REVIEW

Dopamine agonist therapy for prolactinomas: do we need to rethink the place of surgery in prolactinoma management?

Sunita M C De Sousa[1,2,3]

[1]Endocrine & Metabolic Unit, Royal Adelaide Hospital, Adelaide, Australia
[2]South Australian Adult Genetics Unit, Royal Adelaide Hospital, Adelaide, Australia
[3]Adelaide Medical School, University of Adelaide, Adelaide, Australia

Correspondence should be addressed to S M C De Sousa: Sunita.DeSousa@sa.gov.au

Abstract

The current treatment paradigm for prolactinomas involves dopamine agonist (DA) therapy as the first-line treatment, with surgical resection reserved for cases where there is DA failure due to resistance or intolerance. This review highlights how DA therapy can be optimised to overcome its increasingly recognised pitfalls, whilst also addressing the potential for expanding the use of surgery in the management of prolactinomas. The first part of the review discusses the limitations of DA therapy, namely: DA resistance; common DA side effects; and the rare but serious DA-induced risks of cardiac valvulopathy, impulse control disorders, psychosis, CSF rhinorrhoea and tumour fibrosis. The second part of the review explores the role of surgery in prolactinoma management with reference to its current second-line position and recent calls for surgery to be considered as an alternative first-line treatment alongside DA therapy. Randomised trials comparing medical vs surgical therapy for prolactinomas are currently underway. Pending these results, a low surgical threshold approach is herein proposed, whereby DA therapy remains the default treatment for prolactinomas unless there are specific triggers to consider surgery, including concern regarding DA side effects or risks in vulnerable patients, persistent and bothersome DA side effects, emergence of any serious risks of DA therapy, expected need for long-term DA therapy, as well as the traditional indications for surgery. This approach should optimise the use of DA therapy for those who will most benefit from it, whilst instituting surgery early in others in order to minimise the cumulative burden of prolonged DA therapy.

Key Words

- prolactinoma
- dopamine agonists
- surgery
- impulse control disorders
- cardiac valvulopathy

Endocrine Oncology (2022) **2**, R31–R50

Introduction

Prolactinomas are one of the leading presentations in pituitary endocrinology. Prolactinomas are the most common clinically relevant pituitary adenoma, accounting for 57–66% of cases in general practice surveys of patients with symptomatic pituitary adenomas (Daly *et al.* 2006, Fernandez *et al.* 2010). Prolactin-secreting tumours are also the second most common subtype of aggressive pituitary tumour/pituitary carcinoma, accounting for 20% of aggressive pituitary tumours and 38% of pituitary carcinoma (McCormack *et al.* 2018). The 2017 World Health Organization classification of pituitary tumours listed prolactinomas in men as a particular subset of pituitary

https://eo.bioscientifica.com
https://doi.org/10.1530/EO-21-0038

adenoma that is likely to behave aggressively (Lopes 2017). In addition, prolactinomas feature prominently in familial pituitary tumour syndromes. Prolactinomas are the most common pituitary adenoma subtype in individuals with *MEN1* or *SDHx* mutations (Cebrián *et al.* 2003, Papathomas *et al.* 2014, Xekouki *et al.* 2015) and the second most common subtype in individuals with *AIP* mutations (Beckers *et al.* 2013).

Dopamine agonists (DAs) are the current first-line treatment of prolactinomas, with the ability to achieve both prolactin normalisation and tumour shrinkage, even to the extent of complete remission. Bromocriptine has been in use since the 1970s (Wass *et al.* 1979), and cabergoline has been in use since the late 1980s (Melis *et al.* 1989). This differs from other pituitary tumours where the first-line treatment, if required, is surgery.

Despite the clinical significance of prolactinomas, these tumours are relatively understudied in the contemporary pituitary literature. Searching by Medical Subject Headings ('MeSH') terms in PubMed (https://www.ncbi.nlm.nih.gov/pubmed/), the number of publications from 2011 to 2021, inclusive, was 785 for 'prolactinoma' compared to 842 for 'Cushing's disease' and 1606 for 'acromegaly' despite the latter tumours being much less common. The underrepresentation of prolactinomas in recent literature may be explained by the relative success of DAs as a medical treatment that is simple to administer. In the majority of patients, DAs achieve normoprolactinaemia and tumour shrinkage and are well tolerated. However, there remains a subset of patients with failure of DA therapy due to treatment resistance and/or intolerable side effects. Given the paucity of other medical treatment options and the long-term risks of radiotherapy in the relatively young prolactinoma population, surgery is the usual second-line treatment of prolactinomas.

The aims of this review are to outline the limitations of DA therapy and to examine how these limitations can be addressed by optimising medical therapy and, potentially, by expanding the use of surgery in the management of prolactinomas. The review concludes with proposal of a low surgical threshold approach that seeks to optimise the use of DA therapy for those who may most benefit from it, whilst instituting surgery early in other patients to minimise the cumulative burden of prolonged DA therapy. Reference is made to the 2006 Pituitary Society prolactinoma guidelines (Casanueva *et al.* 2006) and the 2011 Endocrine Society Practice hyperprolactinaemia guidelines (Melmed *et al.* 2011), noting the absence of more recent international guidelines on this topic.

Current treatment paradigm

Drawing on the 2006 Pituitary Society guidelines and the 2011 Endocrine Society guidelines, treatment is indicated in all patients with macroprolactinomas (tumour diameter ≥10 mm) as well as select patients with microprolactinomas (<10 mm) causing hypogonadism or bothersome galactorrhoea. The combined oral contraceptive pill may be used in premenopausal women with microprolactinomas and amenorrhoea if fertility is not desired. In all other cases, the first-line treatment of prolactinomas is medical therapy in the form of DAs, with cabergoline showing the greatest efficacy and tolerability. Dose escalation to the maximally tolerated dose is recommended if the initial response to DA therapy is inadequate (Casanueva *et al.* 2006, Melmed *et al.* 2011).

Surgery is reserved as second-line therapy as it has traditionally been associated with lower efficacy, greater risks and higher costs than DA therapy (Yagnik *et al.* 2021). Radiotherapy is regarded as a third-line therapy (Casanueva *et al.* 2006, Melmed *et al.* 2011), being used in <10% of patients following DA failure and surgical treatment (Yagnik *et al.* 2021). Apart from DAs and selective use of the combined oral contraceptive pill, there are currently no other medical treatment options for patients with prolactinomas, with the exception of temozolomide for lactotroph carcinomas that are usually managed by a multimodal approach including medications, surgery and radiotherapy (Melmed *et al.* 2011).

In the event of pregnancy, the decision to continue DA treatment depends on the size of the prolactinoma, with the risk of clinically relevant tumour expansion being 2–3% in microprolactinomas and ~30% in macroprolactinomas (Gillam *et al.* 2006). Tumour growth in the pregnancy setting relates to the stimulatory effect of placental-derived oestrogen on both normal and neoplastic lactotrophs (Gillam *et al.* 2006, Honegger *et al.* 2020). DA therapy can usually be safely ceased in women with microprolactinomas, whereas women with macroprolactinomas may opt for either DA cessation and close clinical monitoring during pregnancy or ongoing DA therapy, particularly if the tumour is near the optic chiasm (Casanueva *et al.* 2006, Melmed *et al.* 2011). Surgery is considered a second-line treatment both prior to conception and in the case of tumour growth during pregnancy (Casanueva *et al.* 2006, Melmed *et al.* 2011, Luger *et al.* 2021).

Withdrawal of DA treatment may be considered in patients with normalisation of serum prolactin and radiological tumour shrinkage. The 2006 Pituitary Society

https://eo.bioscientifica.com
https://doi.org/10.1530/EO-21-0038

guidelines advise waiting until 3 years of DA treatment and marked reduction of tumour volume (Casanueva *et al.* 2006), whilst the 2011 Endocrine Society guidelines advise waiting until 2 years of DA treatment and no visible tumour (Melmed *et al.* 2011). Arguing in favour of waiting until complete tumour resolution, an observational prospective study of 200 hyperprolactinaemic patients by Colao *et al.* found that a persistent tumour remnant at the time of DA withdrawal was significantly associated with the rate of recurrence at 5 years (for macroprolactinomas, 78% vs 33%, $P=0.001$; for microprolactinomas, 42% vs 26%, $P=0.02$) (Colao *et al.* 2003).

Dopamine agonist agents and efficacy

DA therapy is currently the gold-standard first-line treatment for patients with prolactinomas, and it is arguably one of the most effective anti-tumour therapies across medicine. The primary mechanism of action of DAs is stimulation of dopamine type 2 (D2) receptors expressed by normal and neoplastic lactotrophs, leading to inhibition of adenylate cyclase and a subsequent decrease in intracellular cyclic AMP, with downstream reductions in prolactin synthesis and exocytosis, decreased cellular proliferation and increased apoptosis (Cantone *et al.* 2021).

The three DAs used in the contemporary treatment of prolactinomas are cabergoline, bromocriptine and quinagolide. The pharmacological features and relative effects of these three agents are presented in Table 1. The lower D2 receptor selectivity of bromocriptine compared to cabergoline and quinagolide corresponds with increased side effects, such as nausea mediated by the serotonin 5-hydroxytryptamine type 1 (5-HT_1) receptor and postural hypotension mediated by the D1 receptor (Barake *et al.* 2018), and possibly also explains the lower efficacy of bromocriptine (Melmed *et al.* 2011). The derivation of cabergoline and bromocriptine from ergot fungi is noteworthy because of the potential for interaction with serotonin 5-hydroxytrytamine 2B (5-HT_{2B}) receptors and a consequent risk of fibrotic disease (Caputo *et al.* 2015).

Reported success rates of DA therapy vary according to study design and specified endpoints. In general, DA therapy results in prolactin normalisation and tumour shrinkage in the majority of patients, and the biochemical and radiological responses tend to occur in parallel (Gillam *et al.* 2006, Melmed *et al.* 2011). Approximately 60–95% of patients achieve a normal serum prolactin and 50–90% experience tumour shrinkage (Pinzone *et al.* 2000, Gillam *et al.* 2006, Melmed *et al.* 2011). DA response is better with cabergoline compared to bromocriptine (Webster *et al.* 1994), and in microprolactinomas compared to macroprolactinomas (Verhelst *et al.* 1999). However, bromocriptine may rarely induce prolactin normalisation in patients showing resistance to cabergoline (Iyer & Molitch 2011).

Cabergoline is the most commonly used DA in the treatment of prolactinomas, with a typical starting dose of 250–500 µg once or twice weekly and uptitration until normoprolactinaemia is achieved (Casanueva *et al.* 2006). A large retrospective study of 455 patients with pathological hyperprolactinaemia treated with cabergoline demonstrated real-world efficacy rates of 86% for achieving normoprolactinaemia (92% in 244 patients with idiopathic

Table 1 Dopamine agonists used in the contemporary treatment of prolactinomas (Barlier & Jaquet 2006, Gillam *et al.* 2006, Elenkova *et al.* 2012, Primeau *et al.* 2012, Caputo *et al.* 2015, Steeds *et al.* 2019).

	Cabergoline	Bromocriptine	Quinagolide
Derivation	Ergot-derived	Ergot-derived	Non-ergot-derived
D2 receptor selectivity	High	Moderate	High
Agonist activity at 5-HT_{2B} receptors	Full	Partial	Nil
Half-life	65 h	3 h	22 h
Duration of action	7–14 days	8–12 h	24 h
Typical dose frequency	Twice weekly	Twice daily	Daily
Equivalent dosing	0.5 mg twice weekly	2.5 mg twice daily	150 µg daily
Treatment efficacy	+++	+	++
Common side effects	+	++	+
Cardiac valvulopathy	+[a]	–[b]	–
Impulse control disorders	+	+	+
CSF rhinorrhoea	+	+	Uncertain[c]
Tumour fibrosis	+	++	Uncertain[c]

[a]The risk appears very low and only in association with prolonged, high-dose cabergoline use; [b]Clinically relevant valvular regurgitation has not been associated with bromocriptine use for prolactinomas; [c]There are no known reports of quinagolide-induced CSF rhinorrhoea or tumour fibrosis; this may simply reflect less frequent use of this DA agent.

https://eo.bioscientifica.com
https://doi.org/10.1530/EO-21-0038

hyperprolactinaemia or a microprolactinoma, 77% in 181 patients with macroprolactinomas) and 67% for achieving tumour shrinkage (>50% decrease in tumour volume in 31%, 25–50% in 16%, <25% in 21% of 190 prolactinoma patients with available data) (Verhelst *et al.* 1999). Similar results have been demonstrated in other studies (Verhelst *et al.* 1999, Gillam *et al.* 2006).

Pregnancy represents a special case where bromocriptine may be preferred. DAs cross the placenta and whilst both bromocriptine and cabergoline appear safe and effective, there is a greater volume of safety data for bromocriptine (Casanueva *et al.* 2006, Gillam *et al.* 2006, Melmed *et al.* 2011). To date, there have been approximately >6000 cases of bromocriptine exposure and >900 cases of cabergoline exposure in early pregnancy with no increase in the risks of spontaneous abortion, multiple pregnancy or congenital malformations (Honegger *et al.* 2020). By contrast, the limited data regarding quinagolide use in pregnancy suggest increased rates of pregnancy loss and congenital malformations, precluding its use immediately prior to conception and in pregnancy (Webster 1996). There are limited data with respect to prolonged use of bromocriptine and cabergoline during pregnancy, which is reserved for select cases (Honegger *et al.* 2020).

