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i. **Title:** Dopamine Agonists for the Treatment of Pituitary Tumors: From Ergot Extracts to Next Generation Therapies

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vi. **Keywords:** endocrinology, prescribing, drug information, pharmacotherapy, evidence based medicine, pituitary tumors, pituitary adenomas, dopamine agonists, neuroendocrinology

vii. **Word count:** 6,934

viii. **Data availability statement:** Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

ix. **Disclosures:** Gabrielle Page-Wilson: Recordati Rare Diseases – Medical Advisory Board, Consultant; Strongbridge BioPharma – Medical Advisory Board; Xeris Pharmaceuticals – Medical Advisory Board, Consultant. Tamara L. Wexler – Novo Nordisk – Scientific Advisory Board, Sandoz – Scientific Advisory Board.

Abstract

Dopamine agonists are a key tool in the therapeutic arsenal of endocrinologists worldwide. They exert their effects by binding to dopamine 2 (D2) receptors expressed by pituitary tumor cells, to modulate hormonal secretion and tumor size. They are the established first-line treatment for prolactinomas which express high levels of D2 receptors. Growing data supports their use as an adjuvant treatment option for other pituitary tumors including growth hormone, adrenocorticotrophic hormones, thyroid hormone secreting adenomas and non-functional pituitary tumors, all of which have been shown to express D2 receptors as well, albeit to varying extents. For those pituitary tumors inadequately treated by dopamine agonist alone, combined agonism of D2 and somatostatin receptors, represent a new frontier in clinical development. Here we review the development and role of dopamine agonist for the treatment of prolactinomas, the literature supporting their adjuvant use for the treatment of all other pituitary tumors, and recent progress in the development of the next generation of chimeric compounds that target D2 and other receptor subtypes highly expressed on pituitary tumor cells.

Introduction

The striking efficacy of dopamine agonists for the treatment of prolactin secreting pituitary tumors was first recognized over four decades ago,[1] and they remain a critical staple in the pharmaceutical arsenal of endocrinologists worldwide. The approval of bromocriptine (*2-Br-α-bromoergokryptine mesylate)* for the treatment of prolactinomas in 1985 effectively transformed a surgical disease into a medically managed one, and dopamine agonists are now the established first-line therapy for the treatment for prolactin-secreting pituitary tumors. Their efficacy for this indication lies in their ability to inhibit hormone secretion and tumor cell proliferation by binding to dopamine 2 receptors (D2R), which are highly expressed on lactotrophic tumor cells. The recognition that other pituitary tumor subtypes express dopamine 2 receptors as well has spurred investigation into the use of dopamine agonists for the treatment of non-prolactin secreting pituitary tumors. While their efficacy varies widely, they are an accepted treatment option for growth hormone and ACTH-secreting pituitary tumors, and may also have clinical benefits in other pituitary tumor subtypes. Renewed efforts to effectively harness the power of dopamine agonists have led to the development of novel chimeric molecules, targeting both tumoral D2 and somatostatin receptor subtypes, that may represent the next generation of pharmacologic treatments for pituitary tumors. This review focuses on the pharmacology and physiology of dopamine agonists and their development and clinical use in the treatment of pituitary tumors. This review also addresses important considerations and controversies related to treatment with dopamine agonists and discusses the current pipeline of related agents.

Dopamine and Its Receptors

Dopamine is a catecholamine neurotransmitter that mediates a variety of human functions including the regulation of hormonal synthesis and secretion. Dopamine gains access to the pituitary via the hypophyseal portal circulation and is known to inhibit prolactin secretion, decrease prolactin gene expression, and inhibit lactotroph proliferation[2]. Its actions are mediated by dopamine receptors, five of which have been identified and cloned: D_1, D_2, D_3, D_4, D_5 [3]. Dopamine receptors are classified into two families based on their pharmacological, biochemical and molecular features. The D1 family consists of D1 and D5 receptors; the D2 family consists of D2, D3, and D4 receptors [3]. The inhibitory effects of dopamine and dopamine agonists on prolactin secretion are mediated by the D2 receptor (D2R). The D2R exists in two distinct isoforms that arise from the same gene by alternative splicing. The isoforms differ in length by 29 amino acids and are known as the long form of the D2R (D2R-L) and short form (D2R-S)[4]. Both D2R isoforms belong to the G-protein-coupled receptor class and inhibit adenylyl cyclase activity, however different intracellular signaling pathways are activated when dopamine binds to each isoform potentially eliciting different effects [5,6] [7]. Despite similar anatomic distributions, D2R-L is expressed more abundantly in all regions, although the exact ratio of the two isoforms in any one location can vary markedly [8].

