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Dopamine Agonists: From the 1970s to Today

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Abstract
The discovery of dopamine inhibitory effects on prolactin secretion has led to an era of successful dopaminergic therapy for prolactinomas. Herein we provide an overview of the evolution of dopamine agonists and their use in patients with PRL-secreting pituitary tumors, starting from the 1970s up to today, highlighting that normalization of PRL levels, restoration of eugonadism, and reduction of tumor mass can be achieved in the majority of patients by treatment with dopamine agonists.

Introduction

Indications for therapy in patients with prolactinomas include effects of tumor size and effects of hyperprolactinemia [1, 2]. Whereas in asymptomatic patients with microprolactinomas there is no absolute requirement for treatment [1, 2] as a significant growth of these tumors is quite uncommon [3], symptoms of hyperprolactinemia in patients harboring a microadenoma or a macroadenoma encourage the starting of prolactin (PRL)-lowering treatment [1, 2]. The presence of a macroadenoma raises the probability that tumor may have propensity to grow [1]. Moreover, most macroprolactinomas are associated with remarkable PRL elevations so that to elicit symptoms that would require treatment. Therefore, unless specifically contraindicated, therapy is usually advisable for these tumors [1, 2]. Tumor invasiveness and compression of adjacent structures, such as the stalk or optic chiasm, are additional indications for therapy [1, 2]. Other indications are directly ascribable to the hyperprolactinemia itself, and include decreased libido, menstrual dysfunction, galactorrhea, infertility, hirsutism, impotence, and premature osteoporosis [1, 2]. According to international guidelines [2], dopamine agonist therapy is the recommended treatment to lower PRL levels, decrease tumor size, and restore gonadal function in patients harboring symptomatic PRL-secreting microadenomas or macroadenomas [1, 4]. The compounds most commonly used in clinical practice to treat prolactinomas are bromocriptine and cabergoline, whereas pergolide, quinagolide, and lisuride are less frequently used or not available anymore [1]. Bromocriptine, pergolide, and cabergoline are all ergot derivatives, whereas quinagolide is the only nonergot derivative used in clinical practice. Prolactinomas can exhibit variable responsiveness to medical therapy, and resistance to dopamine agonists, defined as failure to achieve normoprolactinemia and at least a 30%

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Table 1. Effects of bromocriptine on PRL normalization and tumor shrinkage

Study	Patients, *n*	Dose, mg/day	PRL normalization cases, *n*	Eugonadism[a] cases, *n*	Tumor shrinkage[b], cases
Seppälä et al. [20]	14	5	12	8	–
Carter et al. [21]	22	–	7	9	–
Thorner et al. [26]	12	2.5–7.5	12	12	–
Beckers et al. [28]	29	50–150 (LAR)	28	8	14
Merola et al. [29]	22	2.5–15	15	13	10
Total	99	–	74 (74.7%)	50 (50.5%)	24 (47%)[c]

[a] Defined as restoration of regular menstrual cycles, pregnancy, and/or a normal libido or potency. [b] Defined as a reduction >25% of the baseline volume. [c] Calculated based on 51 patients with available data about pituitary imaging.

reduction in tumor size, is reported in up to 30% of patients treated with bromocriptine and in approximately 10% of those receiving cabergoline [5, 6]. Treatment approaches for patients resistant to dopamine agonists include a switch to an alternative dopamine agonist, drug escalation beyond conventional doses, surgical tumor resection, radiotherapy, and temozolomide for aggressive or malignant tumors [2, 5, 6].