Dopamine agonist resistance

The definition of DA resistance varies between studies. The 2011 Endocrine Society guidelines defines DA resistance as failure to achieve normoprolactinaemia and/or 50% tumour shrinkage (Melmed *et al.* 2011). Failure to restore fertility may also be considered a marker of DA resistance (Melmed *et al.* 2011). Treatment resistance may be partial, with therapeutic responses evident only upon significant DA dose escalation (Melmed *et al.* 2011). Some studies incorporate DA dose. For example, DA resistance may be defined as persistent hyperprolactinaemia despite higher end doses of 15 mg daily of bromocriptine or 1.5 mg weekly of cabergoline (Yagnik *et al.* 2021).

The molecular basis of DA resistance is unclear. It may at least partly relate to attenuation of dopamine-mediated inhibition of lactotroph proliferation and prolactin production. DA resistance in prolactinomas has been associated with reduced D2 receptor density, overall reduction in D2 receptor mRNA production and altered expression of D2 receptor mRNA isoforms with lower expression of the more efficient short isoform (Wu *et al.* 2010). A nonsense *DRD2* variant has been found in tumour DNA from an aggressive prolactinoma with DA resistance (De Sousa *et al.* 2019*b*). However, *DRD2* variants are not a consistent feature of resistant prolactinomas (Wang *et al.* 2014, De Sousa *et al.* 2019*b*).

Overall, combined data show persistent hyperprolactinaemia in 25–50% of bromocriptine-treated patients and 5–18% of cabergoline-treated patients, and <50% tumour shrinkage in 33% of bromocriptine-treated patients and 5–10% of cabergoline-treated patients (Gillam *et al.* 2006). Biochemical and structural responses to DA treatment are usually, but not always, concordant (Molitch 2005, Gillam *et al.* 2006).

A recent retrospective study evaluated predictors of DA resistance amongst 69 patients with prolactinomas that were predominantly treated with cabergoline. DA resistance was found in 11 (16%) patients, defined by persistent hyperprolactinaemia in 5/11 patients, <50% tumour shrinkage in 1/11 and combined biochemical and structural resistance in 5/11. The four strongest predictors of DA resistance were male sex, greater tumour volume, presence of a cystic, haemorrhagic or necrotic component on baseline imaging and longer time to prolactin normalisation. Combination of these predictors into a four-factor model demonstrated 85% accuracy in predicting DA resistance (Vermeulen *et al.* 2020). Another risk factor for DA resistance is tumour invasiveness (Honegger *et al.* 2020). The DA resistance associated with cystic tumours was addressed in the 2006 Pituitary Society guidelines which state that cystic macroprolactinomas '*generally do not shrink in response to dopamine agonist treatment*' (Casanueva *et al.* 2006); however, a more recent study by Faje *et al* found persistent shrinkage in 20/22 cystic prolactinomas, with an impressive median cyst volume reduction of 84% (Faje *et al.* 2016).

DA resistance is typically managed in the first instance by preferential use of cabergoline over other DAs (Melmed *et al.* 2011) and dose escalation, provided there are no intolerable side effects (Casanueva *et al.* 2006, Melmed *et al.* 2011). In a prospective study of 150 patients with prolactinomas, the rate of prolactin normalisation by 12 months according to weekly cabergoline dose was 84% at 3 mg, 92% at 6 mg and 97% at 9 mg, illustrating the efficacy of dose escalation (Ono *et al.* 2008). Notably, the association between DA resistance and prolactinoma size (Vermeulen *et al.* 2020) and the lower success of DA withdrawal in macroprolactinomas (Colao *et al.* 2003, Dekkers *et al.* 2010, Zamanipoor Najafabadi *et al.* 2020) suggests that the patients requiring high-dose therapy are those that are likely to need DAs over the long term. The possibility of needing prolonged high-dose DA treatment should be considered against the potential

https://eo.bioscientifica.com
https://doi.org/10.1530/EO-21-0038

risk of DA-induced cardiac valvulopathy, which appears to be a function of lifetime cabergoline exposure (Caputo *et al.* 2015).

Side effects of dopamine agonist therapy

Common DA side effects include gastrointestinal symptoms such as nausea, vomiting, abdominal discomfort and constipation; symptoms relating to vasodilatation including postural hypotension, headache, nasal congestion and flushing; and neurological effects such as mood changes, sleep disturbance and fatigue (Gillam *et al.* 2006, Zamanipoor Najafabadi *et al.* 2020). The latter symptoms highlight that these agents cross the blood–brain barrier (Athanasoulia *et al.* 2012), which is of relevance to the neuropsychological risks discussed in the following section. A less common side effect at the DA doses typically used in treating prolactinoma is digital vasospasm, resulting in painless blanching of the extremities following cold exposure (Gillam *et al.* 2006).

Precise frequencies of the common side effects of DA therapy vary between side effects and between studies (Zamanipoor Najafabadi *et al.* 2020). In a randomised double-blind study of bromocriptine vs cabergoline in women with hyperprolactinaemic amenorrhoea, adverse events of any type were experienced in 78% of women taking bromocriptine vs 68% of women taking cabergoline ($P=0.03$), with the most frequent symptoms being nausea, headache, dizziness or vertigo, abdominal pain, weakness, fatigue and constipation. Whilst the majority of patients experienced side effects, these side effects typically abated with ongoing use and cessation of therapy was required only in a small minority (12% with bromocriptine, 3% with cabergoline) (Webster *et al.* 1994). In another study of patients with macroprolactinoma, 42% of patients experienced DA side effects and 18% of all patients ultimately ceased treatment due to these side effects (Kars *et al.* 2009). The high burden of DA side effects may contribute to the reduced quality of life observed amongst patients with prolactinomas, although there are conflicting data as to whether DA use exerts an independent effect on quality of life (Andela *et al.* 2015).

Simple strategies for minimising the common side effects associated with DA use include using cabergoline in preference to bromocriptine and quinagolide, starting treatment at a low dose and only slowly escalating therapy as required, taking DA tablets with food or before bed and splitting or reducing the DA dose if side effects develop (Gillam *et al.* 2006).

Risks of dopamine agonist therapy

As highlighted in the existing international guidelines, DA use poses rare risks of valvulopathy (Melmed *et al.* 2011) and psychosis (Casanueva *et al.* 2006, Melmed *et al.* 2011). Since the publication of these guidelines, there has also been increasing recognition of the risk of DA-induced impulse control disorders (ICDs). CSF rhinorrhoea and tumour fibrosis are also rare, potentially serious risks of DA use.

Cardiac valvulopathy

DA-induced cardiac valvulopathy by its strictest definition refers to the echocardiographic triad of valve leaflet thickening, restricted valve leaflet movement and at least moderate valvular regurgitation (Caputo *et al.* 2015). The underlying pathogenesis appears to be DA activation of 5-HT_{2B} receptors, leading to cardiac fibroblast mitogenesis and subsequent valvular fibroplasia that echocardiographically and histopathologically mimics carcinoid heart disease (Schade *et al.* 2007, Stiles *et al.* 2018). In the Parkinson's disease setting, DA-induced valvulopathy has been definitively demonstrated in association with pergolide and cabergoline, where there is an unequivocal dose-dependent risk. By contrast, there has been no clear relationship with bromocriptine and lisuride, likely reflecting their antagonistic effect at the 5-HT_{2B} receptor despite also being ergot-derived (Schade *et al.* 2007). Valvulopathy has not been associated with non-ergot-derived DAs such as pramipexole, ropinirole and quinagolide (Barlier & Jaquet 2006, Schade *et al.* 2007).

There has been a large body of research into whether or not cabergoline use for hyperprolactinaemia is associated with valvulopathy. The evidence underlying the potential association in hyperprolactinaemia was recently and comprehensively reviewed by Steeds *et al.* in a UK joint position statement of the British Society of Echocardiography, the British Heart Valve Society and the Society for Endocrinology (Steeds *et al.* 2019). There have been numerous monocentric, cross-sectional, case–control studies showing either no changes or only mild valvular alterations (Steeds *et al.* 2019), apart from a prominent cross-sectional study by Colao *et al.* that showed an increased risk of moderate tricuspid regurgitation (Colao *et al.* 2008). Longitudinal studies with a median follow-up of up to 10 years have found no association between cabergoline use for hyperprolactinaemia and valvular dysfunction (Steeds *et al.* 2019). Meta-analyses have suggested a possible increased risk of mild to moderate tricuspid regurgitation

https://eo.bioscientifica.com
https://doi.org/10.1530/EO-21-0038

in the hyperprolactinaemia setting; however, these meta-analyses have all been influenced by the cross-sectional study by Colao *et al.* without replication since (Steeds *et al.* 2019). By contrast, bromocriptine use in patients with hyperprolactinaemia has not been associated with clinically relevant valvular regurgitation (Steeds *et al.* 2019).

The cross-sectional study by Colao *et al.* observed moderate tricuspid regurgitation in 27/50 (54%) treated patients, representing a threefold higher risk compared to 50 matched controls, but no patients had symptoms or the characteristic valve thickening or restriction associated with 5-HT_{2B} receptor activation. Cumulative cabergoline doses above the median of 280 mg produced a twofold higher risk of moderate tricuspid regurgitation compared to lower doses. Other valvular dysfunction was similar between study arms (Colao *et al.* 2008). A subsequent prospective study of 40 newly diagnosed prolactinoma patients at the same centre found no statistically significant increases in any form of valvular regurgitation when comparing echocardiography at baseline and after 2 and 5 years of continuous cabergoline treatment. The echocardiography protocol in the latter study was rigorous, being conducted by two blinded experts, and the extent of tricuspid regurgitation was graded according to American Society of Echocardiography recommendations (Auriemma *et al.* 2013). However, compared to the original study by Colao *et al.*, the prospective study was shorter (60 months vs median 74 months follow-up) and patients had lower cumulative cabergoline doses (median 149 vs 280 mg) (Colao *et al.* 2008, Auriemma *et al.* 2013).

In the latest meta-analysis on the topic, Stiles *et al.* found increased tricuspid regurgitation in cabergoline-treated patients compared to healthy controls, without increases in other valvulopathy. The authors noted a number of caveats: no patients with tricuspid regurgitation presented with cardiac symptoms; the association with tricuspid regurgitation was independent of cabergoline duration and cumulative dose; and there were insufficient data to perform a meta-analysis on tricuspid valve morphology and mobility. Additionally, when looking at only clinically relevant (i.e., moderate or severe) tricuspid regurgitation in patients treated for ≥12 months, only three studies were eligible for meta-analysis, and the authors conceded skewing of the results by the study by Colao *et al.* which involved non-standard measurement of tricuspid regurgitation (Stiles *et al.* 2018). There was no statistically significant difference in clinically relevant tricuspid regurgitation in the other two studies in this meta-analysis, although mean cumulative cabergoline doses were lower in these studies – 282 mg (Vallette *et al.* 2009) and 363 mg (Kars *et al.* 2008) – compared to the study by Colao *et al.* with a mean cumulative cabergoline dose of 414 mg (Colao *et al.* 2008). Supporting a relationship between cabergoline use and tricuspid dysfunction, mild tricuspid regurgitation was found to be higher in patients treated for ≥12 months based on meta-analysis of seven studies (Stiles *et al.* 2018).

When defining cabergoline-induced valvulopathy by its full echocardiographic triad, the risk appears to be exceedingly low. Caputo *et al.* analysed 1811 prolactinoma patients derived from a local prospective study of 40 patients and a systematic review of 21 studies, finding cabergoline-induced valvulopathy in only 2/1811 (0.1%) treated patients who had cumulative cabergoline doses of 252 mg and 5252 mg (Caputo *et al.* 2015). A more recent population-based cohort study found no increase in the risk of heart failure or valve surgery in patients with prolactinomas treated with cabergoline compared to matched controls (Stiles *et al.* 2021).

It is unclear whether the study by Colao *et al.* overestimated the risk of tricuspid regurgitation because of its echocardiographic protocol or other studies have underestimated the risk by involving patients with inadequate treatment durations or cumulative cabergoline doses for the risk to materialise. It is also unclear whether valvular changes without the full echocardiographic triad represent early markers of DA-induced valvulopathy or are unrelated to cabergoline given the pathogenesis is considered to be valvular fibroplasia. Overall, with the majority of studies finding no relationship between cabergoline use for prolactinomas and development of valvulopathy, the risk is most likely small and only applicable to patients receiving cumulative doses surpassing what has been typically studied in the prolactinoma setting. Endocrinologists should be cognisant of the potential for valvulopathy with prolonged, high-dose cabergoline therapy based on biological plausibility of the risk, the consistent evidence of cumulative dose-dependent cabergoline-induced valvulopathy in the Parkinson's disease setting, and meta-analyses in the hyperprolactinaemia setting suggesting a possible increased risk of mild to moderate tricuspid regurgitation (Steeds *et al.* 2019). The question of cabergoline-induced valvulopathy should at least be addressed with patients anticipated to have prolonged, high-dose treatment courses. The potential risk of valvulopathy also underscores the importance of attempting DA withdrawal, where appropriate, to avoid unnecessarily high cumulative doses of cabergoline.