The D2R is expressed throughout the anterior and intermediate pituitary lobes primarily in lactotrophs, but has been localized to all pituitary cell types [2,9-11]. In the case of pituitary tumors, the presence of functional D2Rs on tumoral prolactin-secreting cells is well-established and is central to the first line therapeutic use of dopamine agonists for the treatment of prolactinomas. D2 receptors are expressed by other pituitary tumor subtypes as well, albeit to varying extents [12]. Non-functioning pituitary tumors and growth hormone (GH)-secreting tumors commonly express D2R [13], as do up to 75% of human corticotroph adenomas [14-16]. D2R expression provides a biological basis for the use of dopamine agonists for the treatment of non-prolactin secreting pituitary tumor subtypes, however the observed clinical impact on tumor size and hormone hypersecretion has been variable. Tumor specific differences in dopamine agonist responsiveness may reflect distinct D2R expression patterns and isoforms, however, to date the relationship between clinical response to DA therapy and D2R expression has not been firmly established [13,14].

Dopamine Agonists

Dopamine agonists have diverse chemical structures and are categorized as either ergot-derived (bromocriptine, cabergoline, pergolide, lisuride) or non-ergot derived (quinagolide, ropinirole).

The receptor selectivity of each dopamine agonist varies and impacts the biochemical response and side effect profile of each drug. Ergot DAs exhibit higher affinity for the D2R family than for the D1R family [17].

Non-ergot DAs demonstrate selectivity for the D2R family and have negligible affinity for α receptors and for the 5HT-2b receptors found on cardiac valves [17,18]. The ergot dopamine agonists bromocriptine and cabergoline are used most commonly for the treatment of prolactinomas and other pituitary tumors. Pharmacologically, bromocriptine acts as a D2R agonist, and exhibits D1R antagonism as well [19]. It has high affinity for 5HT-2a receptors, and is a partial agonist at 5HT-2b receptors. Bromocriptine reaches peak concentrations 1-3 hours after oral administration and has an elimination half-life of 3-7 hours, resulting in a recommended dosing schedule of 2-3 times per day[17,19]. Starting doses range from 1.25-2.5mg with a maximum daily dose of 15mg/day. Cabergoline also exhibits D2R agonist activity, but differs from bromocriptine exhibiting a high affinity for D1Rs, and for 5HT-2a and 5HT-2b receptors. Cabergoline's peak concentration occurs 2 hours after oral administration, with concomitant food intake delaying the rate but not the extent of absorption[17]. The half-life of elimination for cabergoline is 63-110 hours, allowing for once or twice weekly dosing[19]. Cabergoline is available in 0.5mg tablets and is typically initiated at a dose of half a tablet (0.25mg) twice weekly.

Both bromocriptine and cabergoline undergo extensive hepatic metabolism, and interactions with the cytochrome P450 (CYP) system have been observed [19,20]. The medications may inhibit CYP3A4 thereby increasing concentrations of CYP3A4 substrates including commonly used medications like simvastatin and codeine. Bromocriptine and cabergoline are also metabolized by CYP3A4, so concomitant treatment with CYP3A4 inhibitors like ketoconazole, erythromycin, and mifepristone can increase plasma concentrations of the drugs [20,21]. Furthermore, the simultaneous use of CYPA34 inducers like St John's Wort can potentially attenuate the therapeutic efficacy of bromocriptine and, in kind, cabergoline [19].

