamine agonists.

Treatment

- Importantly, not all patients with resistance require a change in treatment; dopamine agonist continuation is a good option, for example, in patients without mass effects, in whom tumour shrinkage is not required due to location, or in patients with macroprolactinomas, in whom the adenoma is controlled, but hypogonadism persists due to persistent hyperprolactinaemia and is managed by sex hormone replacement.

- 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 could improve postoperative medical control, and adjuvant radiotherapy could also be considered[143]

Treatment

- When these therapies fail, the alkylating chemotherapeutic agent temozolomide is currently the best option[144] .Longer duration (>6 months) of temozolomide treatment, its early use and its combination with radiation therapy might improve outcomes[142,145–148].

- In prolactin-secreting carcinomas, immunotherapy with the checkpoint inhibitors ipilimumab and nivolumab induced responses, including mass shrinkage, suggesting that these drugs could be an option if temozolomide fails in aggressive prolactinoma[149–151].

Pregnancy and fertility

Recommendations

- Patients with prolactinoma considering pregnancy should be informed about both medical and surgical options (strong).
- A comprehensive examination performed shortly before pregnancy provides baseline information on serum levels of prolactin, visual fields and adenoma size (weak).
- Patients desiring fertility and undergoing pituitary surgery before pregnancy should be informed of the potential risk of hypopituitarism and its impact on fertility (strong).
- Mechanical contraception should be used instead of hormonal forms of contraception to confirm treatment efficacy before pregnancy and establish the menstrual interval (weak).

Pregnancy and fertility

- To reduce exposure of the developing fetus to dopamine agonist therapy, dopamine agonists should be discontinued as soon as pregnancy is confirmed (strong).

- In patients with large macroprolactinomas, maintenance of dopamine agonist 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 centres owing to increasing safety data (weak).

- In patients with macroprolactinoma, adenoma response to dopamine agonist therapy should be confirmed prior to conception (strong). In those without mass response, surgery should be considered prior to conception (strong).

