New information has been provided over the last years regarding treatment of prolactinomas and will be reviewed in this update. Medical treatment with a dopamine agonist (DA) remains the cornerstone of therapy and cabergoline is the first choice, due to its high efficacy and good tolerability profile. Prolonged remission after discontinuation of DA may be observed if treatment has been given for at least two years, normal prolactin has been obtained with a low dose and tumoral diameter has been reduced by at least 50%. Although the risk of restrictive cardiac valve disease is low at the standard doses of cabergoline used for the treatment of hyperprolactinaemia, long-term echocardiographic surveillance is however indicated, in particular in resistant patients who need higher doses of cabergoline (2.0 mg/week or more). Neurosurgical treatment of prolactinomas is less effective than medical therapy and recurrence of hyperprolactinaemia is frequent. Besides classical indications such as drug intolerance, resistance or acute complications, new indications have emerged such as young patients with a high likelihood of complete tumour resection and who do not wish to take prolonged medical treatment, or patients who require high doses of cabergoline, in whom surgical debulking may significantly improve postoperative hormonal control. Finally, recent data indicate that cabergoline is safe for the developing foetus and for the mother, and therefore should not be preventively withdrawn in a young woman wishing to become pregnant.

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Prolactinomas are the most frequent pituitary tumours representing 50 to 66% of all symptomatic pituitary adenomas. Recent epidemiological studies have shown a high prevalence in the general population varying from 30 to 50 per 100,000 with a median age of 30 years at diagnosis [1–3]. Microadenomas are about four to five fold more frequent than macroadenomas, which are defined by a maximal diameter greater than 10 mm. There is also a net female predominance of prolactin-secreting tumours (and of hyperprolactinaemia in general), with a male to female ratio of 1:9 [4,5]. Prolactinomas in men are characterized by a larger size and a high frequency of compressive symptoms at diagnosis (even at a young age), and they are more frequently...
invasive and resistant to medical therapy [6]. In this paper, we will review the most recent advances in the management of prolactin-secreting tumours.

1. Diagnosis of prolactinomas

The diagnosis of prolactinoma is essentially based on the repeated observation of high serum prolactin concentrations together with the radiologic evidence of a pituitary tumour, usually at magnetic resonance imaging (MRI). While diagnosis is usually straightforward for macroprolactinomas, in which prolactin levels almost invariably exceed 200 µg/L (5000 mU/L) [5,7,8], it may be more difficult in the cases of microprolactinomas. Symptoms of hyperprolactinaemia are indeed not specific of a tumoral origin, pituitary incidentalomas are not infrequent, and several other causes of moderate hyperprolactinaemia must be ruled out, such as drugs, renal failure, hypothyroidism, pregnancy, or any disruption or compression of the pituitary stalk, for example by a non prolactin-secreting pituitary or parasellar mass [4,7–10]. Assessment for macroprolactin is also recommended in patients with asymptomatic hyperprolactinaemia [9]. Noteworthily, in patients with a histologically confirmed non-functioning pituitary macroadenoma, prolactin concentrations usually remain lower than 130 µg/L [11,12]. In case of doubt (i.e. a cystic or necrotic pituitary macroadenoma with intermediate levels of prolactin between 100 and 200 µg/L), a therapeutic trial with dopamine agonists may be helpful. The observation of significant tumor shrinkage under medical treatment is a strong argument in favour of a prolactin-secreting adenoma (Fig. 1).

2. Indications for treatment of prolactinomas

Ideally, treatment of prolactinomas should aim at both preventing any tumoral complications and controlling all symptoms related to prolactin excess, such as hypogonadism and infertility [7,9]. Practically, therapeutic objectives are dependent on age, gender and size of the tumour. Microprolactinomas are most frequently seen in young women and have a very low risk of tumoral growth, less than 7% of them growing in the absence of any treatment [4,7–9]. Therefore, the main therapeutic goal here will be prolactin normalization to abrogate related symptoms such as amenorrhea, galactorrhea or loss of libido) and to restore normal gonadal function and fertility [7,8]. Surveillance
without any treatment may also be proposed to asymptomatic peri- or post-menopausal women, whereas hypogonadal pre-menopausal women with microadenomas who do not desire pregnancy might be treated with oral contraceptives instead of DA therapy [9]. Indeed, patients treated with oral contraceptives or estrogen/progesterone replacement for 2 years have not shown an increase of tumour size [13,14].