The ergot DA lisuride is not readily available. Pergolide-- which exhibits agonist activity at D2R, D1R, and at 5HT-2b receptors expressed on cardiac valves--was approved for medical use in 1989, but removed from the U.S. market in 2007 and designated for restricted use in Europe in 2008 due to its frequent association with cardiac valve disease in Parkinson's disease patients treated with the medication [22]. Quinagolide, a single non-ergot derivative, is currently approved for clinical use in several European countries, Canada, and Australia, but not available in the United States. Quinagolide is reported to have 35-fold greater D2R activity than bromocriptine and exhibits little affinity for D1Rs, attenuating its side effect profile [23]. It's half-life of approximately 22 hours allows for once daily administration. The off-label use of the non-ergot dopamine agonist ropinirole, a selective D2R agonist with negligible activity at 5HT-2b receptor subtypes, approved to treat Parkinson's disease and restless leg syndrome, has recently been explored in patients with prolactinomas with biochemical efficacy observed in some patients [24].

Dopamine Agonists for the Treatment of Prolactinomas

Prolactinomas are the most common pituitary tumor subtype, comprising one- to two-thirds of all identified pituitary tumors [25,26]. They are the only secretory pituitary tumor for which medical treatment is first-line therapy. Dopamine agonists exert their effects on prolactinomas via D2R expressed on tumoral prolactin-secreting cells, decreasing prolactin concentrations and tumor size, and restoring gonadal function. The therapeutic origins of dopamine agonists began with the recognition that an ergot extract reduced prolactin. This extract, known as ergocornine, was subsequently modified to retain its prolactin-lowering effects without the oxytocic or vascular sequelae,[26] aiding in the development of bromocriptine for therapeutic use. Bromocriptine was officially approved for the treatment of hyperprolactinemia in 1978 and subsequently for the treatment of prolactinomas in 1985.[26] In the first human study examining its use, bromocriptine reduced prolactin concentrations and stopped galactorrhea in 5 adults (2 men and 3 women), 3 of whom also regained potency/normal menstruation.[27]

Following this early human study, bromocriptine was rapidly accepted as first line therapy for the treatment of hyperprolactinemia, but its efficacy for tumor size reduction was not appreciated until 1980, when a patient with a macroprolactinoma refused surgery, and was treated with bromocriptine in an inpatient setting, achieving a reduction in visual field defects over the course of 3 days and a decrease in tumor volume after 2 weeks of therapy.[1] Bromocriptine's tumor-reducing effect was further demonstrated in 13 treatment-naïve patients with suprasellar prolactinomas treated with bromocriptine 2.5mg three times daily. Bromocriptine therapy not only reduced prolactin levels, but also improved visual field compromise and tumor size.[28] Following cessation of treatment in 7 of 13 patients, prolactin levels rose, and tumor growth and visual field compromise were observed in one patient, with the sequelae reversing upon re-initiation of therapy.[28] A subsequent prospective multicenter trial confirmed bromocriptine's efficacy for reducing prolactin secretion and tumor size and established its role as first-line therapy for the treatment of macroprolactinomas [29].

Commercial development of other dopamine agonists followed in the 1980's and 1990's. Cabergoline was patented in 1980, introduced for commercial use in the Netherlands in 1992, and approved by the FDA in 1996. Cabergoline has since become the preferred dopamine agonist for the treatment of prolactinomas, based on a superior efficacy and tolerability profile in head-to-head trials with bromocriptine. The mechanisms underlying cabergoline's superior efficacy for treating prolactinomas have not been firmly established, but may relate to its higher affinity for dopamine receptor binding sites relative to bromocriptine.[30] In a prospective study of 459 women with hyperprolactinemia and prolactinomas (279 microprolactinomas, 3 macroprolactinomas), prolactin normalization was achieved in

83% of subjects on cabergoline compared to 59% treated with bromocriptine. Ovulatory cycles were restored in 72% of cabergoline-treated subjects, and in 52% of those treated with bromocriptine.[31] Similarly, a retrospective study of 455 patients with hyperprolactinemia treated with cabergoline, confirmed prolactin normalization in 86% of all patients, with a range of efficacy depending on the etiology of the hyperprolactinemia.[32] Biochemical reductions in prolactin concentrations have not been shown to consistently correlate with decreases in tumor size.[33] Nonetheless, decreases in tumor volume have been observed following treatment with both bromocriptine and cabergoline, although there have been no single head-to-head studies comparing their efficacy regarding tumor size. Individual studies have reported significant progressive tumor volume reductions over a 3 year treatment period in patients treated with cabergoline, [34] and similar decreases in tumor size have been observed following one year of bromocriptine therapy.[29]