Pregnancy and fertility

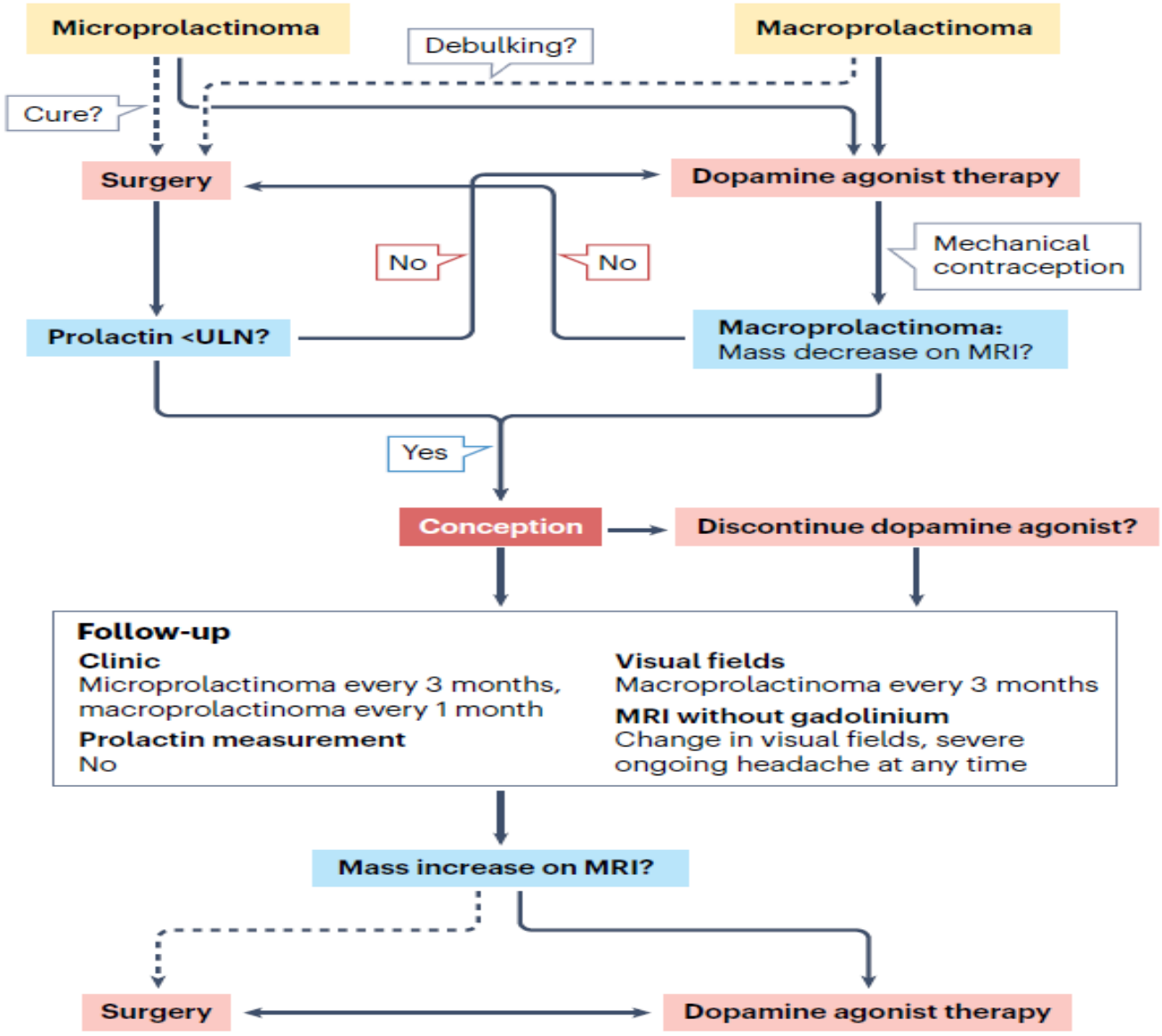
- Pregnancy in patients with microprolactinomas is usually uneventful, and patients should be followed clinically every 3 months (strong).
- Patients with macroprolactinoma have a risk of clinically relevant adenoma expansion and apoplexy during pregnancy. Patients should be seen monthly during pregnancy and questioned about local mass effects, and should undergo visual field evaluation every 3 months (strong).
- Patients with suspicion of clinically relevant adenoma growth during pregnancy should undergo MRI without gadolinium (strong).
- Re-initiation of dopamine agonist therapy that was discontinued at conception should be considered in patients with clinically relevant adenoma growth (strong).

Pregnancy and fertility

- In patients with an enlarged adenoma that does not respond to re-initiation of dopamine agonist therapy, consideration should be given to pituitary surgery or delivery if the pregnancy is sufficiently advanced (strong).

- Serum levels of prolactin should not be used to assess for adenoma growth during pregnancy(strong) .

- Breastfeeding is usually not contraindicated and could be allowed for a period depending on whether treatment reintroduction is needed for mass control (strong).


Microprolactinoma
Debulking?
Macroprolactinoma
Cure?
Surgery
Dopamine agonist therapy
No
No
Mechanical contraception
Prolactin <ULN?
Macroprolactinoma: Mass decrease on MRI?
Yes
Conception
Discontinue dopamine agonist?
Follow-up
Clinic
Microprolactinoma every 3 months, macroprolactinoma every 1 month
Prolactin measurement
No
Visual fields
Macroprolactinoma every 3 months
MRI without gadolinium
Change in visual fields, severe ongoing headache at any time
Mass increase on MRI?
Surgery
Dopamine agonist therapy

Prolactinomas in children and adolescents

- In addition to the clinical signs and symptoms present in adults(that is, secondary amenorrhoea and galactorrhoea), delayed puberty due to hypogonadotrophic hypogonadism should trigger evaluation for hyperprolactinaemia in children (strong).

- As apoplexy and aggressive prolactinoma behaviour are more common in children than in adults, high clinical suspicion warrants prompt investigation (strong).

- Children with macroprolactinoma should undergo genetic testing for *MEN1* and *AIP* germline mutations (strong).

- Dopamine agonist therapy is initiated at low doses (for example, 0.25 mg per week of cabergoline)(weak), with slow dose increases due to increased probability of adverse effects in children (strong).