In regards to monitoring, the 2011 Endocrine Society guidelines advise that echocardiography may be

https://eo.bioscientifica.com
https://doi.org/10.1530/EO-21-0038

necessary to identify valvular abnormalities in patients exposed to prolonged, high-dose cabergoline, although a precise threshold was not provided (Melmed *et al.* 2011). Caputo *et al.* subsequently advised annual cardiovascular examination in all patients taking cabergoline, with the indications for echocardiography being restricted to cabergoline use at an equivalent dose of 3 mg weekly for 5 years (equating to a cumulative dose of 720 mg, drawing on the Parkinson's disease literature), development of a new murmur or DA treatment beyond age 50 years (Caputo *et al.* 2015). By contrast, the UK joint position statement recommended baseline echocardiography in all patients before DA commencement, and 5-yearly follow-up echocardiography if the cabergoline dose is ≤2 mg weekly or annual echocardiography if >2 mg weekly (Steeds *et al.* 2019). In the absence of prospective validation of these screening protocols, and given that the risk of cabergoline-induced valvulopathy appears very small in the hyperprolactinaemia setting, a reasonable approach is to obtain baseline echocardiography in patients anticipated to later meet the echocardiography criteria outlined by Caputo *et al.* – for example, patients with giant prolactinomas – and then maintain annual cardiovascular examinations in all cabergoline-treated patients and a low index of suspicion in patients with cardiac symptoms. Any valvular changes detected on echocardiography should be interpreted in the context of previous echocardiograms (especially prior to cabergoline use if available), the degree of cabergoline exposure and other risk factors for valvulopathy. Experienced echocardiographers should be involved wherever possible given the complexity of the diagnosis, the tendency to overestimate valvular changes and the ramifications for prolactinoma management. In consultation with a multidisciplinary team, patients with suspected cabergoline-induced valvulopathy should be counselled about their management options, including switching to bromocriptine or pituitary surgery (Steeds *et al.* 2019).

The risk of other fibrotic disease in treated prolactinoma patients appears to be low, with isolated reports of retroperitoneal fibrosis after use of cabergoline (Jarzynska *et al.* 2019) or bromocriptine (Herzog *et al.* 1989).

Psychosis

DA-induced psychosis is a long-known treatment risk. A cohort study of 600 patients treated with DA agents for prolactinoma or acromegaly observed psychosis in 8 (1.3%) patients. The risk was irrespective of tumour type and despite the absence of a personal or family history of mental illness. Doses as low as 7.5 mg daily of bromocriptine were causative, although there was evidence of intraindividual dose effects. Psychosis resolved in each case after DA cessation or reduction, and the three patients who resumed DA therapy experienced relapses (Turner *et al.* 1984). In further support of DAs as the cause of psychosis rather than the underlying pituitary disorder, psychosis has been induced in the setting of DA therapy for other indications, including Parkinson's disease and the treatment of antipsychotic-induced galactorrhoea (Boyd 1995). DA-induced psychosis has also been described in the puerperium when used to terminate lactation (Boyd 1995, Snellen *et al.* 2016). DAs may be a trigger for psychosis in susceptible individuals as dopamine is an established central mediator of psychosis, and most contemporary antipsychotics act via dopamine antagonism (Boyd 1995, Snellen *et al.* 2016). On the other hand, there are prospective studies that have shown no worsening of psychiatric symptoms in patients with antipsychotic-induced hyperprolactinaemia treated with bromocriptine (Beumont *et al.* 1975, Perovich *et al.* 1989, Lee *et al.* 2010) or cabergoline (Cavallaro *et al.* 2004).

Psychosis represents the extreme end of the psychological risks posed by DA therapy. Data are conflicting as to whether DAs cause milder psychiatric conditions such as depression and anxiety, with some studies showing no effect (Rocco *et al.* 1993, Korali *et al.* 2003) and others showing higher scores for depression and anxiety compared to controls (De Sousa *et al.* 2019*a*).

It is prudent to warn patients of the risk of mild and more serious psychiatric effects from DA therapy and to be cognisant of this risk during clinical follow-up. DA therapy should be ceased immediately if psychosis develops given that prolactinomas are rarely life-threatening and alternative treatment exists in the form of surgery, if required.

Impulse control disorders

A recently recognised risk of DA therapy is the development of ICDs. The defining feature of ICDs is the failure to resist impulses to engage in a pleasurable activity that is harmful to self or others (American Psychiatric Association 2000). Specific DA-induced ICDs include pathological gambling, hypersexuality, compulsive buying, compulsive eating, and compulsive behaviours related to medication use, punding (preoccupation with meaningless motor activities, e.g. cleaning, arranging objects), hobbyism (preoccupation with a specific activity, e.g. writing, repairing machinery) or walkabout (excessive wandering by car or foot without

https://eo.bioscientifica.com
https://doi.org/10.1530/EO-21-0038

purpose) (Weintraub *et al.* 2009). DA-induced ICDs are thought to be mediated by stimulation of reward pathways in the mesolimbic system which bears dopamine receptors, particularly the D3 subtype (Ioachimescu *et al.* 2019).

ICDs were once considered to be rare in the setting of hyperprolactinaemia, likely explaining omission of this risk in previous guidelines (Casanueva *et al.* 2006, Melmed *et al.* 2011). In an FDA study of drug-induced ICD reports from 2002 to 2012, only 3.5% of ICD cases occurred in hyperprolactinaemic patients, compared to 61.7% and 23.8% of cases occurring in the setting of Parkinson's disease and restless legs syndrome, respectively (Moore *et al.* 2014). The apparent rarity of ICDs in hyperprolactinaemia has previously been attributed to the use of less D3-selective agents and DA doses that are 5–10 times lower compared to the Parkinson's disease setting (Bancos *et al.* 2014).

Recent studies of select hyperprolactinaemic patient samples have since shown ICD prevalence to be 8–25% in DA-treated patients (Martinkova *et al.* 2011, Bancos *et al.* 2014, Celik *et al.* 2018, Dogansen *et al.* 2019). In one of the early case series of DA-induced ICDs in hyperprolactinaemic patients, we proposed the term 'dopa-testotoxicosis' to highlight the male predilection and hypersexuality predominance in DA-induced ICDs in the prolactinoma setting (De Sousa *et al.* 2017). This prompted debate in the literature as to the role of testosterone in contributing to hypersexuality in this context (Bancos *et al.* 2017, Athanasoulia-Kaspar *et al.* 2018, Barake *et al.* 2018, Celik *et al.* 2018, Dogansen *et al.* 2019, Ioachimescu *et al.* 2019). We subsequently explored this association and other potential risk factors in a large cross-sectional analysis of 113 hyperprolactinaemic patients vs 99 healthy controls. We observed higher rates of any ICD, multiple ICDs, hypersexuality, compulsive buying and punding in DA-treated patients compared to controls. Independent risk factors for ICD development were male gender, eugonadism at the time of assessment, a lower Hardy's tumour score at diagnosis and psychiatric comorbidity for hypersexuality and younger age at the time of assessment for compulsive buying. DA dose and duration were not predictive of ICD development (De Sousa *et al.* 2019*a*).

Although a risk factor approach would be desirable in targeting certain patients for closer monitoring of ICDs during DA therapy, there have been conflicting results regarding ICD risk factors (Celik *et al.* 2018, De Sousa *et al.* 2019*a*, Dogansen *et al.* 2019). It is thus more useful to consider all DA-treated hyperprolactinaemic patients to be at risk of developing ICDs, with a systematic approach for all DA-treated patients. This should include educating patients regarding the risk of DA-induced ICDs at the time of initial DA prescription and directly asking patients about ICD symptoms at follow-up. The importance of involving family members in these discussions is exemplified by a study in the Parkinson's disease setting, where 44% of ICDs would have been missed without corroborative history from family or caregivers (Weiss *et al.* 2010).

Written questionnaires to screen for ICDs may help overcome communication barriers in this sensitive area, but there are currently no tools validated in the hyperprolactinaemia setting and varying questionnaires have been used in the studies to date. Furthermore, endocrinologists may need to adopt a more nuanced approach compared to neurologists in screening for DA-induced hypersexuality as increased libido is an expected and usually desired effect of DA treatment of hyperprolactinaemia. Until the optimal tool for clinical practice has been determined by prospective case-controlled validation studies, any of the studied questionnaires may be employed to prompt patient–clinician discussions about ICD symptoms. Such questionnaires may need to be repeated over time as ICD onset can occur anytime from days to years after DA initiation (De Sousa *et al.* 2017, 2019*a*, Dogansen *et al.* 2019).

Patients suspected to have a DA-induced ICD should be assessed for other neuropsychological disorders given the risk of multiple concurrent ICDs in one-third of DA-treated prolactinoma patients and the association between ICDs and depression/anxiety (De Sousa *et al.* 2019*a*). Formal review by a psychologist or psychiatrist may be helpful in equivocal cases or in severe cases where there is concern of significant harm. In confirmed cases of DA-induced ICDs, DA therapy should be ceased and treatment options revisited. Sex hormone replacement and tumour monitoring may be appropriate in the case of a microprolactinoma (Barake *et al.* 2018), whereas surgery, possibly with adjuvant radiotherapy, should be considered for larger tumours with established or potential mass effect.

Whilst ICDs may occasionally resolve spontaneously (De Sousa *et al.* 2017), a wait-and-see approach with continued DA use or subsequent resumption of DA therapy may result in severe, long-lasting social consequences even in the setting of transient ICDs (De Sousa *et al.* 2017). Another potentially hazardous approach is use of the antipsychotic, aripiprazole. This has been raised as a potential treatment alternative to DAs in hyperprolactinaemic patients who develop ICDs because of its partial agonist activity at the D2 receptor which can reverse hyperprolactinaemia and obviate the need for DA treatment in contrast to other antipsychotics that typically raise serum prolactin by D2 receptor antagonism

https://eo.bioscientifica.com
https://doi.org/10.1530/EO-21-0038

(Ioachimescu *et al.* 2019). However, aripiprazole also has agonist activity at the D3 receptor, and the aforementioned FDA study found an increased risk of ICDs in aripiprazole-treated individuals (Moore *et al.* 2014). Dose reduction or switching to another DA has also been suggested in the management of DA-induced ICDs as lowering the dose in particular may reduce ICD symptoms (Bancos *et al.* 2014, 2017, De Sousa *et al.* 2017, Celik *et al.* 2018, Dogansen *et al.* 2019). However, this is not substantiated by other data showing that the risk of ICD development is not associated with DA type or dose (Martinkova *et al.* 2011, Bancos *et al.* 2014, De Sousa *et al.* 2017, 2019*a*, Celik *et al.* 2018, Dogansen *et al.* 2019). Successful use of psychotherapy and citalopram with ongoing cabergoline treatment in a man with a giant prolactinoma and ICD-induced gambling and depression (Athanasoulia-Kaspar *et al.* 2018) suggests that conventional psychiatric treatments can be attempted in patients where ongoing DA treatment is required, but further research is required.

CSF rhinorrhoea

CSF rhinorrhoea arises when an invasive prolactinoma creates a CSF fistula through the dura and osseous skull base, followed by DA-induced tumour shrinkage and unmasking of the skull base defect, resulting in a clear nasal drip of CSF (Suliman *et al.* 2007, Milton *et al.* 2021). CSF rhinorrhoea may occur anytime from 1 week to 5 years after initiation of DA therapy (Milton *et al.* 2021). Potentially fatal complications include meningitis, intracranial abscess and pneumocephalus (Suliman *et al.* 2007). In a retrospective review of 114 patients with macroprolactinomas and 181 patients with non-functioning pituitary adenomas (NFPA), non-surgical CSF rhinorrhoea occurred in 8.7% of prolactinoma patients (2.6% spontaneous, 6.1% DA-induced) and none of the NFPA patients. The development of spontaneous CSF rhinorrhoea prior to any treatment suggests an interaction between a tumour effect and a drug effect in the pathogenesis of this complication (Suliman *et al.* 2007). Risk factors for DA-associated CSF rhinorrhoea include male gender, DA resistance and sphenoid sinus invasion (Suliman *et al.* 2007, Milton *et al.* 2021).

Surgical intervention is required in most cases of CSF rhinorrhoea in order to repair the dural defect and stop the CSF leak (Suliman *et al.* 2007). However, CSF rhinorrhoea may occasionally resolve spontaneously despite ongoing DA treatment and without surgical intervention (Netea-Maier *et al.* 2006, Suliman *et al.* 2007). This may be because of a reduction in intracranial pressure following ongoing tumour shrinkage, with resolution of the previously raised intracranial pressure allowing healing of the CSF fistula (Suliman *et al.* 2007).

In the absence of recommendations from the existing international prolactinoma guidelines, it is reasonable to warn and clinically monitor patients considered to be at high risk of CSF rhinorrhoea. Thin-slice CT imaging of the sinus may help delineate the extent of osseous involvement in patients with sphenoid sinus invasion seen on MRI, thereby identifying patients requiring closer monitoring for CSF rhinorrhoea (Milton *et al.* 2021). However, it is not yet clear if this can be used to guide pre-emptive surgical intervention (Milton *et al.* 2021). Beta-2-transferrin should be measured in any suspicious nasal discharge in order to diagnose CSF rhinorrhoea (Suliman *et al.* 2007). Patients with confirmed CSF rhinorrhoea should be referred for surgical review, noting that surgical correction is not necessarily required and DA therapy may potentially be continued with – or even without – surgical intervention (Netea-Maier *et al.* 2006, Suliman *et al.* 2007, Milton *et al.* 2021). Pending prospective studies in this area, patients should be managed on a case-by-case basis.