In contrast, macroadenomas have a more significant growth potential and induce mass symptoms in about 50% of the cases [6–8]. Some tumours may also show signs of aggressiveness, especially in men where cavernous sinus invasion is frequently observed [15] and potentially complicated by oculomotor nerve palsy. When the tumour mass extend beyond the suprasellar region towards the temporal lobes, temporal epilepsy may also occur in 20–25%, but is often difficult to recognize as symptoms are atypical (olfactory hallucinations, disorientation, absence, oral automatism, . . .) [16]. Treatment of macroadenomas is therefore mandatory and should aim at both tumoral and hormonal control.

3. Medical therapy with dopamine agonists (DAs)

Since the introduction of bromocriptine (BRC) more than 35 years ago [17], DAs have convincingly demonstrated their remarkable efficacy for both micro- and macroadenomas, thus remaining in 2012, the undisputed primary treatment of this affection [7–10,18]. A very large majority of patients with a prolactinoma treated with DAs (70–90% depending on the study and the type of DA used) show indeed normalization of prolactin levels, resolution of amenorrhea, galactorrhoea, and infertility, reduction in tumour size and disappearance of mass effects [9]. Even in the case of large adenomas with suprasellar extension, cabergoline therapy induces in 80–90% of patients an improvement of visual field, which is often rapid, occurring within a few days following drug onset.

3.1. Which dopamine agonist to use?

Cabergoline, a long-acting ergot-derivative, is nowadays used in preference to other DAs because it has a higher efficacy in normalizing prolactin levels and reducing tumour size, has a better tolerance and is a more convenient drug to take on a chronic basis [7–10,18–20]. Cabergoline is usually administered once to twice weekly, at a mean dose of 0.5 mg/week for microprolactinomas and 1.0 mg/week for macroadenomas [7,20,21]. The most frequent side effects are headaches, gastrointestinal symptoms, dizziness, nasal congestion and peripheral vasoasospasm [7–10]. Most of these symptoms wane with time and they rarely require drug discontinuation. In a large multicentre study [19], only 3% of women treated with cabergoline did stop drug intake because of side effects, as opposed to 12% in the group treated with bromocriptine. Other studies have confirmed these findings and also showed that a significant proportion of patients who were resistant to bromocriptine responded well to cabergoline [20,21]. In case of marked intolerance to both bromocriptine and cabergoline, it is worth to try quinagolide, another dopamine agonist, which is a non-ergot derivative and express a much higher affinity for the type 2 dopamine receptors (D2) than for D1 or serotoninergic (5-HT) receptors in the brain [22]. Consequently, quinagolide has often less gastro-intestinal and vascular side effects.

3.2. Efficacy of cabergoline on prolactin (PRL) concentrations and tumour size

In a multicentre study of 455 patients, cabergoline normalized prolactin levels in 92% of patients with microprolactinomas and in 77% of patients with macroadenomas [20]. Furthermore, 91% of patients who were intolerant to BRC and 70% of patients resistant to this drug showed PRL normalization under CAB. Only seven out of the 455 patients (1.5%) were resistant to medical treatment [20], a proportion reaching 5–6% when only macroadenomas are considered [23]. About 75% of the patients bearing a macroadenoma will also show a significant tumoral response to CAB, which may be complete or partial (i.e. a reduction of maximal diameter by at least 30%) [24–26].