The non-ergoline dopamine agonist quinagolide has been shown to effectively decrease prolactin levels and tumor size, and restore gonadal function in both men and women in several small studies.[35-41] Quinagolide's specificity for the D2 receptor is a favorable attribute, and may facilitate its improved side effect profile relative to bromocriptine, making it an effective treatment alternative for patients who are bromocriptine intolerant.[42] [43] Additionally, approximately 50% of patients who do not respond to bromocriptine exhibit a biochemical response to quinagolide.[43,44] When compared to bromocriptine, quinagolide has been shown to reduce prolactin levels with similar efficacy. When compared to cabergoline, quinagolide was shown to be comparable for inducing prolactin normalization, however after 12 months of treatment cabergoline was associated with a greater degree of tumor shrinkage (30-31%) than quinagolide (22-25%) making cabergoline the preferred treatment overall.[36] Given quinagolide is not available in the US, the non-ergot dopamine agonist ropinirole has recently been explored as a potential treatment alternative for patients with hyperprolactinemia and prolactinomas. The administration of single doses of ropinirole ranging from 0.5-2.0 mg resulted in a dose-response reduction in prolactin concentrations.[45] While an open-label dose-escalation trial examining its long-term use for patients with prolactin secreting tumors is currently underway (NCT03038308), interim data suggests it may effectively normalize prolactin levels in patients with microprolactinomas. [46]

Withdrawal of Dopamine Agonists in Prolactinomas

DA treatment need not be chronic to control prolactin levels or tumor size. Cabergoline dose can often be successfully reduced after prolactin normalization without loss of efficacy[31,32]**.** Current Endocrine Society guidelines suggest that, among patients who have achieved normalization of prolactin levels and

have either no visible tumor remnant[47] or a significant reduction in tumor size on MRI for two years,[48] treatment can be withdrawn without recurrence of hyperprolactinemia in 30-40% of patients [49-51]. The Pituitary Society recommends a minimum treatment duration of 1 year, and a trial of tapering off therapy following 3 years of treatment if prolactin levels are normal and tumor size is significantly reduced.[48] Importantly, while hyperprolactinemia may recur after withdrawal of DAs, tumor recurrence has not been observed even in those who exhibit increased prolactin levels. [49,51] When hyperprolactinemia does recur, it is observed most often during the first year after DA withdrawal[51] and is more likely to occur in those with high baseline prolactin levels and larger pre-withdrawal tumor remnants. [50,51]

Dopamine Agonist Resistance in Prolactinomas

While the majority of patients with prolactinomas respond to DA therapy, resistance to treatment with both cabergoline and bromocriptine has been observed. Dopamine agonist resistance is defined as failure to normalize prolactin levels on maximally tolerated doses and a failure to reduce tumor size by 50%.[47 52] Based on this definition, approximately 10% of patients are resistant to cabergoline and 25% are resistant to bromocriptine. Resistance is more common in men, and in patients with macroadenomas and high baseline prolactin levels.[53] The pathogenic mechanisms underlying DA resistance remain incompletely understood. While poor drug absorption and a decreased affinity for D2R have largely been excluded, many resistant prolactinomas do exhibit reduced D2R expression.[54,55] Additional downstream alterations in the G-protein coupled intracellular transduction pathway that facilitates dopamine mediated prolactin inhibition, have been observed in resistant prolactinomas as well. [56] The transforming growth factor beta-1 (TGFB1) pathway, which mediates the inhibitory effect of dopamine on prolactin release, has also been implicated in the pathogenesis of DA resistance because downregulation of the TGF-B/Smad signaling pathway has been observed in DA resistant prolactinomas. [57] In clinical practice, those who are resistant to bromocriptine should receive a trial of cabergoline, since 80% of bromocriptine-resistant patients are reported to be responsive to this therapeutic alternative.[32,58] Superstandard doses of cabergoline as high as 11 mg/week have also proven effective in some patients, although the risk of concomitant side effects increases at such doses.[59,60] It should be noted that, while less common, there are case reports of patients who are resistant to cabergoline but responsive to bromocriptine.[61] Accordingly, a trial of bromocriptine in patients exhibiting resistance to cabergoline is not unreasonable.