Tumour fibrosis

A notable issue in considering the optimal place of surgery for prolactinomas is the potential for initial DA therapy to induce tumour fibrosis, thereby hampering subsequent surgical resection. This appears to be a particular issue with use of bromocriptine, with Menucci *et al.* describing operative findings of fibrosis in 77% of bromocriptine-exposed prolactinomas compared to 22% of cabergoline-exposed prolactinomas (Menucci *et al.* 2011). In this study, biochemical remission was observed after surgery in 37% of the non-fibrous tumours compared to none of the fibrous tumours. In the original publication reporting the risk of DA-induced tumour fibrosis, Landolt *et al.* found a significantly lower rate of postoperative normoprolactinaemia in patients pretreated with bromocriptine (33 vs 81%, ($n = 0.005$) (Landolt *et al.* 1982). However, there has since been conflicting data as to whether surgical outcomes are worse for prolactinomas that have been pretreated with DAs (Gillam *et al.* 2006). A recent systematic review and meta-analysis of the determinants of surgical remission in prolactinomas found that DA pretreatment was associated with lower rates of postoperative remission (Wright *et al.* 2021). This could reflect DA-induced tumour fibrosis making surgical resection more difficult, although cabergoline is preferentially used over bromocriptine in current practice

https://eo.bioscientifica.com
https://doi.org/10.1530/EO-21-0038

and cabergoline has not been associated with tumour fibrosis in recent data (Baussart *et al.* 2021). Alternatively, the need for DA treatment followed by surgery may reflect a greater proportion of DA-resistant, and hence more aggressive, prolactinomas (Wright *et al.* 2021).

Current role of surgery

Since the advent of DA therapy, surgery has typically been reserved as a second-line treatment for prolactinomas in patients with DA failure due to DA resistance or DA intolerance. Exceptions to this are patients presenting with pituitary apoplexy who may require urgent sellar decompression that can only be achieved by surgery; patients with progressive visual loss; cystic macroprolactinomas that typically fail to shrink with DA therapy; patients with spontaneous or DA-induced CSF rhinorrhoea; and patients with discordance between the degree of prolactin elevation and tumour size, raising the possibility of a non-functioning pituitary adenoma causing stalk effect hyperprolactinaemia where the tumour would not be expected to shrink with DA therapy (Casanueva *et al.* 2006, Donoho & Laws 2019, Honegger *et al.* 2020). Notably, the 2006 Pituitary Society guidelines explicitly list patient preference as an indication for surgery, but it is placed as a second-line treatment in the algorithm accompanying these guidelines (Casanueva *et al.* 2006).

Contemporary surgery for prolactinomas typically involves endoscopic transsphenoidal resection of the tumour. The aim is selective adenomectomy with preservation of the normal pituitary gland and hence pituitary function. The overall long-term surgical remission rate is approximately 67%, with remission achieved in 83% of microprolactinomas and 60% of macroprolactinomas (Zamanipoor Najafabadi *et al.* 2020). When specifically used as a second-line treatment in patients who have failed DA therapy due to intolerance or resistance, 38% of patients achieve normoprolactinaemia from surgery alone and 62% achieve normoprolactinaemia with the addition of other therapies (Yagnik *et al.* 2021). Again, patients with microprolactinomas fare better, with 66% of such cases achieving remission from surgery alone (Yagnik *et al.* 2021). Surgical remission rates are similar between microscopic and endoscopic approaches (Cho & Liau 2002, Zamanipoor Najafabadi *et al.* 2020), although the latter is typically favoured for its panoramic view and randomised data in the prolactinoma setting showing shorter operative time, shorter hospital stays and fewer complications (Cho & Liau 2002). As expected, remission rates are better in patients undergoing surgery because of DA intolerance rather than DA resistance which indicates a more aggressive tumour (Donoho & Laws 2019). Long-term remission is predicted by immediate postoperative prolactin levels, with serum prolactin ≤10 ng/mL at 24 h postoperatively yielding an 86% chance of long-term remission (Mattogno *et al.* 2021).

At least some degree of pituitary function recovery is achieved in up to 51% of surgically managed prolactinoma patients (Fatemi *et al.* 2008). Regarding the gonadal axis specifically, 42% of patients with prolactinomas and hypogonadism experience a return of eugonadism postoperatively (Fatemi *et al.* 2008).

Prolactinoma recurrence occurs in 15–20% of surgically managed patients (Gillam *et al.* 2006, Kreutzer *et al.* 2008, Wright *et al.* 2021, Yagnik *et al.* 2021), at a mean time of 27 months (Yagnik *et al.* 2021). Some authors have found increasing recurrence rates with increasing prolactinoma size and invasion (Kreutzer *et al.* 2008), whilst others have not (Gillam *et al.* 2006).

The most frequent complications of transsphenoidal surgery for prolactinomas are transient diabetes insipidus (16%) and syndrome of inappropriate antidiuretic hormone secretion (9%), which are short-term. More serious long-term complications include CSF leakage (3%), hypopituitarism (2%), permanent diabetes insipidus (2%), meningitis (1%) and visual deterioration (1%) (Zamanipoor Najafabadi *et al.* 2020). Bleeding and cranial nerve injuries may rarely occur (De Vries *et al.* 2021).

The ideal candidate for surgery is a surgically fit patient with a visible microprolactinoma without parasellar extension (Zamanipoor Najafabadi *et al.* 2020). There are several tumour and patient characteristics that predict failure of surgical remission in patients with prolactinomas, with some variability between studies. Factors predictive of poor surgical outcomes include cavernous sinus invasion (Gillam *et al.* 2006, Zielinski *et al.* 2020, Andereggen *et al.* 2021*a*, Baussart *et al.* 2021, Mattogno *et al.* 2021, Wright *et al.* 2021), suprasellar extension – particularly if accompanied by visual deficits (Kreutzer *et al.* 2008, Wright *et al.* 2021), sphenoid invasion (Kreutzer *et al.* 2008), macroprolactinomas (defined as >10 mm) (Gillam *et al.* 2006, Zamanipoor Najafabadi *et al.* 2020, Zielinski *et al.* 2020, Andereggen *et al.* 2021*a*, Mattogno *et al.* 2021, Wright *et al.* 2021), higher preoperative serum prolactin level (Gillam *et al.* 2006, Andereggen *et al.* 2021*a*, Baussart *et al.* 2021, Wright *et al.* 2021), previous pituitary surgery or radiotherapy (Gillam *et al.* 2006), higher Ki-67 index (Song *et al.* 2017), plurihormonality (Zielinski *et al.* 2020), preoperative DA treatment (Wright *et al.* 2021) and male gender (Andereggen *et al.* 2021*a*, Mattogno *et al.* 2021,

https://eo.bioscientifica.com
https://doi.org/10.1530/EO-21-0038

Wright *et al.* 2021). In particular, surgical remission is rarely achieved in giant prolactinomas (defined as ≥40 mm) (Honegger *et al.* 2020).

Revival of surgery as a first-line treatment

The utility of surgery for patients with DA failure is clear given that surgical remission is achieved in the majority, with only a small minority experiencing serious operative complications. There are now also calls for surgery to be considered alongside DA therapy as equivalent first-line options for prolactinomas based on increasing recognition of the adverse event profile of DA therapy and improving surgical techniques. This was most prominently proposed in a recent meta-analysis by Zamanipoor Najafabadi *et al.*, showing that long-term prolactinoma remission was higher after surgery than after DA withdrawal (67% vs 34%). The superiority of surgery compared to DA therapy for long-term remission was especially evident for microprolactinomas (83% vs 36%) and less so for macroprolactinomas (60% vs 28%). In addition, DA side effects were common, with the most frequent side effects being fatigue in 30%, sleep disorders in 25% and nausea in 17%. By contrast, permanent severe operative complications were infrequent, affecting 3% of patients (Zamanipoor Najafabadi *et al.* 2020).

The findings of Zamanipoor Najafabadi *et al.* have been corroborated by subsequent retrospective studies. An Italian study of 259 prolactinoma patients undergoing surgery (n = 119) or DA therapy (n = 140) as first-line treatment found that surgery yielded higher rates of combined biochemical and radiological cure in female patients only, whereas cure rates were comparable in the overall cohort. When use of surgery at any time was considered, surgery yielded higher cure rates in female patients and in the overall cohort; women with microadenomas experienced the greatest advantage from surgery (Mattogno *et al.* 2021). A French series of 114 surgically treated patients with non-invasive microprolactinoma demonstrated disease-free survival rates of 91% at 1 year and 81% at 5 years (Baussart *et al.* 2021). A Swiss series of 86 surgically treated prolactinoma patients with median follow-up of almost 7 years showed similarly good surgical outcomes for macroprolactinomas without cavernous sinus invasion as for microprolactinomas, with DA required on follow-up in 24% of microprolactinomas and 29% of Knosp grade 0 macroprolactinomas compared to 76% of Knosp grade 1 macroprolactinomas (Andereggen *et al.* 2021*a*). A Korean study of 70 patients with non-invasive prolactinomas treated with surgery (n = 29) or DA agents (n = 41) found similar rates of prolactin normalisation and gonadal recovery between the groups, whilst surgery improved rates of tumour shrinkage and recurrence. Disease control, defined as normoprolactinaemia and >50% tumour shrinkage, was similar in macroprolactinoma patients treated with medical vs surgical therapy, whereas microprolactinoma patients experienced better responses with surgical rather than medical therapy (83.3% vs 19.2%, $P < 0.05$) (Park *et al.* 2021). In addition, an earlier meta-analysis of medically treated patients with prolactinomas or idiopathic hyperprolactinaemia demonstrated low long-term remission at only 21% after DA withdrawal (Dekkers *et al.* 2010).

When comparing surgical outcomes between different functioning pituitary adenomas, prolactinomas show superior results. De Vries *et al.* recently proposed a novel two-dimensional outcome square incorporating remission and complications from pituitary surgery, rather than considering these two surgical outcomes separately. Prolactinoma cases demonstrated the highest proportion of good outcomes, defined as surgical remission without complication (67.9% for prolactinoma, 60.6% for Cushing's disease and 56.4% for acromegaly), and the lowest proportion of poor outcomes, defined as no remission without complication (1.8% for prolactinoma, 2.8% for Cushing's disease and 4.2% for acromegaly) (De Vries *et al.* 2021). The primary place of surgery in the management of Cushing's disease and acromegaly despite these figures highlights the inadequacy of pharmacological options in these tumours.

To summarise, the general arguments supporting the return of surgery as a first-line treatment for prolactinoma include the following:

- Surgery produces high remission rates, especially for microprolactinomas and intrasellar macroprolactinomas (Zamanipoor Najafabadi *et al.* 2020, Andereggen *et al.* 2021*a*, Baussart *et al.* 2021, Mattogno *et al.* 2021, Park *et al.* 2021), and non-randomised data show superiority in long-term remission compared to DA therapy (Zamanipoor Najafabadi *et al.* 2020, Mattogno *et al.* 2021, Park *et al.* 2021).
- Surgery provides definitive treatment with no need for DA therapy or pituitary hormone replacement in the majority of cases when performed by experienced pituitary surgeons (Donoho & Laws 2019). By contrast, DA withdrawal is only possible for select patients and often fails (Dekkers *et al.* 2010, Zamanipoor Najafabadi *et al.* 2020), necessitating prolonged DA therapy in

https://eo.bioscientifica.com
https://doi.org/10.1530/EO-21-0038

these patients, with its associated mild but common side effects, rare serious risks and potential impact on quality of life. Whilst some surgically treated patients will ultimately require DA therapy, long-term DA dependence is lower in surgically treated patients than medically treated patients (Andereggen *et al.* 2017).
- In the absence of gross total remission, debulking surgery may be sufficient to achieve eugonadism and to cease DA therapy or to require lower DA doses that are safer and more tolerable (Cho & Liau 2002, Kars *et al.* 2009, Vroonen *et al.* 2012).
- Surgery carries a low risk of surgical complications and negligible mortality (Zamanipoor Najafabadi *et al.* 2020, Andereggen *et al.* 2021*a*, Park *et al.* 2021).
- Both endoscopic and microscopic transsphenoidal surgery involve minimally invasive techniques with reduced nasal discomfort compared to historical procedures (Honegger *et al.* 2020).
- Upfront surgery prior to DA exposure circumvents the potential issue of DA-induced fibrosis that may lead to poorer surgical outcomes.
- Development of DA-induced psychosis, ICDs or CSF rhinorrhoea can quickly lead to serious, permanent consequences, hence it is desirable to avoid these risks of DA therapy altogether by upfront surgical management. However, precise figures of severe permanent complications from DA therapy are unavailable, as DA-induced adverse events tend to be compiled without regard to the severity or timeframe of these events.
- Whilst thoughtful selection of the DA agent used might circumvent one risk and obviate the need for surgery, it may lead to another. For example, the potential risk of cabergoline-induced valvulopathy with prolonged, high-dose therapy may be circumvented by using bromocriptine in patients with high DA dose requirements (Iyer & Molitch 2011). However, bromocriptine is more strongly associated with tumour fibrosis (Menucci *et al.* 2011), which may hamper later attempts at surgical resection in these patients who are more likely to require multimodal therapy for their resistant prolactinomas.
- American simulation data show surgery to be a more cost-effective treatment for prolactinomas compared to DA therapy (Jethwa *et al.* 2016, Zygourakis *et al.* 2017), although opposite findings have been reported in China (Duan *et al.* 2017). The most effective model for treating prolactinomas may vary between countries in relation to different resources and funding systems; however, surgery is more cost-effective than DA therapy down to surgical remission rates above 30% (Zygourakis *et al.* 2017), and it is increasingly more cost-effective with progressive follow-up (Jethwa *et al.* 2016).