3.3. Medical treatment: for how long?

Because of possible cardiac side effects with the chronic use of high doses of CAB (vide infra), significant cost of long-term medical treatment, and poor compliance in some patients, it may be interesting to consider withdrawal of dopamine agonist therapy. This seems indeed possible in well-defined conditions, without recurrence of hyperprolactinaemia [9,27]. A few studies have reported high remission rates after DA withdrawal [28,29], provided that strict criteria were observed: at least two years of medical treatment, normalisation of prolactin with a low dose of cabergoline, and disappearance of or a more than 50% reduction in the maximal diameter of the pituitary tumour. When such criteria were met, about 70% of microprolactinomas and 45% of macroadenomas did not recur after cessation of cabergoline treatment. Other studies have however reported less optimistic remission rates. A recent meta-analysis including a total of 19 studies and 743 patients showed a global remission rate of only 21% of all prolactinomas after DA withdrawal [27]. Better results were observed however in patients with a microprolactinoma (25%) than macroadenomas (16%), in patients treated for at least 2 years (34%) and in those treated with cabergoline (35%) rather than bromocriptine (20%).

Current guidelines [9,30] recommend therefore to discontinue treatment with reasonably good chances of remission if:

- the patient has been continuously treated for at least two years;
- a low normal prolactin concentration is obtained with a low dose of DA (≤ 0.5 mg/week of cabergoline);
- a reduction in the maximal tumoral diameter of at least 50% has been observed;
- there is no cavernous sinus invasion.

These patients require long-term follow-up with PRL measurements every 3 months for the first year and annually thereafter, and MRI if prolactin increases above normal
levels [30,31]. The majority of relapses occur within the first year following treatment withdrawal and in one study the risk of recurrence was 18% per mm of residual tumour mass [29]. In women with asymptomatic microprolactinomas, it may also be possible to discontinue dopaminergic therapy when menopause occurs [9].

3.4. Long-term side effects of cabergoline therapy

For many years, livelong treatment with dopamine agonists has been considered without any particular fear and no harmful side effect was expected once medical treatment had been initially well tolerated [7,8]. Over the last 5 years, attention has been drawn to the possibility of severe cardiac complications with the chronic use of high doses of some dopamine agonists including pergolide and cabergoline and, to a lesser extent, bromocriptine [32–35]. Two studies [32,33] have indeed reported a significant risk of moderate-to-severe cardiac valve regurgitation in patients with Parkinson’s disease receiving high doses of DAs, and in particular a five-fold increased risk in those treated with cabergoline at a dose of at least 3 mg daily. These valvular abnormalities usually include typical fibrotic thickening of the leaflets (Fig. 2), calcifications and reduction of the valve tenting area (an index of valve closure ability). These alterations involve mainly the tricuspid, mitral and aortic valves, inducing regurgitation, pulmonary hypertension and eventually cardiac failure, as previously described in carcinoid syndrome or as a consequence of prolonged intake of drugs with serotoninergic activity [34].

As the cardiac risk seems to be related to the intrinsic agonist properties of the DA for the serotoninergic cardiac 5-HT-2B receptors [35], it is more important for pergolide and cabergoline than for bromocriptine and likely negligible for quinagolide which has a very low serotoninergic activity in vitro [35,36].

Since 2007, several retrospective cross-sectional studies have been conducted to search for an increased prevalence of cardiac complications in patients treated with BRC or CAB for a prolactinoma [37–48]. Most of them have found no evidence of clinically significant valvular disease in over 700 patients receiving standard doses of cabergoline and the only study that did report a high incidence of tricuspid regurgitation in Table 1