Ergot-Mediated Inhibition of Prolactin Secretion

At the beginning of 1970s, administration of the PRL inhibitor 2-bromo-a-ergokryptine to lactating cows was shown to display, besides a remarkable reduction in serum PRL levels, only a small effect on the milk yield [7]. However, treatment immediately before parturition effectively inhibited the onset of lactation [8]. In female rats 1-h treatment with the ergot alkaloids ergocornine and ergocristine at 0.25–1 mg was shown to induce persistent PRL decrease [9]. Both compounds were found to block the proestrus surge of PRL levels as well as the PRL increase induced by estradiol benzoate at 5–50 μg in oophorectomized rats [9], whereas high-dose ergocornine (2 mg) induced abrupt cessation of lactation with a concomitant fall in PRL levels. These findings led to the conclusion that ergot alkaloids had an intense inhibitory effect on PRL secretion and might be used in medical therapeutics. Moreover, increasing evidence ruled out the capability of some ergot alkaloids or their derivatives, such as ergometrine, agroclavine, or 2-bromo-α-ergocryptine (bromocriptine), to act as potential dopamine-mimetic drugs [10–13], therefore raising the question of whether these compounds might be used in clinical settings, mainly for patients with Parkinson's disease [14] or hyperprolactinemia [15] whose symptoms have been demonstrated to be relieved by dopamine-mimetic drugs. Particularly, agents able for stimulate α-adrenergic or dopaminergic receptors were found to inhibit PRL release [16]. The evidence that hypothalamic catecholamines, including dopamine, can directly inhibit in vitro PRL secretion supported the hypothesis that dopamine physiologically inhibits PRL secretion by stimulating specific receptors at the pituitary level [16]. Similarly, in cultured pituitary cells maintained in serum-free medium, dopamine and the dopamine agonist bromocriptine were demonstrated to inhibit PRL synthesis and PRL mRNA levels [17], suggesting that this might be useful for therapeutic application [17].

Bromocriptine

The greatest experience with dopamine agonists has been gained with the semisynthetic ergot alkaloid bromocriptine, which was specifically developed to inhibit PRL secretion, with low oxytocic and cardiovascular effects compared to other ergot alkaloids. The therapeutic effects of bromocriptine on PRL levels, restoration of eugonadism, and tumor shrinkage are shown in Table 1. In patients suffering from hyperprolactinemia-hypogonadism syndrome bromocriptine, administered at a dose of 2.5 mg 2 or 3 times/day, allowed the resumption of menstruation in hypogonadal women and immediately improved symptoms which, however, returned upon cessation of the drug [18]. In women and men receiving treatment with bromocriptine, PRL levels normalized and galactorrhea improved in the first few weeks of therapy [19], cyclical ovarian function resumed within 6 weeks to 9 months [19], and

Table 2. Effects of pergolide on PRL normalization and tumor shrinkage

Study	Patients, *n*	Dose, μg/day	PRL normalization cases, *n*	Eugonadism[a] cases, *n*	Tumor shrinkage[b] cases, *n*
Kleinberg et al. [36]	41	50–350	37	27	15
Orrego et al. [37]	22	50–500	15	5	19
Total	63	-	52 (82.5%)	32 (50.8%)	34 (54%)

[a] Defined as restoration of regular menstrual cycles, pregnancy, and/or a normal libido or potency. [b] Defined as a reduction >25% of the baseline volume.

testosterone levels increased in approximately 70% of the patients [20]. Similar results were seen in 32 patients with secondary amenorrhea (14 patients with PRL levels from 32 to 620 ng/mL) receiving bromocriptine 2.5 mg twice daily [21], with approximately 78% of patients achieving PRL normalization. In cultures of human pituitary tumors [22] bromocriptine was demonstrated to inhibit acutely PRL secretion by 64.4 ± 2.7% and after a 3-day therapy by 76.9 ± 3–8% [22]. When administered in patients with PRL-secreting pituitary tumors, a significant reduction of tumor mass or complete tumor regression were reported [23–25]. Moreover, spontaneous pregnancies were found to occur in women treated for infertility with bromocriptine. No evidence of teratogencity associated with bromocriptine was highlighted; nevertheless, women should have been recommended to stop treatment as soon as pregnancy was suspected [26, 27].