By contrast, arguments in favour of ongoing use of DA therapy as the sole first-line treatment for prolactinoma include the following:

- There are multiple flaws in the studies showing the high efficacy of surgery for prolactinomas, namely:
  - Existing studies have been retrospective observational studies, with no randomised trials of surgery vs DA therapy performed to date (Zamanipoor Najafabadi *et al.* 2020).
  - There is likely an inherent reporting bias in surgical series as publications are expected to be produced by the neurosurgeons with the highest surgical remission rates.
  - Patients in the surgical studies evaluated by Zamanipoor Najafabadi *et al.* had a lower median prolactin level and smaller tumours at study entry compared to medically treated patients, suggesting frequent preoperative DA treatment in the surgical studies (Zamanipoor Najafabadi *et al.* 2020). It is not yet clear whether surgery will perform as well in DA-naïve patients.
  - There is heterogeneity between studies in regard to how prolactinoma remission is defined. Most studies focus on prolactin normalisation, with or without the need for additional therapies, at variable lengths of follow-up. Most studies omit other clinically relevant parameters such as tumour diameter, gonadal status, fertility and pregnancy outcomes. There may also be heterogeneity in surgical techniques. These limitations in individual studies also affect the meta-analyses of these studies (Zamanipoor Najafabadi *et al.* 2020, Yagnik *et al.* 2021).
  - Most surgical series lack comprehensive hormonal assessments, potentially underestimating rates of postoperative hypopituitarism (Zamanipoor Najafabadi *et al.* 2020).
  - Surgical complication rates in the meta-analysis by Zamanipoor Najafabadi *et al.* were mostly derived from macroprolactinoma cases, with relatively limited data pertaining specifically to microprolactinomas (Zamanipoor Najafabadi *et al.* 2020). Although, the subsequent French series of 114 patients with surgically managed microprolactinomas has been reassuring in showing a low rate of surgical complications at 4%, with no cases of anterior pituitary insufficiency (Baussart *et al.* 2021).

https://eo.bioscientifica.com
https://doi.org/10.1530/EO-21-0038

- Transsphenoidal surgery outcomes for prolactinomas depend on case volume of the neurosurgeon, but not all patients will have access to a highly experienced pituitary surgeon (Tampourlou *et al.* 2016).
- Surgery carries lower remission rates in certain subgroups, such as patients with cavernous sinus invasion (Gillam *et al.* 2006, Zielinski *et al.* 2020, Andereggen *et al.* 2021*a*), arguing against routine consideration of upfront surgery for all patients.
- Some patients with tumoural-level hyperprolactinaemia may have an occult prolactinoma and it is uncertain whether these patients benefit from surgical exploration (Zamanipoor Najafabadi *et al.* 2020).
- Whilst long-term remission rates after DA withdrawal are low, DA therapy remains highly effective at controlling hyperprolactinaemia during DA treatment, with normoprolactinaemia achieved in 81% of patients overall. The DA biochemical control rate in macroprolactinomas is notably superior at 77% compared to the surgical remission rate of 60% for this subgroup (Zamanipoor Najafabadi *et al.* 2020).
- DA-induced side effects are frequently transient and often reversible (Gillam *et al.* 2006). Although the proportion of operated patients experiencing severe permanent surgical complications is low, the absolute number of patients experiencing such adverse events will rise if surgery is used more frequently.
- The young people who may most benefit from upfront surgery in order to avoid the potential duration-dependent risks of DA-induced tumour fibrosis (Landolt *et al.* 1982) and cardiac valvulopathy (Colao *et al.* 2008, Stiles *et al.* 2018, Steeds *et al.* 2019) and the age-dependent risk of some DA-induced ICDs (De Sousa *et al.* 2019*a*) are also susceptible to a greater cumulative burden if they develop permanent postoperative complications such as permanent diabetes insipidus.
- As outlined in this review, it is possible to minimise DA therapy side effects and mitigate the serious risks of DA therapy – for example, by adjusted dosing and proactive monitoring for ICDs.
- Hyperprolactinaemia may resolve spontaneously, especially in microprolactinomas (Gillam *et al.* 2006), arguing against definitive treatment in the form of surgery which carries a risk – albeit small – of permanent complications such as hypopituitarism. In particular, normalisation of prolactin has been reported in 24% of women after childbirth and 45% of women after menopause (Karunakaran *et al.* 2001), although confounding treatment effects have not been excluded.

There is no clear evidence from a quality of life perspective to favour surgical or DA therapy for patients with prolactinomas. Some data show an adverse impact on quality of life from prolactinoma surgery and DA therapy whilst other studies have found no effect from either treatment (Andela *et al.* 2015, Zamanipoor Najafabadi *et al.* 2020). These mixed results might reflect interindividual variability relating to patient circumstances and tumour characteristics.

Bone and metabolic parameters also appear to be unaffected by treatment modality. Patients with prolactinomas exhibit increased bone turnover and reduced bone mineral density, especially at the lumbar spine, even after long-term treatment. Bone loss is particularly associated with the durations of hypogonadism and hyperprolactinaemia, emphasising the importance of timely and effective treatment (Naliato *et al.* 2008, Andereggen *et al.* 2021*c*). However, the prevalence of impaired bone mineral density in men and women with prolactinomas at long-term follow-up is unchanged by whether DA therapy or surgery is employed as the primary treatment strategy (Andereggen *et al.* 2021*c*). Body mass index and fasting glucose decrease, and lipid profile marginally improves, with treatment of prolactinomas, but these metabolic changes are also independent of whether patients are treated medically or surgically (Andereggen *et al.* 2021*b*).

Management of prolactinomas in the preconception setting requires additional consideration. In the case of microprolactinomas, the risk of expansion in pregnancy is low, allowing for the safe use of bromocriptine or cabergoline until pregnancy is confirmed, but surgery may be considered preferable as selective adenectomy can be readily achieved with correction of hyperprolactinaemia, restoration of menstrual cycles and preservation of other pituitary axes (Honegger *et al.* 2020, Mattogno *et al.* 2021). Macroprolactinomas carry a higher risk of tumour expansion, necessitating either continued DA therapy throughout pregnancy or DA interruption with recommencement if symptomatic regrowth occurs. Whilst bromocriptine and cabergoline appear safe in pregnancy, these agents do cross the placenta. Surgery prior to conception in women with macroprolactinomas offers a lower risk of clinically relevant tumour expansion in pregnancy (5% in surgically treated women vs 31% in women only ever treated with DAs), thereby lowering the chance of requiring DA treatment in pregnancy (Gillam *et al.* 2006, Honegger *et al.* 2020). However, surgery carries a risk of hypopituitarism which may affect fertility in addition to requiring close treatment monitoring and

https://eo.bioscientifica.com
https://doi.org/10.1530/EO-21-0038

modifications if pregnancy is achieved. Furthermore, pregnancy itself may be associated with subsequent resolution of hyperprolactinaemia (Karunakaran *et al.* 2001), obviating the need for definitive treatment in the form of preconception surgery.

The Dutch Prolactinoma Study Group is endeavouring to provide a conclusive answer as to whether upfront surgery is superior to DA treatment in its planned randomised clinical trial entitled 'PRolaCT' (Zandbergen *et al.* 2021). Due to conclude in 2022, this trial involves multiple arms comparing DA treatment against neurosurgical counselling, with surgery in consenting patients, at different time points in patients with a non-invasive prolactinoma. The primary outcomes of this much awaited trial are quality of life and long-term remission, both being critical to patient-centred care (Zandbergen *et al.* 2021).

Low surgical threshold approach

Pending the outcomes of the PRolaCT randomised controlled trials, a practical and balanced approach may be to aim for DA therapy as the first-line of therapy in a dosing regimen that is tailored to the individual case, but with a low threshold for considering surgery either upfront or as issues emerge. In this 'low surgical threshold' approach illustrated in Fig. 1, the critical points at which to consider surgery in a patient's clinical course are:

- Upfront, if there is concern regarding the potential development of DA side effects or risks in an especially vulnerable patient (e.g. history of psychiatric illness and, possibly, prior to conception given that DAs cross the placenta);
- Development of simple but bothersome DA side effects that are not manageable with dosing strategies (e.g. split dosing);
- Immediately upon emergence of any serious risks of DA therapy (e.g. ICDs) because of the possibility of irreversible consequences; and
- Evidence of the need for long-term DA therapy (e.g. failed attempt at DA withdrawal) in a patient who does not wish to continue DA therapy because of inconvenience, persistent albeit tolerable side effects or concern about the potential risk of valvulopathy with prolonged, high-dose cabergoline use.

Surgery is also recommended for patients meeting the traditional indications for surgical intervention, including pituitary apoplexy requiring urgent surgical decompression, spontaneous or DA-induced CSF

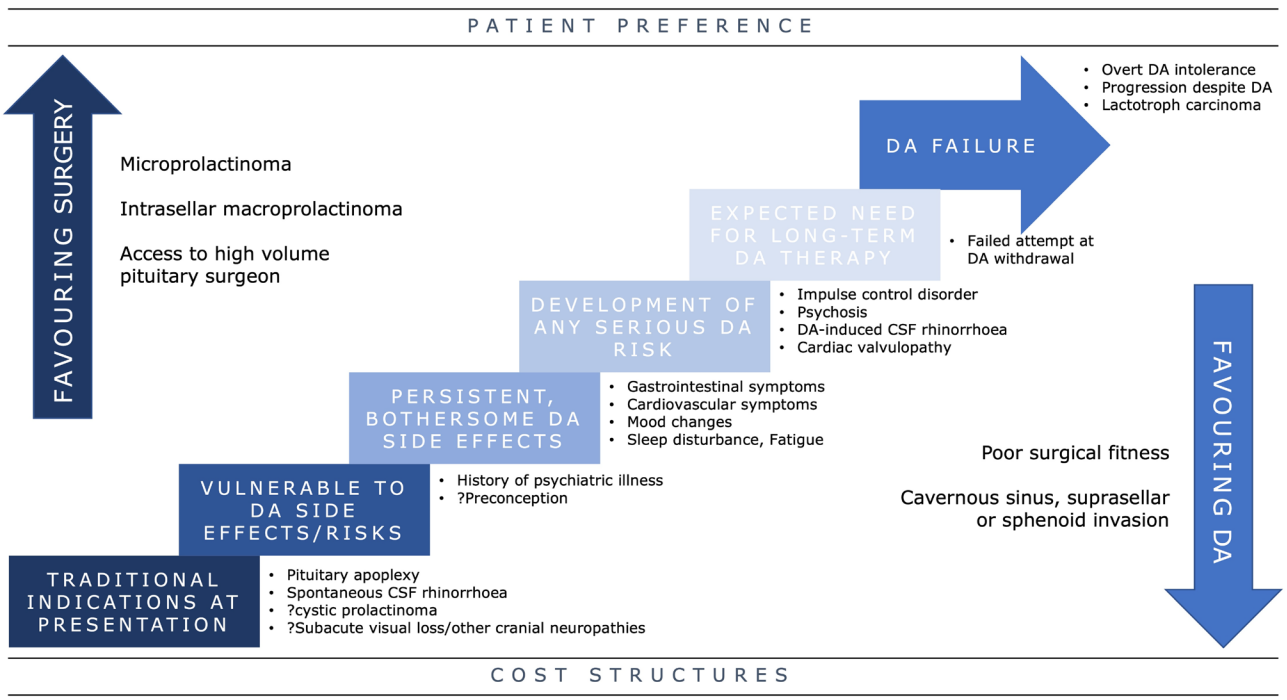

Figure 1
The low surgical threshold approach to prolactinoma management. Specific triggers to consider surgery are outlined, with the ultimate decision to pursue surgery guided by individual case characteristics, patient preference and local medical cost structures.

https://eo.bioscientifica.com
https://doi.org/10.1530/EO-21-0038

rhinorrhoea, prolactinoma expansion, persistent mass effect and/or clinically symptomatic hyperprolactinaemia despite escalating DA dose, and resectable lactotroph carcinoma (Casanueva *et al.* 2006, Honegger *et al.* 2020). Upfront surgery should also be considered in cystic prolactinomas and prolactinomas causing subacute visual field deficits or other cranial neuropathies as patients in these scenarios may respond better to surgery than DA therapy (Donoho & Laws 2019).

At each of the trigger points, the role of surgery may be further supported by features predictive of a good surgical outcome or negated by risk factors for incomplete resection or operative complications. Tumour diameter should not be the sole factor determining the best treatment path as macroprolactinomas show poorer outcomes than microprolactinomas across treatment modalities. Moreover, microprolactinomas exhibit higher surgical response rates but with a relative paucity of data regarding surgical complication rates compared to macroprolactinomas.

Whenever surgery is indicated, this should prompt an in-depth discussion with the patient regarding the relative pros and cons of surgery vs DA therapy, tailored to the patient's individual circumstances and tumour characteristics. Patient preference and local cost structures will guide the ultimate decision.

The preconception stage requires a nuanced discussion with the patient. The lack of randomised studies assessing medical vs surgical treatment of prolactinomas prior to conception should be noted. The patient should be counselled regarding her specific risks of prolactinoma progression in pregnancy, the likelihood of a complete DA response allowing DA withdrawal prior to conception compared to expected surgical outcomes depending on tumour characteristics, and the potential risks of continuing DA therapy in pregnancy vs long-term operative risks such as hypopituitarism and their impact on conception and pregnancy. This should allow women to make informed personal choices regarding their management.