Dopamine Agonists for the Treatment of Acromegaly

While surgery is first-line therapy for growth hormone secreting tumors and is effective in approximately 2/3 of all cases,[62,63] medical therapy is recommended if surgery is not possible, or if biochemical control

is not achieved by 12 weeks post-operatively.[64] GH-secreting cells in normal tissue and in adenomas express both dopamine and somatostatin receptors.[65] Notably, dopamine agonists were the first medical therapy used for the treatment of acromegaly. In 1972, Liuzzi and colleagues demonstrated suppression of GH levels in eight acromegalic patients following administration of oral L-Dopa, establishing the potential utility of DA for the treatment of acromegaly.[66] The group went on to demonstrate GH suppression in 7 patients with acromegaly after a single dose of the dopamine agonist 2-Br-*alpha*-ergocryptine (later known as bromocriptine).[67] In 1977, Wass and colleagues treated 73 subjects with acromegaly with bromocriptine over 3-25 months, confirming sustained clinical and biochemical improvement in 97% and 79% of subjects respectively.[68] Twenty years later, cabergoline was similarly shown to decrease GH and IGF-1 concentrations. In a cohort of 64 subjects with acromegaly (48 with GH-secreting tumors and 16 with GH/PRL co-secreting tumors), cabergoline doses ranging from 1-1.75 mg weekly reduced GH levels in 73% of subjects and achieved levels <2 mg/L in 46%. In parallel, IGF-1 levels decreased in 67% of subjects and fell to levels < 300 mg/L in 39%.[69] While subjects with lower pre-treatment IGF-levels and those with co-secreting tumors responded better to treatment,[68,69] neither characteristic has been consistently shown to predict dopamine agonist responsiveness in patients with acromegaly, and cabergoline's efficacy appeared to wane over time.[70] Additionally, in a subsequent meta-analysis of cabergoline monotherapy in 160 acromegalic patients across ten trials, the efficacy of dopamine agonists for IGF-1 normalization were more modest. IGF-1 normalization was observed in only 34% of all subjects, an effect associated with baseline IGF-1 and PRL levels. [71]

Following the introduction of the somatostatin analogs, which reduce GH and IGF-1 levels in up to 70% of patients, and the GH receptor antagonist pegvisomant, the use of dopamine agonists for the treatment of acromegaly markedly declined. For moderate to severe cases of acromegaly, somatostatin analogs are the first-line medical treatment.[72] Current guidelines recommend an initial trial of cabergoline or another dopamine agonist in patients with milder post-operative elevations in IGF-1 and mild clinical symptoms, as its therapeutic efficacy is greatest in this cohort.[64] Dopamine agonists may also be used as adjuvant medical therapy in patients in whom first-line surgical tumor resection is not curative, when somatostatin analogs and pegvisomant prove inadequate for disease control. In a meta-analysis of five studies and 77 patients, 52% of patients with acromegaly who failed to normalize IGF-1 concentrations on somatostatin analogs achieved biochemical control with the addition of cabergoline.[71] The addition of cabergoline may also be useful in moderate-severe acromegaly if accompanied by significant elevations in prolactin.[70] At doses of 0.5-2.0 mg week (similar to dosing for prolactinomas) cabergoline controls IGF-1 levels in approximately one-third of patients.[25] Higher doses (> 2.0 mg/week) have not been shown to improve biochemical control in the majority of patients with acromegaly.[69] Tumor shrinkage has been

observed in patients with co-secreting GH/prolactinomas treated with cabergoline, but reductions in tumor volume are less frequently observed in patients with GH-secreting tumors alone.[69,70] Thus, while first-line treatment for acromegaly is surgical, dopamine agonists may prove useful as adjuvant medical therapy in patients with persistent disease.