<table>
<thead>
<tr>
<th>Authors</th>
<th>Reference</th>
<th>Number of patients</th>
<th>Number of controls</th>
<th>Mean or median dose of cabergoline (mg)</th>
<th>Median duration of treatment (months)</th>
<th>↑ risk of valvulopathy</th>
<th>Thickening/calcifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lancellotti et al.</td>
<td>[37]</td>
<td>102</td>
<td>51</td>
<td>204</td>
<td>79</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Bogazzi et al.</td>
<td>[38]</td>
<td>100</td>
<td>100</td>
<td>279</td>
<td>67</td>
<td>NS</td>
<td>NA</td>
</tr>
<tr>
<td>Vallette et al.</td>
<td>[39]</td>
<td>70</td>
<td>70</td>
<td>282</td>
<td>55</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Kars et al.</td>
<td>[40]</td>
<td>47</td>
<td>78</td>
<td>363</td>
<td>62</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Colao et al.</td>
<td>[41]</td>
<td>50</td>
<td>50</td>
<td>414</td>
<td>NA</td>
<td>Moderate TR</td>
<td>NS</td>
</tr>
<tr>
<td>Wakil et al.</td>
<td>[42]</td>
<td>44</td>
<td>566</td>
<td>311</td>
<td>45</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Nachitgall et al.</td>
<td>[43]</td>
<td>100</td>
<td>100</td>
<td>253</td>
<td>48</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Herring et al.</td>
<td>[44]</td>
<td>50</td>
<td>50</td>
<td>443</td>
<td>78 ± 6</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Lafeber et al.</td>
<td>[45]</td>
<td>117</td>
<td>117</td>
<td></td>
<td></td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Tan et al.</td>
<td>[46]</td>
<td>72</td>
<td>72</td>
<td>126</td>
<td>53</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>752</td>
<td>1254</td>
<td></td>
<td></td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

TR: tricuspid regurgitation; NA: not available; NS: not significant.
Resistance to dopamine agonist treatment is usually defined by a failure to achieve normal prolactin levels on maximally tolerated doses of DAs and/or failure to achieve a 50% reduction in tumour size [8,9]. Some patients may have discordant responses, that is, reduction in tumour size without prolactin normalization and vice versa, while others may be partially resistant, requiring higher than standard doses of cabergoline (i.e., ≥ 2.0 mg/week) to achieve a full response [21,52–54]. Resistance is rare in microprolactinomas, more frequent in cases of macroprolactinomas (3–6%), and quite characteristic of invasive tumours and male gender [15,21]. Although a decreased expression of D2 receptor has been evidenced in resistant prolactinomas, the mechanisms are still not completely understood [53].

Several therapeutic options may be considered in case of DA resistance. If the patient is treated with another dopamine agonist, it is recommended to switch to cabergoline. About 70–80% of patients resistant to bromocriptine may indeed achieve prolactin normalization on cabergoline [9,20]. Next, standard dose of cabergoline may be increased stepwise to maximal tolerable doses. In a recent Japanese study [52], increasing the cabergoline dose up to 12 mg/week allowed to overcome DA resistance in a few patients, but perhaps at the price of future undesirable side effects. Therefore, in the absence of any intolerable symptoms or emergency situation, we rather recommend to keep the maximal dose at 3.5 mg/week, which may in turn lead to hormonal control in half of the cases after a time interval of 15 to 72 months [23]. Finally, the resistant prolactinoma is also a valuable indication for transsphenoidal neurosurgery, aiming at large tumoral debulking and improved postoperative medical control (vide infra). For patients who fail surgical treatment and harbour aggressive prolactinomas, radiation therapy may be a last option [9]. Although radiotherapy may control tumour growth, it may require up to 20 years for maximal effects to be achieved and normalization of hyperprolactinaemia occurs in only one third of the cases [8]. Furthermore, irradiation is associated with side effects including pituitary insufficiency, cognitive disorders, cerebrovascular alterations and rarely second tumour formation [55].

5. The malignant prolactinoma

A malignant prolactinoma is defined as a prolactin-secreting tumour that exhibits metastases within or outside the central nervous system, as it is not possible to differentiate histologically between carcinoma and adenoma [9]. They are fortunately very rare tumours for which treatment options have remained very limited until recently. Debunking surgery, radiotherapy and maximal doses of dopamine agonists have been proposed to these patients but have shown very poor efficacy, with a median survival time of about one year [56,57].

Several reports have recently outlined a significant efficacy of temozolomide, an orally-administered alkylating agent used in the treatment of gliomas, in reducing prolactin levels and controlling tumour growth in about 50% of pituitary carcinomas [58–60]. Interestingly, the overall response to chemotherapy is already predicted by the response obtained after three cycles of drug administration [60].