The low surgical threshold approach allows for the use of surgical management in the patients most likely to benefit from surgery instead of ongoing DA therapy. It takes into account the high frequency of DA side effects and the severity of DA-induced risks together with the apparently favourable outcomes of surgery, whilst acknowledging the ability of endocrinologists to optimise DA therapy and the limitations of the current evidence regarding the superiority of surgery over DA therapy. Trialling DA therapy before resorting to surgery as soon as indicated may also mitigate the potential duration-dependent risks of DA-induced tumour fibrosis and cardiac valvulopathy, accepting that the evidence for these risks is mixed and controversial. Supporting early use of surgery, the aforementioned study by Landolt *et al.* on the risk of DA-induced tumour fibrosis observed postoperative normoprolactinaemia in 44% of patients exposed to bromocriptine for ≤1 year vs none of the patients exposed for >1 year ($P < 0.05$) (Landolt *et al.* 1982). Prompt consideration of surgery in patients with apparent DA resistance may also minimise effects related to the duration of hypogonadism and hyperprolactinaemia, including impaired bone density (Naliato *et al.* 2008, Andereggen *et al.* 2021*c*). Surgery has been shown to be an independent prognosticator of long-term cure, irrespective of whether it is used as a primary or secondary therapy (Mattogno *et al.* 2021), also supporting the low surgical threshold approach as opposed to making surgery a routine first-line therapy. Finally, lowering the threshold for surgery should increase prolactinoma caseload for treating neurosurgeons, potentially improving remission rates over time (Tampourlou *et al.* 2016, Honegger *et al.* 2020).

Although data support the long-term cost-effectiveness of surgery over DA therapy (Jethwa *et al.* 2016, Zygourakis *et al.* 2017), this is reliant upon access to subspecialised neurosurgical and radiological expertise and equipment, with high upfront costs. These requirements may prohibit a low surgical threshold approach to prolactinoma management in less wealthy nations, where DA therapy will likely remain preferable apart from cases of overt DA failure.

Future directions

The clear need for randomised data directly comparing surgery vs DA therapy in patients with prolactinomas will be addressed by the PRolaCT trials. The results of these trials will be integral in determining the clinical utility of expanding the patient population referred for surgery. Without such data, it is possible that the treatment outcomes observed to date reflect confounding variables and various selection biases. For example, surgery may have been reserved for patients with better surgical fitness and thus a lower complication rate than in an unselected population. On the other hand, surgery may have been reserved for the most difficult to treat prolactinomas which would therefore have lower surgical remission rates than an unselected population. When surgery is employed as a second-line therapy in patients with DA failure, the indication of DA resistance is more common than DA intolerance (Wright *et al.* 2021, Yagnik *et al.* 2021), perhaps reflecting reduced awareness

https://eo.bioscientifica.com
https://doi.org/10.1530/EO-21-0038

of the burden of DA adverse events and a reluctance for surgical therapy. Even better surgical outcomes may be seen with increasing use of surgery beyond predominantly DA-resistant patients who would be expected to have poorer surgical outcomes. Prospective studies of DA therapy may also show improved outcomes as endocrinologists become more cognisant of the pitfalls of DA therapy and how these pitfalls may be overcome.

Future studies will ideally assess the effects of surgical vs medical therapy on prolactinoma diameter, fertility, pregnancy outcomes, bone and metabolic indices and other pituitary axes in addition to prolactin normalisation. Extended follow-up is also critical as remission rates after surgery compared to DA withdrawal may vary over time and with repeated surgery or DA treatment courses. Applying the outcome squares model proposed by De Vries *et al.* would be especially valuable in comparing both the success and risk profiles of DA and surgical management (De Vries *et al.* 2021). This model may also help to delineate the relative utility of surgery vs DA therapy in more challenging subsets, such as prolactinomas in women imminently planning for pregnancy, prolactinomas in men and giant prolactinomas.

Further research is needed to address the optimal sequence of therapy in the subset of patients that ultimately require both medical and surgical management. Some data show that preoperative DA treatment is associated with lower surgical cure rates, which might reflect either DA-induced tumour fibrosis or a selection bias for more aggressive tumours ultimately requiring surgery after DA treatment (Wright *et al.* 2021). Other data show that preoperative DA treatment is associated with greater prolactin lowering and improved long-term surgical remission, potentially due to DA-induced tumour debulking leading to improved resectability (Sughrue *et al.* 2009). These divergent findings are likely to be clarified by the PRolaCT trials, including the PRolaCT-2 substudy comparing ongoing DA therapy to surgery at 4–6 months of DA therapy which will at least partly reflect the low surgical threshold approach described above.

As features such as larger tumour size and greater tumour invasiveness are predictive of both DA resistance and poorer surgical outcomes (Honegger *et al.* 2020, Wright *et al.* 2021), there is a need for research into novel prolactinoma treatments that overcome the limitations of both DA therapy and surgery. Understanding the molecular basis of prolactinoma tumorigenesis may reveal new medical treatment targets, although genomic studies to date have not shown druggable driver mutations (De Sousa *et al.* 2019*b*).

Conclusions

In summary, increasing awareness of the limitations of DA therapy coupled with improving surgical outcomes are challenging the current place of surgery as a second-line treatment in prolactinoma management. We await the outcomes of current randomised trials comparing surgical and medical management, which may finally show surgery to be non-inferior or even superior to DA therapy. For now, the combination of optimised DA therapy tailored to the individual case coupled with a low surgical threshold approach should maximise the proportion of patients with optimally managed prolactinomas. By this approach, DA therapy retains its position as the primary treatment modality unless there are specific triggers for surgery, including concern regarding DA side effects or risks in vulnerable patients, development of bothersome DA side effects, emergence of any serious risks of DA therapy, expected need for long-term DA therapy that is not desired, as well as the traditional indications for surgery.

The emerging complexity of prolactinoma management underscores the importance of patients having access to interdisciplinary teams at Pituitary Tumor Centers of Excellence (PTCOE) (Casanueva *et al.* 2017). Providing care within a PTCOE will hopefully promote a considered approach to treatment, including contemplation of surgery as soon as appropriate. Ensuring access to experienced pituitary surgeons will be especially important in providing equitable management options for all patients with prolactinomas.

Finally, the gathering momentum for surgical management highlights the need for updated prolactinoma guidelines that address the far increased use of cabergoline over bromocriptine, improved surgical outcomes and more recently recognised risks of DA therapy. Of particular concern, there is no mention of the risk of DA-induced ICDs in either the 2006 Pituitary Society guidelines or the 2011 Endocrine Society guidelines (Casanueva *et al.* 2006, Melmed *et al.* 2011), despite multiple class actions against pharmaceutical companies for failure to warn patients of ICD risks prior to DA therapy for Parkinson's disease and restless legs syndrome. A new set of prolactinoma guidelines will address the unmet needs of patients with inadequately treated prolactinomas, noting that the relatively small subsets of patients with intolerable DA side effects or DA resistance still exceeds the total number of patients with either Cushing's disease or acromegaly.

https://eo.bioscientifica.com
https://doi.org/10.1530/EO-21-0038

Declaration of interest
The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

Funding
S M C D receives research funding from the Royal Adelaide Hospital Mary Overton Early Career Research Fellowship, the Royal Australasian College of Physicians Fellows Research Establishment Fellowship and the Endocrine Society of Australia Postdoctoral Award.

References

American Psychiatric Association 2000 *Diagnostic and Statistical Manual of Mental Disorders*. Washington, DC: American Psychiatric Association.

Andela CD, Scharloo M, Pereira AM, Kaptein AA & Biermasz NR 2015 Quality of life (QoL) impairments in patients with a pituitary adenoma: a systematic review of QoL studies. *Pituitary* **18** 752–776. (https://doi.org/10.1007/s11102-015-0636-7)

Andereggen L, Frey J, Andres RH, El-Koussy M, Beck J, Seiler RW & Christ E 2017 10-year follow-up study comparing primary medical vs. surgical therapy in women with prolactinomas. *Endocrine* **55** 223–230. (https://doi.org/10.1007/s12020-016-1115-2)

Andereggen L, Frey J, Andres RH, Luedi MM, El-Koussy M, Widmer HR, Beck J, Mariani L, Seiler RW & Christ E 2021*a* First-line surgery in prolactinomas: lessons from a long-term follow-up study in a tertiary referral center. *Journal of Endocrinological Investigation* **44** 2621–2633. (https://doi.org/10.1007/s40618-021-01569-6)

Andereggen L, Frey J, Andres RH, Luedi MM, Gralla J, Schubert GA, Beck J, Mariani L & Christ E 2021*b* Impact of primary medical or surgical therapy on prolactinoma patients' BMI and metabolic profile over the long-term. *Journal of Clinical and Translational Endocrinology* **24** 100258 doi:10.1016/j.jcte.2021.100258.

Andereggen L, Frey J, Andres RH, Luedi MM, Widmer HR, Beck J, Mariani L & Christ E 2021*c* Persistent bone impairment despite long-term control of hyperprolactinemia and hypogonadism in men and women with prolactinomas. *Scientific Reports* **11** 5122. (https://doi.org/10.1038/s41598-021-84606-x)

Athanasoulia AP, Sievers C, Ising M, Brockhaus AC, Yassouridis A, Stalla GK & Uhr M 2012 Polymorphisms of the drug transporter gene ABCB1 predict side effects of treatment with cabergoline in patients with PRL adenomas. *European Journal of Endocrinology* **167** 327–335. (https://doi.org/10.1530/EJE-12-0198)

Athanasoulia-Kaspar AP, Popp KH & Stalla GK 2018 Neuropsychiatric and metabolic aspects of dopaminergic therapy: perspectives from an endocrinologist and a psychiatrist. *Endocrine Connections* **7** R88–R94. (https://doi.org/10.1530/EC-18-0030)

Auriemma RS, Pivonello R, Perone Y, Grasso LF, Ferreri L, Simeoli C, Iacuaniello D, Gasperi M & Colao A 2013 Safety of long-term treatment with cabergoline on cardiac valve disease in patients with prolactinomas. *European Journal of Endocrinology* **169** 359–366. (https://doi.org/10.1530/EJE-13-0231)

Bancos I, Nannenga MR, Bostwick JM, Silber MH, Erickson D & Nippoldt TB 2014 Impulse control disorders in patients with dopamine agonist-treated prolactinomas and nonfunctioning pituitary adenomas: a case-control study. *Clinical Endocrinology* **80** 863–868. (https://doi.org/10.1111/cen.12375)

Bancos I, Nippoldt TB & Erickson D 2017 Hypersexuality in men with prolactinomas treated with dopamine agonists. *Endocrine* **56** 456–457. (https://doi.org/10.1007/s12020-017-1247-z)

Barake M, Klibanski A & Tritos NA 2018 MANAGEMENT OF ENDOCRINE DISEASE: Impulse control disorders in patients with hyperpolactinemia treated with dopamine agonists: how much should we worry? *European Journal of Endocrinology* **179** R287–R296. (https://doi.org/10.1530/EJE-18-0667)

Barlier A & Jaquet P 2006 Quinagolide-a valuable treatment option for hyperprolactinaemia. *European Journal of Endocrinology* **154** 187–195. (https://doi.org/10.1530/eje.1.02075)

Baussart B, Villa C, Jouinot A, Raffin-Sanson ML, Foubert L, Cazabat L, Bernier M, Bonnet F, Dohan A, Bertherat J, *et al.* 2021 Pituitary surgery as alternative to dopamine agonists treatment for microprolactinomas: a cohort study. *European Journal of Endocrinology* **185** 783–791. (https://doi.org/10.1530/EJE-21-0293)

Beckers A, Aaltonen LA, Daly AF & Karhu A 2013 Familial isolated pituitary adenomas (FIPA) and the pituitary adenoma predisposition due to mutations in the aryl hydrocarbon receptor interacting protein (AIP) gene. *Endocrine Reviews* **34** 239–277. (https://doi.org/10.1210/er.2012-1013)

Beumont P, Bruwer J, Pimstone B, Vinik A & Utian W 1975 Bromergocryptine in the treatment of phenothiazine-induced galactorrhoea. *British Journal of Psychiatry* **126** 285–288. (https://doi.org/10.1192/bjp.126.3.285)

Boyd A 1995 Bromocriptine and psychosis: a literature review. *Psychiatric Quarterly* **66** 87–95. (https://doi.org/10.1007/BF02238717)

Cantone MC, Dicitore A & Vitale G 2021 Somatostatin-dopamine chimeric molecules in neuroendocrine neoplasms. *Journal of Clinical Medicine* **10** 201. (https://doi.org/10.3390/jcm10030501)

Caputo C, Prior D & Inder WJ 2015 The need for annual echocardiography to detect cabergoline-associated valvulopathy in patients with prolactinoma: a systematic review and additional clinical data. *Lancet: Diabetes and Endocrinology* **3** 906–913. (https://doi.org/10.1016/S2213-8587(14)70212-8)

Casanueva FF, Molitch ME, Schlechte JA, Abs R, Bonert V, Bronstein MD, Brue T, Cappabianca P, Colao A, Fahlbusch R, *et al.* 2006 Guidelines of the Pituitary Society for the diagnosis and management of prolactinomas. *Clinical Endocrinology* **65** 265–273. (https://doi.org/10.1111/j.1365-2265.2006.02562.x)