Dopamine Agonists for the Treatment of Cushing's Disease

Cushing's disease is a rare disorder, characterized by chronic hypercortisolism resulting from ACTH-secreting tumors of the pituitary gland. Transsphenoidal surgery (TSS) is recommended as first-line treatment for Cushing's disease, but biochemical remission is achieved in only 80% of patients with microadenomas and in 60% of those with macroadenomas, even when surgery is performed by an experienced surgeon.[73-75] Furthermore, recurrence rates after successful pituitary surgery range from 5-35%.[73] Pharmacotherapy can be used to treat hypercortisolism in patients with persistent or recurrent disease, in those who are not candidates for surgery, and in those undergoing radiotherapy when short-term control of hypercortisolism is needed.[73,76] An individualized approach to medical management is preferred, and the medications selected to treat hypercortisolism vary accordingly based on the clinical scenario. While adrenal steroidogenesis inhibitors are recommended as the first choice following transsphenoidal surgery, tumor directed therapy with the dopamine agonists can be considered in patients who are not surgical candidates or who have persistent disease after TSS,[76] given receptor-ligand binding, immunohistochemistry, and RT-PCR studies have demonstrated D2R expression in approximately 80% of corticotropic adenomas.[14] In tumoral cells exhibiting high concentrations of D2 receptors, dopamine agonists have been shown to suppress ACTH secretion by up to 60% in vitro[14]. Consistent with a DR receptor mediated mechanism of action, ACTH secretion does not appear to be inhibited by dopamine agonists in ACTH secreting pituitary tumors that do not express D2R *in vitro*.[77] Notably, variability in responsiveness to DA therapy based on differences in patterns of tumoral receptor subtype expression in Cushing's disease is also demonstrated in clinical studies. While neither bromocriptine nor cabergoline is FDA approved for the treatment of Cushing's disease, a small subset of Cushing's disease patients, have been shown to respond to chronic dopamine agonist therapy.[78,79] Early retrospective studies of bromocriptine treatment in 25 patients with Cushing's disease showed normalization of urine or plasma cortisol concentration in 42% of patients treated for at least 3 weeks. However, in prospective studies, only 3 of 13 patients with Cushing's disease achieved a biochemical response when treated acutely with 2.5mg bromocriptine,[80] and data showing clinical benefits with longer term bromocriptine therapy at doses ranging from 5-15mg/day are limited to very small studies and case reports.[81,82]

Due to its more favorable pharmacologic profile, characterized by a longer half-life and increased binding capacity and specificity for D2, one would anticipate greater efficacy with cabergoline. However, its utility in the treatment of Cushing's disease remains controversial. The first prospective study examining the use of cabergoline for the treatment of Cushing's disease in patients unsuccessfully treated with transsphenoidal surgery, demonstrated prolactin normalization in 40% (4/10) patients after 3 months of treatment at doses ranging from 1-3mg/week.[14] A subsequent evaluation over up to 24 months in 20 patients with Cushing's disease demonstrated a similar overall response rate, with 10/20 (50%) patients exhibiting biochemical control after 12 months of treatment with a median cabergoline dose of 6 mg/wk (1–7 mg/wk) and eight (40%) patients demonstrating persistent control at 24 months with a median cabergoline dose of 3.5 mg/wk (1–7 mg/wk). Furthermore, cabergoline induced tumor shrinkage in 20% of patients and clinical improvements in hypertension and glucose intolerance were observed.[79] A retrospective study by Godabout and colleagues in 30 patients with persistent Cushing's disease, showed complete responses in 30% of patients treated for up to 37 months (range from 12 to 60 months) at mean doses of 2.1mg/week, and a notable rise in urine free cortisol concentrations in 50% of the treated cohort.[83] In a more recent multicenter retrospective study of 53 patients, although 40% of were complete biochemical responders at 12 months, 28% discontinued the medication due to intolerance or loss of efficacy, and sustained control was present in only 23% following 32.5 months of treatment.[84] The observed variability in the efficacy of cabergoline in the treatment of ACTH secreting tumors is further underscored by a recent prospective study in 20 patients with Cushing's disease, that called cabergoline's clinical value for Cushing's disease into question when only a single patient exhibited a congruent decline in all relevant cortisol parameters following treatment with escalating doses of cabergoline 0.5-5.0mg over the course of six weeks. Cabergoline's efficacy for the treatment of Cushing's may be enhanced when it is used in combination with other cortisol lowering therapies. Remission rates ranging from 56-78% have been reported when cabergoline is used in combination with steroidogenesis inhibitors, in CD patients with persistent hypercortisolism following pituitary surgery. [85] [86] Notably, when used in combination with the somatostatin receptor ligand pasireotide in a Cushing's cohort, the addition of cabergoline normalized urine free cortisol levels in 24% more patients than cabergoline alone.[87] Overall, in the absence of placebo-controlled trials to inform the use of dopamine agonists for the medical management of Cushing's disease, practice patterns are likely to be informed by the availability of pharmacologic options and by the clinical experiences of independent providers.