Side effects of bromocriptine included postural hypotension, nausea, and vomiting [16] and were avoided by slow initiation of the therapy [16].

Therefore, at the beginning of the 1990s bromocriptine was recommended as the standard medical treatment for prolactinomas, as it could induce inhibition of PRL synthesis and secretion at the pituitary level as well as tumor shrinkage [28, 29]. Nevertheless, some studies performed in the 1980s [30–33] documented a resistance to bromocriptine in 9–46% of patients, raising the question of whether other dopamine agonists might be useful to treat hyperprolactinemia when bromocriptine has failed to allow disease control.

Pergolide

Pergolide mesylate, a synthetic ergot derivative that shares similar pharmacologic properties with bromocriptine but has a longer duration of activity, was shown to induce a dose-dependent and prolonged decrease in or suppression of PRL levels in 4 healthy volunteers [34], allowing disease control with only 1 daily dose with greater patient compliance [35]. At higher doses, uncomfortable symptoms, including nausea, emesis, postural lightheadedness, emotional lability, mood changes, tremor, headache, and nasal stuffiness, were reported [34, 35]. In a study on 41 patients with hyperprolactinemia treated for 19–31 months with pergolide at 25–1,600 μg/day, PRL levels normalized in 90% and the tumor mass shrank in 77% of patients [36]. In women, gonadal function was restored in two thirds of the cases, with 76% of the patients achieving regular menses and 24% achieving pregnancy [36]. Similarly, male patients experienced testosterone normalization in 58%, increased libido in 59%, and increased potency in 35% of the cases [36]. Treatment was generally well tolerated, and therapy discontinuation was required only in 3 patients because of nausea and vomiting [36]. When used as the primary treatment in 22 patients with macroprolactinomas for 3–36 months at a dose of 0.1–0.75 mg/day, PRL normalization and tumor shrinkage (at least 25%) were found to occur in 68.2 and 86.4% of the cases, respectively [37]. The therapeutic effects of pergolide on PRL levels, restoration of eugonadism, and tumor shrinkage are shown in Table 2.

However, the enthusiasm for the use of pergolide ended at the beginning of the 2000s due to the finding of restrictive valvular heart disease in 33% of patients with Parkinson's disease who had received pergolide but in none of those who had never been treated with this drug [38]. A few years later, the increased risk of newly diagnosed moderate to severe valvular regurgitation was confirmed in patients with Parkinson's disease treated with pergolide or cabergoline as compared to those receiving different anti-Parkinsonian medications [39, 40], with the risk of valvular disease being significantly related to cumulative dose and treatment duration.

Table 3. Effects of quinagolide on PRL normalization and tumor shrinkage

Study	Patients, *n*	Dose, μg/day	PRL normalization cases, *n*	Eugonadism[a] cases, *n*	Tumor shrinkage cases[b], *n*
van der Lely et al. [49]	20	25–300	13	13	20
Brue et al. [50]	21	25–500	10	5	11
Merola et al. [51]	40	75–600	31	31	24
Total	81	–	54 (66.7%)	49 (60.5%)	55 (67.9%)

[a] Defined as restoration of regular menstrual cycles, pregnancy, and/or a normal libido or potency. [b] Defined as a reduction >25% of the baseline volume.

Consequently, in 2007 pergolide was withdrawn from US market [41].

Lisuride

Lisuride hydrogen maleate is an isoergolene derivative with strong peripheral anti-serotoninergic and central dopaminergic activity which is able to inhibit PRL secretion [42, 43]. Given orally or subcutaneously, lisuride was found to be very effective in lowering serum PRL concentrations in both intact reserpinized and ovariectomized rats primed with estradiol benzoate, with or without additional pretreatment with reserpine [43]. In 11 women with hyperprolactinemia and secondary amenorrhea, long-term treatment (7–18 weeks) with lisuride at 50–200 μg/day induced PRL normalization in 81.8%, regular menses resumption in 81.8%, and ovulation restoration in 72.7% of the cases [44]. In 53 women receiving lisuride at 300 μg (n = 26) or 600 μg (n = 27) daily, lactation was effectively inhibited and PRL levels suppressed in a dose-related manner [45]. Nausea and drowsiness were the most commonly reported side effects of lisuride [45, 46].