Casanueva FF, Barkan AL, Buchfelder M, Klibanski A, Laws ER, Loeffler JS, Melmed S, Mortini P, Wass J, Giustina A, *et al.* 2017 Criteria for the definition of pituitary tumor centers of excellence (PTCOE): a Pituitary Society Statement. *Pituitary* **20** 489–498. (https://doi.org/10.1007/s11102-017-0838-2)

Cavallaro R, Cocchi F, Angelone SM, Lattuada E & Smeraldi E 2004 Cabergoline treatment of risperidone-induced hyperprolactinemia: a pilot study. *Journal of Clinical Psychiatry* **65** 187–190. (https://doi.org/10.4088/jcp.v65n0207)

Cebrián A, Ruiz-Llorente S, Cascon A, Pollan M, Diez JJ, Pico A, Telleria D, Benitez J & Robledo M 2003 Mutational and gross deletion study of the MEN1 gene and correlation with clinical features in Spanish patients. *Journal of Medical Genetics* **40** e72. (https://doi.org/10.1136/jmg.40.5.e72)

Celik E, Ozkaya HM, Poyraz BC, Saglam T & Kadioglu P 2018 Impulse control disorders in patients with prolactinoma receiving dopamine agonist therapy: a prospective study with 1 year follow-up. *Endocrine* **62** 692–700. (https://doi.org/10.1007/s12020-018-1744-8)

Cho DY & Liau WR 2002 Comparison of endonasal endoscopic surgery and sublabial microsurgery for prolactinomas. *Surgical Neurology* **58** 371–375; discussion 375–376. (https://doi.org/10.1016/s0090-3019(02)00892-3)

Colao A, Di Sarno A, Cappabianca P, Di Somma C, Pivonello R & Lombardi G 2003 Withdrawal of long-term cabergoline therapy for tumoral and nontumoral hyperprolactinemia. *New England Journal of Medicine* **349** 2023–2033. (https://doi.org/10.1056/NEJMoa022657)

Colao A, Galderisi M, Di Sarno A, Pardo M, Gaccione M, D'Andrea M, Guerra E, Pivonello R, Lerro G & Lombardi G 2008 Increased prevalence of tricuspid regurgitation in patients with prolactinomas chronically treated with cabergoline. *Journal of Clinical Endocrinology and Metabolism* **93** 3777–3784. (https://doi.org/10.1210/jc.2007-1403)

Daly AF, Rixhon M, Adam C, Dempegioti A, Tichomirowa MA & Beckers A 2006 High prevalence of pituitary adenomas: a cross-

sectional study in the province of Liege, Belgium. *Journal of Clinical Endocrinology and Metabolism* **91** 4769–4775. (https://doi.org/10.1210/jc.2006-1668)

De Sousa SM, Chapman IM, Falhammar H & Torpy DJ 2017 Dopa-testotoxicosis: disruptive hypersexuality in hypogonadal men with prolactinomas treated with dopamine agonists. *Endocrine* **55** 618–624. (https://doi.org/10.1007/s12020-016-1088-1)

De Sousa SMC, Baranoff J, Rushworth RL, Butler J, Sorbello J, Vorster J, Thompson T, McCormack AI, Inder WJ & Torpy DJ 2019*a* Impulse control disorders in dopamine agonist-treated hyperprolactinemia: prevalence and risk factors. *Journal of Clinical Endocrinology and Metabolism* **105** dgz076. (https://doi.org/10.1210/clinem/dgz076)

De Sousa SMC, Wang PPS, Santoreneos S, Shen A, Yates CJ, Babic M, Eshraghi L, Feng J, Koszyca B, Roberts-Thomson S, *et al.* 2019*b* The genomic landscape of sporadic prolactinomas. *Endocrine Pathology* **30** 318–328. (https://doi.org/10.1007/s12022-019-09587-0)

De Vries F, Lobatto DJ, Verstegen MJT, Schutte PJ, Notting IC, Kruit MC, Ahmed SF, Pereira AM, Van Furth WR & Biermasz NR 2021 Outcome squares integrating efficacy and safety, as applied to functioning pituitary adenoma surgery. *Journal of Clinical Endocrinology and Metabolism* **106** e3300–e3311. (https://doi.org/10.1210/clinem/dgab138)

Dekkers OM, Lagro J, Burman P, Jørgensen JO, Romijn JA & Pereira AM 2010 Recurrence of hyperprolactinemia after withdrawal of dopamine agonists: systematic review and meta-analysis. *Journal of Clinical Endocrinology and Metabolism* **95** 43–51. (https://doi.org/10.1210/jc.2009-1238)

Dogansen SC, Cikrikcili U, Oruk G, Kutbay NO, Tanrikulu S, Hekimsoy Z, Hadzalic A, Gorar S, Omma T, Mert M, *et al.* 2019 Dopamine agonist-induced impulse control disorders in patients with prolactinoma: a cross-sectional multicenter study. *Journal of Clinical Endocrinology and Metabolism* **104** 2527–2534. (https://doi.org/10.1210/jc.2018-02202)

Donoho DA & Laws Jr ER 2019 The role of surgery in the management of prolactinomas. *Neurosurgery Clinics of North America* **30** 509–514. (https://doi.org/10.1016/j.nec.2019.05.010)

Duan L, Yan H, Huang M, Zhang Y & Gu F 2017 An economic analysis of bromocriptine versus trans-sphenoidal surgery for the treatment of prolactinoma. *Journal of Craniofacial Surgery* **28** 1046–1051. (https://doi.org/10.1097/SCS.0000000000003456)

Elenkova A, Shabani R, Kalinov K & Zacharieva S 2012 Increased prevalence of subclinical cardiac valve fibrosis in patients with prolactinomas on long-term bromocriptine and cabergoline treatment. *European Journal of Endocrinology* **167** 17–25. (https://doi.org/10.1530/EJE-12-0121)

Faje A, Chunharojrith P, Nency J, Biller BM, Swearingen B & Klibanski A 2016 Dopamine agonists can reduce cystic prolactinomas. *Journal of Clinical Endocrinology and Metabolism* **101** 3709–3715. (https://doi.org/10.1210/jc.2016-2008)

Fatemi N, Dusick JR, Mattozo C, McArthur DL, Cohan P, Boscardin J, Wang C, Swerdloff RS & Kelly DF 2008 Pituitary hormonal loss and recovery after transsphenoidal adenoma removal. *Neurosurgery* **63** 709–718; discussion 718–719. (https://doi.org/10.1227/01.NEU.0000325725.77132.90)

Fernandez A, Karavitaki N & Wass JA 2010 Prevalence of pituitary adenomas: a community-based, cross-sectional study in Banbury (Oxfordshire, UK). *Clinical Endocrinology* **72** 377–382. (https://doi.org/10.1111/j.1365-2265.2009.03667.x)

Gillam MP, Molitch ME, Lombardi G & Colao A 2006 Advances in the treatment of prolactinomas. *Endocrine Reviews* **27** 485–534. (https://doi.org/10.1210/er.2005-9998)

Herzog A, Minne H & Ziegler R 1989 Retroperitoneal fibrosis in a patient with macroprolactinoma treated with bromocriptine. *BMJ* **298** 1315. (https://doi.org/10.1136/bmj.298.6683.1315-a)

Honegger J, Nasi-Kordhishti I, Aboutaha N & Giese S 2020 Surgery for prolactinomas: a better choice? *Pituitary* **23** 45–51. (https://doi.org/10.1007/s11102-019-01016-z)

Ioachimescu AG, Fleseriu M, Hoffman AR, Vaughan III TB & Katznelson L 2019 Psychological effects of dopamine agonist treatment in patients with hyperprolactinemia and prolactin-secreting adenomas. *European Journal of Endocrinology* **180** 31–40. (https://doi.org/10.1530/EJE-18-0682)

Iyer P & Molitch ME Positive prolactin response to bromocriptine in 2 patients with cabergoline-resistant prolactinomas 2011. *Endocrine Practice* **17** e55–e58. (https://doi.org/10.4158/EP10369.CR)

Jarzynska A, Khan HH & Chandran S 2019 A case of retroperitoneal fibrosis on low dose cabergoline. In *Society for Endocrinology British Ecological Society 2019*. Brighton, UK: Endocrine Abstracts. (https://doi.org/10.1530/endoabs.65.P312)

Jethwa PR, Patel TD, Hajart AF, Eloy JA, Couldwell WT & Liu JK 2016 Cost-effectiveness analysis of microscopic and endoscopic transsphenoidal surgery versus medical therapy in the management of microprolactinoma in the United States. *World Neurosurgery* **87** 65–76. (https://doi.org/10.1016/j.wneu.2015.10.090)

Kars M, Delgado V, Holman ER, Feelders RA, Smit JW, Romijn JA, Bax JJ & Pereira AM 2008 Aortic valve calcification and mild tricuspid regurgitation but no clinical heart disease after 8 years of dopamine agonist therapy for prolactinoma. *Journal of Clinical Endocrinology and Metabolism* **93** 3348–3356. (https://doi.org/10.1210/jc.2007-2658)

Kars M, Pereira AM, Smit JW & Romijn JA 2009 Long-term outcome of patients with macroprolactinomas initially treated with dopamine agonists. *European Journal of Internal Medicine* **20** 387–393. (https://doi.org/10.1016/j.ejim.2008.11.012)

Karunakaran S, Page RC & Wass JA 2001 The effect of the menopause on prolactin levels in patients with hyperprolactinaemia. *Clinical Endocrinology* **54** 295–300. (https://doi.org/10.1046/j.1365-2265.2001.01190.x)

Korali Z, Wittchen HU, Pfister H, Hofler M, Oefelein W & Stalla GK 2003 Are patients with pituitary adenomas at an increased risk of mental disorders? *Acta Psychiatrica Scandinavica* **107** 60–68. (https://doi.org/10.1034/j.1600-0447.2003.02383.x)

Kreutzer J, Buslei R, Wallaschofski H, Hofmann B, Nimsky C, Fahlbusch R & Buchfelder M 2008 Operative treatment of prolactinomas: indications and results in a current consecutive series of 212 patients. *European Journal of Endocrinology* **158** 11–18. (https://doi.org/10.1530/EJE-07-0248)

Landolt AM, Keller PJ, Froesch ER & Mueller J 1982 Bromocriptine: does it jeopardise the result of later surgery for prolactinomas? *Lancet* **2** 657–658. (https://doi.org/10.1016/s0140-6736(82)92756-8)

Lee MS, Song HC, An H, Yang J, Ko YH, Jung IK & Joe SH 2010 Effect of bromocriptine on antipsychotic drug-induced hyperprolactinemia: eight-week randomized, single-blind, placebo-controlled, multicenter study. *Psychiatry and Clinical Neurosciences* **64** 19–27. (https://doi.org/10.1111/j.1440-1819.2009.02032.x)

Lopes MBS 2017 The 2017 World Health Organization classification of tumors of the pituitary gland: a summary. *Acta Neuropathologica* **134** 521–535. (https://doi.org/10.1007/s00401-017-1769-8)

Luger A, Broersen LHA, Biermasz NR, Biller BMK, Buchfelder M, Chanson P, Jorgensen JOL, Kelestimur F, Llahana S, Maiter D, *et al.* 2021 ESE clinical practice guideline on functioning and nonfunctioning pituitary adenomas in pregnancy. *European Journal of Endocrinology* **185** G1–G33. (https://doi.org/10.1530/EJE-21-0462)

Martinkova J, Trejbalova L, Sasikova M, Benetin J & Valkovic P 2011 Impulse control disorders associated with dopaminergic medication in patients with pituitary adenomas. *Clinical Neuropharmacology* **34** 179–181. (https://doi.org/10.1097/WNF.0b013e3182281b2f)

Mattogno PP, D'Alessandris QG, Chiloiro S, Bianchi A, Giampietro A, Pontecorvi A, De Marinis L, Olivi A, Anile C & Lauretti L 2021 Reappraising the role of trans-sphenoidal surgery in prolactin-secreting pituitary tumors. *Cancers* **13** 3252. (https://doi.org/10.3390/cancers13133252)

McCormack A, Dekkers OM, Petersenn S, Popovic V, Trouillas J, Raverot G & Burman P 2018 Treatment of aggressive pituitary tumours and

carcinomas: results of a European Society of Endocrinology (ESE) survey 2016. *European Journal of Endocrinology* **178** 265–276. (https://doi.org/10.1530/EJE-17-0933)

Melis GB, Gambacciani M, Paoletti AM, Mais V, Sghedoni D & Fioretti P 1989 Reduction in the size of prolactin-producing pituitary tumor after cabergoline administration. *Fertility and Sterility* **52** 412–415. (https://doi.org/10.1016/s0015-0282(16)60909-3)

Melmed S, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, Schlechte JA & Wass JA 2011 Diagnosis and treatment of hyperprolactinemia: an endocrine society clinical practice guideline. *Journal of Clinical Endocrinology and Metabolism* **96** 273–288. (https://doi.org/10.1210/jc.2010-1692)

Menucci M, Quiñones-Hinojosa A, Burger P & Salvatori R 2011 Effect of dopaminergic drug treatment on surgical findings in prolactinomas. *Pituitary* **14** 68–74. (https://doi.org/10.1007/s11102-010-0261-4)

Milton CK, Lee BJ, Voronovich ZA, Conner AK, McKinney KA, El Rassi ET, Lim J & Glenn CA 2021 Prolactinoma extension as a contributing factor in dopamine agonist-induced CSF rhinorrhea: a systematic review of the literature. *British Journal of Neurosurgery* [epub]. (https://doi.org/10.1080/02688697.2021.1903389)