Dopamine Agonist for the Treatment of TSH-secreting adenomas

TSH-secreting adenomas (TSHomas) are rare, accounting for 0.5-3% of functional pituitary tumors.[88,89] Up to 25% percent of TSHomas co-secrete GH and/or prolactin.[90] While surgery is considered first-line

treatment, safe surgery requires a clinically euthyroid state necessitating the preoperative use of medication.[91] Because surgical resection of TSHomas leads to biochemical remission in only 50-70% patients, due in part to the fibrotic nature of the tumor type,[92,93] dopamine agonists can also be used as adjuvant medical therapy post-operatively. D2R are expressed on thyrotrophs, and dopamine regulates TSH: TSH levels fall after dopamine exposure and rise after dopamine receptor antagonism. [94,95] However, dopamine is rarely effective at reducing tumoral TSH secretion from TSHomas, potentially due to tumor-specific impairments in dopamine receptor function or to deficiencies in dopamine receptor expression.[96,97] Somatostatin analogues are much more effective at suppressing tumoral TSH secretion, achieving biochemical remission in 90% of patients in whom surgery is not curative, and are consequently first line therapy for post-operative and pre-operative medical management of TSHomas.[88] Dopamine agonists may be used as second-line medical therapy to facilitate euthyroid states pre-operatively if somatostatin agonists are not tolerated, and can also be used to treat TSHomas if surgery is contraindicated, although the reported benefits have been modest. The successful pre-operative use of bromocriptine in a case of a TSHoma not responsive to somatostatin analogs has been reported,[98] and there are scattered case reports of hormonal control achieved with dopamine agonists when surgery is contraindicated.[99,100] However, in a case series by Socin and colleagues describing the use of dopamine agonists in seven TSHoma patients, a response was only observed in a single subject whose tumor co-secreted prolactin.[93] Thus, while post-operative remission with dopamine agonist monotherapy may occur, it is rare, and is more likely to be observed in TSHomas that co-secrete prolactin.[93,100]

Dopamine Agonists in the Treatment of Non-functioning Pituitary Adenomas

The use of dopamine agonists in the treatment of non-functioning pituitary adenomas remains an area of controversy. Despite some proponents, the practice is not widespread and current guidelines do not endorse it. Nonetheless, Greenman and colleagues have been vocal in their recommendation for the preventative use of DA post-TSS for macroadenomas when tumor remnant exists, based on observational and historical studies from their group.[101] In a study examining changes in tumor size in cohorts of patients with non-functioning pituitary tumors from two pituitary centers, one that used DA following transsphenoidal surgery to treat tumor remnants (n=55) or recurrent pituitary tumors (n=24), and one that did not (n=60), dopamine agonist use was associated with higher rates of tumor shrinkage or stabilization, and with a higher 15-year progression-free survival.[101] Pivonello and colleagues described a reduction in both tumor volume and clinical symptoms (headache and visual fields) in 9 patients with post-operative tumors treated with cabergoline for one year.[13] In a cohort of 19 patients with non-functioning macroadenomas treated with cabergoline (2 mg/week) for 6 months, Garcia and colleagues observed > 25% tumor volume reduction in 6 patients, and a $\geq$10% volume decrease in 9

patients, with tumor growth in 4 patients.[102] In a separate study, statistically significant tumor remnant volume reduction was observed following 6 months of treatment with 3.0 mg/week cabergoline in 66% of patients.[103] A single-center retrospective study of 44 patients treated with 3mg/week cabergoline for a median of 30 months found tumor shrinkage in 4 of 12 patients given cabergoline as primary therapy and 23 of 32 patients given cabergoline after surgery; there was no control arm.[104] When tumor shrinkage does occur, it is most likely to be observed in the first year of treatment. However, efforts to predict response to cabergoline based on dopamine receptor expression in tumoral tissue have not yielded consistent or clinically meaningful results and other factors predicting responsiveness have not been identified.[101,103,105,106]