Quinagolide

Quinagolide is the most active nonergot oral medication that also functions as a dopamine agonist with specific D2 receptor activity, and it is about 35 times more potent than bromocriptine. In normal rat and tumoral human pituitary cells, low doses of quinagolide were demonstrated to induce immediate and sustained PRL suppression [47]. These effects were more potent and longer acting than the previously described in vitro effects of bromocriptine. In 7 patients resistant to bromocriptine up to 15 mg daily, a 6-month treatment with quinagolide at 75–800 μg/day induced a PRL decrease in 42.8% and PRL normalization in 28.6% of the cases, albeit with no relevant change in tumor size [48]. One woman became pregnant during quinagolide treatment [48]. In 3 independent studies [49–51] (Table 3) including overall 81 patients with prolactinomas resistant to bromocriptine, a 6- to 12-month treatment with quinagolide at variable daily doses induced PRL normalization in 66.7% of the cases and tumor shrinkage in 68% of the patients; libido/potency increased in 86% of the men and regular menses were restored in 67% of the women [49]. These findings suggested that at least half of patients resistant to bromocriptine quinagolide can overcome such a resistance probably due to its higher affinity toward the D2 dopamine receptor [50]. In general, the tolerability was high, and only in a few cases were nausea, vomiting, and postural hypotension reported [51].

Cabergoline

Cabergoline was first synthesized by scientists working for an Italian drug company who were experimenting with semisynthetic derivatives of the ergot alkaloids. In cultured pituitary cells from estradiol-induced rat pituitary tumors, a significant PRL inhibition was found within 12 h after treatment with cabergoline [52, 53]. Continued oral administration of cabergoline significantly reduced both PRL levels and pituitary weight during 15–60 days of treatment as compared with bromocriptine [52]. In healthy male volunteers, a single cabergoline administration (0.2–0.6 mg) induced a dose-dependent PRL inhibition [54]. In healthy men, single doses of 0.5, 1, and 1.5 mg of cabergoline induced complete PRL suppression [55], whereas in healthy women with regular menses dos-

Table 4. Effects of cabergoline on PRL normalization and tumor shrinkage

Study	Patients, *n*	Dose, mg/week	PRL normalization cases, *n*	Eugonadism[a] cases, *n*	Tumor shrinkage[b] cases, *n*
Wenster et al. [58]	223	0.25–2	186	201	–
Colao et al. [59]	23	0.5–3	19	21	14
Colao et al. [60]	110	0.25–3.5	88	94	93
Total	356	–	293 (82.3%)	316 (88.8%)	107 (80.4%)[c]

[a] Defined as restoration of regular menstrual cycles, pregnancy, and/or a normal libido or potency. [b] Defined as a reduction >25% of the baseline volume. [c] Calculated based on 133 patients with available data about pituitary imaging.