6. Surgical indications for prolactinomas

Although not indicated as primary treatment of prolactinomas, transsphenoidal surgery should be offered to symptomatic patients who cannot tolerate any of the currently available dopamine agonists or who are not responsive to maximally tolerated doses of DAs [9]. Surgery may also be required in patients with acute complications such as apoplexy or cerebrospinal fluid (CSF) leak, which may sometimes result from a dramatic tumour reduction under medical therapy. It is essential that the surgical procedure is performed by an experienced pituitary

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Table 2
Outcome of transsphenoidal surgery for micro- and macroprolactinomas (main series published since 2000).

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Reference</th>
<th>Number of patients</th>
<th>M/F</th>
<th>% remission for microprolactinomas</th>
<th>% remission for macroprolactinomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Losa et al.</td>
<td>2002</td>
<td>[61]</td>
<td>120</td>
<td>27/93</td>
<td>46/59 (78%)</td>
<td>31/61 (51%)</td>
</tr>
<tr>
<td>Amar et al.</td>
<td>2002</td>
<td>[62]</td>
<td>222</td>
<td>NA</td>
<td>142/156 (91%)</td>
<td>22/66 (33%)</td>
</tr>
<tr>
<td>Hamilton et al.</td>
<td>2005</td>
<td>[63]</td>
<td>79</td>
<td>30/49</td>
<td>18/25 (72%)</td>
<td>16/54 (30%)</td>
</tr>
<tr>
<td>Kreutzer et al.</td>
<td>2008</td>
<td>[64]</td>
<td>212</td>
<td>79/133</td>
<td>47/56 (84%)</td>
<td>54/156 (34.6%)</td>
</tr>
<tr>
<td>Raverot et al.</td>
<td>2010</td>
<td>[65]</td>
<td>94</td>
<td>62/32</td>
<td>40/43 (93%)</td>
<td>20/51 (39%)</td>
</tr>
</tbody>
</table>

Total          | 727  | 293/339                           | 143/388                         |

NA: information not available.
neurosurgeon, in order to optimize cure rate and minimize the risk of complications, including hypopituitarism, diabetes insipidus, CSF leak and local infection [9,10]. In such centres, immediate postoperative remission rates of 70–90% have been reported for microprolactinomas and of 30–50% for macroprolactinomas [61–65] (Table 2). Later recurrence of hyperprolactinaemia is however frequent, occurring in 10–50% of patients depending on the study [61–68] and is predicted by high preoperative prolactin level and tumour invasiveness at the time of surgery [64,66–68].

Other surgical indications of prolactinomas have emerged over the recent years. Young patients with a high likelihood of complete tumour resection and who do not wish to take prolonged medical treatment are good candidates for surgery, as are patients with cystic tumours [64]. Patients who are partially resistant to treatment and who require higher than standard doses of cabergoline may also benefit from surgery, even though tumour resection is incomplete. We have indeed recently demonstrated that surgical debulking of prolactinomas significantly improves hormonal control with normalization of prolactin levels in half of the cases under lower postoperative doses of cabergoline [69]. Finally, a potential future indication for surgery might be the rare patients who might develop cardiac complications under chronic dopamine agonist therapy, and in whom drug withdrawal might become mandatory.

7. Prolactinoma and pregnancy

As discussed above, hyperprolactinaemia is frequently associated with anovulation and infertility in young women wishing to become pregnant and dopamine agonists will usually correct these symptoms. Two major issues arise when a pregnancy begins in a woman harbouring a prolactinoma and treated with a DA. (a) What are the effects of the medication on early foetal development before the pregnancy is diagnosed and the drug eventually stopped? (b) What are the effects of the pregnancy itself on the pituitary tumour?