Molitch ME Pharmacologic resistance in prolactinoma patients 2005. *Pituitary* **8** 43–52. (https://doi.org/10.1007/s11102-005-5085-2)

Moore TJ, Glenmullen J & Mattison DR 2014 Reports of pathological gambling, hypersexuality, and compulsive shopping associated with dopamine receptor agonist drugs. *JAMA Internal Medicine* **174** 1930–1933. (https://doi.org/10.1001/jamainternmed.2014.5262)

Naliato EC, Violante AH, Caldas D, Farias ML, Bussade I, Lamounier Filho A, Loureiro CR, Fontes R, Schrank Y, Loures T, *et al.* 2008 Bone density in women with prolactinoma treated with dopamine agonists. *Pituitary* **11** 21–28. (https://doi.org/10.1007/s11102-007-0064-4)

Netea-Maier RT, Van Lindert EJ, Timmers H, Schakenraad EL, Grotenhuis JA & Hermus AR 2006 Cerebrospinal fluid leakage as complication of treatment with cabergoline for macroprolactinomas. *Journal of Endocrinological Investigation* **29** 1001–1005. (https://doi.org/10.1007/BF03349214)

Ono M, Miki N, Kawamata T, Makino R, Amano K, Seki T, Kubo O, Hori T & Takano K 2008 Prospective study of high-dose cabergoline treatment of prolactinomas in 150 patients. *Journal of Clinical Endocrinology and Metabolism* **93** 4721–4727. (https://doi.org/10.1210/jc.2007-2758)

Papathomas TG, Gaal J, Corssmit EP, Oudijk L, Korpershoek E, Heimdal K, Bayley JP, Morreau H, Van Dooren M, Papaspyrou K, *et al.* 2014 Non-pheochromocytoma (PCC)/paraganglioma (PGL) tumors in patients with succinate dehydrogenase-related PCC-PGL syndromes: a clinicopathological and molecular analysis. *European Journal of Endocrinology* **170** 1–12. (https://doi.org/10.1530/EJE-13-0623)

Park JY, Choi W, Hong AR, Yoon JH, Kim HK, Jang WY, Jung S & Kang HC 2021 Surgery is a safe, effective first-line treatment modality for noninvasive prolactinomas. *Pituitary* **24** 955–963. (https://doi.org/10.1007/s11102-021-01168-x)

Perovich RM, Lieberman JA, Fleischhacker WW & Alvir J 1989 The behavioral toxicity of bromocriptine in patients with psychiatric illness. *Journal of Clinical Psychopharmacology* **9** 417–422. (https://doi.org/10.1097/00004714-198912000-00006)

Pinzone JJ, Katznelson L, Danila DC, Pauler DK, Miller CS & Klibanski A 2000 Primary medical therapy of micro-and macroprolactinomas in men. *Journal of Clinical Endocrinology and Metabolism* **85** 3053–3057. (https://doi.org/10.1210/jcem.85.9.6798)

Primeau V, Raftopoulos C & Maiter D 2012 Outcomes of transsphenoidal surgery in prolactinomas: improvement of hormonal control in dopamine agonist-resistant patients. *European Journal of Endocrinology* **166** 779–786. (https://doi.org/10.1530/EJE-11-1000)

Rocco A, Mori F, Baldelli R, Aversa A, Munizzi MR, Nardone MR, Fabbrini A & Falaschi P 1993 Effect of chronic bromocriptine treatment on psychological profile of patients with PRL-secreting pituitary adenomas. *Psychoneuroendocrinology* **18** 57–66. (https://doi.org/10.1016/0306-4530(93)90055-p)

Schade R, Andersohn F, Suissa S, Haverkamp W & Garbe E 2007 Dopamine agonists and the risk of cardiac-valve regurgitation. *New England Journal of Medicine* **356** 29–38. (https://doi.org/10.1056/NEJMoa062222)

Snellen M, Power J, Blankley G & Galbally M 2016 Pharmacological lactation suppression with D2 receptor agonists and risk of postpartum psychosis: a systematic review. *Australian and New Zealand Journal of Obstetrics and Gynaecology* **56** 336–340. (https://doi.org/10.1111/ajo.12479)

Song YJ, Chen MT, Lian W, Xing B, Yao Y, Feng M & Wang RZ 2017 Surgical treatment for male prolactinoma: a retrospective study of 184 cases. *Medicine* **96** e5833. (https://doi.org/10.1097/MD.0000000000005833)

Steeds R, Stiles C, Sharma V, Chambers J, Lloyd G & Drake W 2019 Echocardiography and monitoring patients receiving dopamine agonist therapy for hyperprolactinaemia: a joint position statement of the British Society of Echocardiography, the British Heart Valve Society and the Society for Endocrinology. *Clinical Endocrinology* **90** 662–669. (https://doi.org/10.1111/cen.13940)

Stiles CE, Tetteh-Wayoe ET, Bestwick J, Steeds RP & Drake WM 2018 A meta-analysis of the prevalence of cardiac valvulopathy in hyperprolactinemic patients treated with cabergoline. *Journal of Clinical Endocrinology and Metabolism* **104** 523–538. (https://doi.org/10.1210/jc.2018-01071)

Stiles CE, Lloyd G, Bhattacharyya S, Steeds RP, Boomla K, Bestwick JP & Drake WM 2021 Incidence of cabergoline-associated valvulopathy in primary care patients with prolactinoma using hard cardiac endpoints. *Journal of Clinical Endocrinology and Metabolism* **106** e711–e720. (https://doi.org/10.1210/clinem/dgaa882)

Sughrue ME, Chang EF, Tyrell JB, Kunwar S, Wilson CB & Blevins Jr LS 2009 Pre-operative dopamine agonist therapy improves post-operative tumor control following prolactinoma resection. *Pituitary* **12** 158–164. (https://doi.org/10.1007/s11102-008-0135-1)

Suliman SG, Gurlek A, Byrne JV, Sullivan N, Thanabalasingham G, Cudlip S, Ansorge O & Wass JA 2007 Nonsurgical cerebrospinal fluid rhinorrhea in invasive macroprolactinoma: incidence, radiological, and clinicopathological features. *Journal of Clinical Endocrinology and Metabolism* **92** 3829–3835. (https://doi.org/10.1210/jc.2007-0373)

Tampourlou M, Trifanescu R, Paluzzi A, Ahmed SK & Karavitaki N 2016 THERAPY OF ENDOCRINE DISEASE: Surgery in microprolactinomas: effectiveness and risks based on contemporary literature. *European Journal of Endocrinology* **175** R89–R96. (https://doi.org/10.1530/EJE-16-0087)

Turner TH, Cookson JC, Wass JA, Drury PL, Price PA & Besser GM 1984 Psychotic reactions during treatment of pituitary tumours with dopamine agonists. *BMJ* **289** 1101–1103. (https://doi.org/10.1136/bmj.289.6452.1101)

Vallette S, Serri K, Rivera J, Santagata P, Delorme S, Garfield N, Kahtani N, Beauregard H, Aris-Jilwan N, Houde G, *et al.* 2009 Long-term cabergoline therapy is not associated with valvular heart disease in patients with prolactinomas. *Pituitary* **12** 153–157. (https://doi.org/10.1007/s11102-008-0134-2)

Verhelst J, Abs R, Maiter D, Van Den Bruel A, Vandeweghe M, Velkeniers B, Mockel J, Lamberigts G, Petrossians P, Coremans P, *et al.* 1999 Cabergoline in the treatment of hyperprolactinemia: a study in 455 patients. *Journal of Clinical Endocrinology and Metabolism* **84** 2518–2522. (https://doi.org/10.1210/jcem.84.7.5810)

Vermeulen E, D'Haens J, Stadnik T, Unuane D, Barbe K, Van Velthoven V & Gläsker S 2020 Predictors of dopamine agonist resistance in prolactinoma patients. *BMC Endocrine Disorders* **20** 68. (https://doi.org/10.1186/s12902-020-0543-4)

Vroonen L, Jaffrain-Rea ML, Petrossians P, Tamagno G, Chanson P, Vilar L, Borson-Chazot F, Naves LA, Brue T, Gatta B, *et al.* 2012 Prolactinomas resistant to standard doses of cabergoline: a multicenter study of 92

patients. *European Journal of Endocrinology* **167** 651–662. (https://doi.org/10.1530/EJE-12-0236)

Wang F, Gao H, Li C, Bai J, Lu R, Cao L, Wu Y, Hong L, Wu Y, Lan X, *et al.* 2014 Low levels of PRB3 mRNA are associated with dopamine-agonist resistance and tumor recurrence in prolactinomas. *Journal of Neuro-Oncology* **116** 83–88. (https://doi.org/10.1007/s11060-013-1276-2)

Wass JA, Moult PJ, Thorner MO, Dacie JE, Charlesworth M, Jones AE & Besser GM 1979 Reduction of pituitary-tumour size in patients with prolactinomas and acromegaly treated with bromocriptine with or without radiotherapy. *Lancet* **2** 66–69. (https://doi.org/10.1016/s0140-6736(79)90120-x)

Webster J 1996 A comparative review of the tolerability profiles of dopamine agonists in the treatment of hyperprolactinaemia and inhibition of lactation. *Drug Safety* **14** 228–238. (https://doi.org/10.2165/00002018-199614040-00003)

Webster J, Piscitelli G, Polli A, Ferrari CI, Ismail I & Scanlon MF 1994 A comparison of cabergoline and bromocriptine in the treatment of hyperprolactinemic amenorrhea. *New England Journal of Medicine* **331** 904–909. (https://doi.org/10.1056/NEJM199410063311403)

Weintraub D, Hoops S, Shea JA, Lyons KE, Pahwa R, Driver-Dunckley ED, Adler CH, Potenza MN, Miyasaki J, Siderowf AD, *et al.* 2009 Validation of the questionnaire for impulsive-compulsive disorders in Parkinson's disease. *Movement Disorders* **24** 1461–1467. (https://doi.org/10.1002/mds.22571)

Weiss HD, Hirsch ES, Williams JR, Swearengin L & Marsh L 2010 Detection of impulse control disorders in Parkinson disease patients. *Neurologist* **16** 406–407. (https://doi.org/10.1097/NRL.0b013e3181e8868b)

Wright K, Chaker L, Pacione D, Sam K, Feelders R, Xia Y & Agrawal N 2021 Determinants of surgical remission in prolactinomas: a systematic review and meta-analysis. *World Neurosurgery* **154** e349–e369. (https://doi.org/10.1016/j.wneu.2021.07.035)

Wu ZB, Zheng WM, Su ZP, Chen Y, Wu JS, Wang CD, Lin C, Zeng YJ & Zhuge QC 2010 Expression of D2RmRNA isoforms and ERmRNA isoforms in prolactinomas: correlation with the response to bromocriptine and with tumor biological behavior. *Journal of Neuro-Oncology* **99** 25–32. (https://doi.org/10.1007/s11060-009-0107-y)

Xekouki P, Szarek E, Bullova P, Giubellino A, Quezado M, Mastroyannis SA, Mastorakos P, Wassif CA, Raygada M, Rentia N, *et al.* 2015 Pituitary adenoma with paraganglioma/pheochromocytoma (3PAs) and succinate dehydrogenase defects in humans and mice. *Journal of Clinical Endocrinology and Metabolism* **100** E710–E719. (https://doi.org/10.1210/jc.2014-4297)

Yagnik KJ, Erickson D, Bancos I, Atkinson JLD, Choby G, Peris-Celda M & Van Gompel JJ 2021 Surgical outcomes of medically failed prolactinomas: a systematic review and meta-analysis. *Pituitary* **24** 978–988. (https://doi.org/10.1007/s11102-021-01188-7)

Zamanipoor Najafabadi AH, Zandbergen IM, De Vries F, Broersen LHA, Van Den Akker-Van Marle ME, Pereira AM, Peul WC, Dekkers OM, Van Furth WR & Biermasz NR 2020 Surgery as a viable alternative first-line treatment for prolactinoma patients. A systematic review and meta-analysis. *Journal of Clinical Endocrinology and Metabolism* **105** 105.e32–105.e41. (https://doi.org/10.1210/clinem/dgz144)

Zandbergen IM, Zamanipoor Najafabadi AH, Pelsma ICM, Van Den Akker-Van Marle ME, Bisschop PHLT, Boogaarts HDJ, Van Bon AC, Burhani B, Le Cessie S, Dekkers OM, *et al.* 2021 The PRolaCT studies – a study protocol for a combined randomised clinical trial and observational cohort study design in prolactinoma. *Trials* **22** 653. (https://doi.org/10.1186/s13063-021-05604-y)

Zielinski G, Ozdarski M, Maksymowicz M, Szamotulska K & Witek P 2020 Prolactinomas: prognostic factors of early remission after transsphenoidal surgery. *Frontiers in Endocrinology* **11** 439–439. (https://doi.org/10.3389/fendo.2020.00439)

Zygourakis CC, Imber BS, Chen R, Han SJ, Blevins L, Molinaro A, Kahn JG & Aghi MK 2017 Cost-effectiveness analysis of surgical versus medical treatment of prolactinomas. *Journal of Neurological Surgery: Part B, Skull Base* **78** 125–131. (https://doi.org/10.1055/s-0036-1592193)

Received in final form 2 April 2022
Accepted 20 April 2022
Accepted Manuscript published online 21 April 2022