es of 0.4–0.6 mg induced 43–76% PRL suppression [56], with PRL remaining suppressed until 5 days after the administration of 0.6 mg [56]. In 31 hyperprolactinemic patients randomized to cabergoline at 0.3 or 0.6 mg once weekly for 9 weeks, PRL normalization occurred in 74.2% of the patients and regular menses resumption was seen in 15 out of 17 premenopausal women with amenorrhea [57]. The tolerability to cabergoline was very high, and nausea, vomiting, arterial hypotension, and dizziness were reported only by a few patients [57]. In a large patient series including 459 hyperprolactinemic women randomly assigned to cabergoline at 0.5–1.0 mg/week or to bromociptine 2.5–5.0 mg twice daily, PRL normalization was achieved in 83% of patients treated with cabergoline (92% of patients with idiopathic hyperprolactinemia or microprolactinoma and 77% of patients with macroprolactinoma) as compared to 59% of those receiving bromocriptine [58], and ovulatory cycles or spontaneous pregnancies were seen in 72 and 52% of patients treated with cabergoline and bromocriptine, respectively [58]. Side effects were less frequent and less severe in women treated with cabergoline as compared to bromocriptine [58], suggesting that cabergoline was more effective and better tolerated as compared to bromocriptine [58]. Remarkable tumor shrinkage (>20% of the baseline tumor size) was observed in more than 80% of the patients after 12–24 months of therapy with cabergoline, with complete disappearance of the tumor mass in 26–36% of the cases [59]. Moreover, cabergoline treatment was seen to induce further tumor shrinkage in 60% of patients previously treated with other dopamine agonists as compared to 82.3% of previously untreated patients [60]. The therapeutic effects of cabergoline on PRL levels, restoration of eugonadism, and tumor shrinkage are shown in Table 4.

Nowadays, according to the last international guidelines [2] cabergoline is recommended as the treatment of choice for patients with prolactinomas because of its greater efficacy over bromocriptine and other dopamine agonists in inducing PRL normalization and a clinically relevant (≥50% of baseline size) reduction in tumor volume [1, 2, 61].

Resistance to Dopamine Agonists

Despite the remarkable efficacy in lowering of PRL levels and tumor mass shrinkage, patients with prolactinomas may develop a resistance to dopamine agonists. This condition of resistance has not merited a unique definition in the literature, and different hypotheses, including failure to normalize or to reduce PRL levels sufficiently to achieve ovulation, failure to induce a 50% reduction of hyperprolactinemia, and/or failure to reduce tumor size [1], have been proposed. On the other hand, there is no standard dose threshold for dopamine agonists above which a patient may be considered resistant to dopamine agonists [5]. Actually, resistance to dopamine agonists is defined as a failure to achieve normoprolactinemia and at least a 30% reduction in tumor size [6]. Several molecular mechanisms, including decreased medication absorption, a decreased number of D2 receptors on the resistant tumors, a decreased affinity of the D2 receptors for the dopamine agonists, and altered signal transduction, have been proposed as being responsible for resistance to dopamine agonists [1, 62]. More recently, sequence variants of some genes, including the proline-rich salivary protein PRB3 [63] and the retinoblastoma interacting zinc finger protein PRDM2 [64], as well as alterations in the TGF-β/Smad signaling pathway [65], have been reported as pos-

sible mechanisms of tumor resistance or recurrence for prolactinomas. Genetic predisposition has been also investigated as a potential factor underlying resistance to dopamine agonists. Mutations in *MEN1* and *AIP* genes have been found to be associated with a larger tumor size, aggressive clinical behavior, and reduced responsiveness to dopamine agonists in patients with prolactinomas [66–68]. Clinical predictive factors of resistance to medical treatment with dopamine agonists include male gender [68–70], a young age [71, 72], large [68, 70] or cystic [71, 72] tumors, and tumor invasiveness [68, 70]. Resistance to dopamine agonists may be defeated by drug escalation beyond conventional doses, surgical tumor resection, radiotherapy, and temozolomide for aggressive or malignant tumors [2, 5, 6].

Conclusions

The introduction of dopamine agonists in the therapeutic algorithm for prolactinomas completely changed the natural history of these tumors over last 50 years, offering an effective treatment strategy that progressively replaced surgery and radiotherapy in the routine clinical management of such tumors. Dopamine agonist therapy, mainly cabergoline, is nowadays recommended as the treatment of choice to lower PRL levels, decrease the tumor size, and restore gonadal function in patients harboring PRL-secreting microadenomas or macroadenomas. Nevertheless, multimodal therapy involving also surgery and/or radiotherapy may be necessary in patients resistant to the effects of dopamine agonists or for those with aggressive prolactinomas.

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