7.1. Effects of dopamine agonists on the developing foetus

From a large database of over 6000 pregnancies, bromocriptine has a good safety record in this area and has not been found to cause any increase in spontaneous abortions, ectopic pregnancies or congenital malformations, with rates similar to those observed in the general population (11, 0.5 and 3%, respectively) [70–73]. Experience with the use of cabergoline has remained scarce until recently but is now accumulating. Data on exposure of the foetus or embryo during the first several weeks of pregnancy have now been reported in almost 800 cases, and no increased percentage of spontaneous miscarriage, premature delivery, multiple births or neonatal malformations [74–79]. Moreover, follow-up studies of the children for up to 12 years after foetal exposure to cabergoline did not show any physical or developmental abnormalities in about 230 children [77–79]. In contrast, quinagolide does not appear to be so safe during pregnancy [74] although it has the advantage over cabergoline to be quickly eliminated after withdrawal at pregnancy diagnosis [22].

7.2. Effects of pregnancy on prolactinoma size

The risk of symptomatic tumour enlargement during pregnancy is low for microprolactinomas (3–5%) and therefore it is recommended to stop medical treatment as soon as
Diagnosis of pregnancy is established [70,74]. Periodic checking of prolactin levels is not recommended. Visual field-testing and MRI scanning should be performed only in patients who become symptomatic. Nevertheless, if a routine MRI scan is performed in these women between 24 and 32 weeks of gestation, an increase in the size of the microadenoma is observed in about 40% of the cases, which may exceed 5 mm in about 10% [77]. There are no data to suggest that breast-feeding causes any harm on tumour growth and if needed, treatment with DA may be postponed as long as breast-feeding is desired. Interestingly enough, a significant subset of patients with a microprolactinoma may be in prolonged remission after a pregnancy, for still unknown reasons [80].

In women with a large macroadenoma without previous surgery or irradiation, the risk of symptomatic growth is much higher (25–30%) [70,74]. In some cases, continuation of the DA treatment throughout pregnancy may be discussed with an informed patient. However, in most cases, treatment will be stopped after pregnancy is diagnosed and careful follow-up is advised, including MRI without contrast injection at 5–6 months of gestation, or earlier if symptoms or visual disturbances develop. If a symptomatic tumour enlargement does occur, reinstition of the dopamine agonist is indicated rather than surgery, and we now favor the use of cabergoline in such event.

8. Conclusions

Treatment of micro- and macroprolactinomas remains nowadays essentially medical and the dopamine agonist of first choice is cabergoline, which is highly efficient and has an excellent safety and tolerability profile. Several issues regarding medical treatment have been raised however over the last years and are reviewed in this update.

First, discontinuation of DA treatment may be considered with a reasonably good chance of remission if the patient has been treated for at least two years, if normal prolactin is obtained with a low cabergoline dose, and if tumoral diameter has been reduced by at least 50%. These patients will require long-term follow-up but relapses generally occur within the first year.

At standard doses of cabergoline used for the treatment of hyperprolactinaemia (0.5–1.0 mg/week), the risk of cardiac valve disease appears to be very low. Echocardiographic surveillance is however indicated with long-term use of cabergoline, in particular in resistant patients who need higher than standard doses of cabergoline (2.0 mg/week or more) and further long-term prospective studies on this safety aspect are needed.

Neurosurgical treatment of prolactinomas is less effective than medical therapy, even in the most experienced centres, and recurrence of hyperprolactinaemia is frequent. Besides classical indications such as intolerance or resistance to DAs, or acute complications requiring surgery, new indications have emerged such as young patients with a high likelihood of complete tumour resection and who do not wish to take prolonged medical treatment, or patients who require high doses of cabergoline, in whom surgical debulking may significantly improve postoperative hormonal control.

Finally, recent data indicate that cabergoline is safe for the developing foetus and for the mother, and therefore should not be withdrawn in a young woman wishing to become pregnant, until pregnancy has begun. At the light of these recent advances in the management of prolactinomas, a modern therapeutic algorithm is proposed in Fig. 3, starting with a patient with a micro- or macroprolactinoma initially treated with cabergoline.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References