Prolactinomas in children and adolescents

- Surgery should be considered in patients in whom vision is threatened, if severe neurological symptoms or CSF leakage is present, or if the mass is resistant to dopamine agonist therapy (strong).

- Surgery could be considered in children with macroprolactinoma to avoid long-term medical treatment (weak).

- Radiation therapy should be limited to patients with an aggressive adenoma that is unresponsive to dopamine agonist therapy and surgery (weak).

Patients with an underlying psychiatric disorder

- Management of prolactinoma in patients with an underlying psychiatric disorder requires collaboration between the endocrinologist, neurosurgeon and psychiatrist (strong).
- Initiation of dopamine agonist treatment in patients with an underlying psychiatric illness is probably safe but requires caution and psychiatric consultation (weak).
- Prolactin should be measured prior to initiation of an antipsychotic drug (strong).
- Serum levels of prolactin more than ten times ULN are uncommon in antipsychotic-mediated hyperprolactinaemia and should trigger suspicion for a prolactinoma (strong).

Patients with an underlying psychiatric disorder

- Dose reduction or switching to a second-generation antipsychotic that does not cause hyperprolactinaemia, such as aripiprazole, distinguishes prolactinoma from drug-induced hyperprolactinaemia in most patients (strong). MRI might exclude a large lesion with stalk effect (weak).

MRI indication: 1. patients on antipsychotic drugs with serum levels of prolactin more than ten times ULN,

2. mass effect symptoms such as headache or visual disturbance,

3. pituitary hormone deficiencies other than the gonadal axis.

Patients with an underlying psychiatric disorder

- Dopamine agonist therapy efficacy might be reduced in patients treated with antipsychotics, requiring higher doses (weak).

- Prolactin-sparing antipsychotics alone or in combination with established antipsychotic therapy could enable dopamine agonist dose reduction (weak).

Prolactinomas and menopause

- Menopause is associated with a physiological decrease in circulating levels of prolactin[173]. Normalization of serum prolactin levels occurs in 45% of untreated women with microprolactinoma entering menopause[174]

- Furthermore, serum levels of prolactin remained normal in 52–71% of postmenopausal women with prolactinoma (mostly microadenoma) after withdrawal of dopamine agonist treatment, irrespective of serum levels of prolactin prior to treatment discontinuation[175,176].

Prolactinomas and menopause

- Women with well-controlled microprolactinoma entering menopause should undergo a trial of dopamine agonist withdrawal (strong).
- In postmenopausal women with macroprolactinoma, treatment should be targeted to controlling adenoma growth (strong).
- Normalization of serum levels of prolactin in postmenopausal women with macroprolactinoma is not indicated to improve metabolic parameters or improve bone density (weak).

Transgender individuals

- In transgender women, combined treatment with oestradiol and cyproterone acetate usually causes mild and asymptomatic hyperprolactinaemia (strong).
- A diagnosis of prolactinoma should be considered when prolactin increases markedly or with symptoms of mass effect or galactorrhoea (weak).
- There is no evidence for increased incidence of prolactinomas in transgender women receiving gender-affirming hormone therapy (weak).

Hyperprolactinaemia and renal failure

- Serum levels of prolactin are elevated in patients with CKD. 23% of patients with CKD and serum levels of creatinine <6.8 mg/dl have hyperprolactinaemia; the proportion increased to 77% of those with creatinine levels >6.8 mg/dl and 78% of those on haemodialysis[186]

- Most of the prolactin in these patients is monomeric and not due to accumulated macroprolactin[188]. Hyperprolactinaemia is caused by delayed circulating prolactin clearance as well as increased prolactin production[189]

- Hyperprolactinaemia is not influenced by intensification of dialysis[190], but is reversed by renal transplantation.

Hyperprolactinaemia and renal failure

- Bromocriptine effectively lowers serum levels of prolactin, increases levels of testosterone and restores sexual potency in men with CKD and hyperprolactinaemia[191].

- Interestingly, treatment of patients with CKD on haemodialysis with recombinant erythropoietin could result in normalization of serum prolactin levels[192].

• Assessment for hyperprolactinaemia in patients with CKD should be individualized depending on symptoms and presence of hypogonadism (weak).

THANKS FOR YOUR ATTENTION