While data from these small studies may hold promise, a lack of prospective randomized placebo-controlled clinical trials has made interpreting the results difficult, and in the absence of a secreted hormone from tumor cells, there is no serum biomarker to track efficacy of treatment in observational studies in real-time. Recently, a larger-scale prospective open-label randomized trial comparing two years of treatment with cabergoline at 3.5 mg/week to no intervention in 140 patients after transsphenoidal surgery for NFPA, found significantly higher rates of tumor shrinkage (28.8% vs 10%) and lower rates of tumor growth (5.1% vs 15.8%) in treated patients.[106] Although the study was limited by the inclusion of patients with hyperprolactinemia, albeit asymptomatic, in the cohort. Another phase 3 randomized controlled study of tumor reduction on cabergoline vs nonintervention is expected to be completed in 2026 (Clinicaltrials.gov: NCT02288962); however, at this time, there is insufficient evidence to recommend dopamine agonists for the routine treatment of non-functional pituitary adenomas, either as primary or adjuvant treatment. [107,108]

Clinical Considerations and Controversies in the Use of Dopamine Agonists

Dopamine Agonists for Fertility Pursuits & Pregnancy

Bromocriptine is the preferred dopamine agonist for women who are pursuing fertility or are pregnant, despite the fact that it crosses the placenta, due to its longer history of use.[109] In reports from over 6000 women taking bromocriptine during pregnancy, there has been no data to suggest an increase in congenital malformations or spontaneous abortions.[48 47,109] While there is less published experience with cabergoline in pregnancy, cabergoline use at the times of conception and before 5 weeks also appears to be safe with no reported teratogenic or abortifacient effects.[110,111,112,113] Similarly, quinagolide can be

used until pregnancy is confirmed and teratogenic effects in early pregnancy have not been reported; long-term effects are unknown and it should be withdrawn once pregnancy is confirmed. [43,114]

Side Effects of Dopamine Agonists

Nausea, dizziness, and headaches are the most commonly reported side effects of dopamine agonists and are associated with both non-ergot and ergot derivatives. These side effects are independent of target, and may be seen at similar doses in patients being treated for all types of pituitary adenomas The frequency of gastrointestinal side effects with bromocriptine is notable, with nausea occurring in 30%, vomiting in 20%, and constipation in approximately 10% of treated patients. [52] Postural hypotension is reported in up to 25% of bromocriptine treated patients as well, and can be complicated in rare cases by syncope.[52,115] While reported much less frequently, nasal congestion, flushing, and leg cramps have also been associated with bromocriptine use. Even more rarely, bromocriptine can cause peripheral vasospasm and digital erythromelalgia. This side effect appears to be specific to ergot dopamine agonists and has also been observed with cabergoline use; it is unlikely to occur with the non-ergot derivative quinagolide.[43] Cabergoline has been associated with similar side effects, but is reported to have a lower rate of gastrointestinal side effects than bromocriptine [31] and a more favorable tolerability profile, with adverse events occurring in up to 68% of patients treated for hyperprolactinemia and prolactinomas, in comparison to an adverse events rates of up to 78% with bromocriptine.[116] Furthermore, the frequency of cabergoline discontinuation due to side effects is reportedly less than 3% versus an approximate 12% of patients who do not tolerate bromocriptine at therapeutic doses.[31,52]

Common DA side effects occur primarily upon medication initiation and following any dose increase. When medication continuation is feasible, side effects often dissipate after the first few weeks of use. Side effects may be minimized by bedtime administration, and by starting at a quarter of the intended dose with gradual increase.[117] Intravaginal administration of bromocriptine and cabergoline has also been described as an effective alternative for the treatment of prolactinomas in patients with oral DA intolerance. [118] The non-ergot dopamine agonist quinagolide has a better tolerability profile than bromocriptine as demonstrated in a head-to-head double-blind randomized clinical trial, a characteristic that may be attributable to its marked specificity for D2 receptors;[38] dopaminergic side effects including nausea and headache are still reported, but changes in blood pressure and heart rate have not been observed.[114]

Cardiac Valve Disease and Fibrosis

Complications arising from the use of dopamine agonists for treatment of Parkinson's Disease illuminated a link between the use of ergot-derived DA and valvular heart disease. Dose-related increases in regurgitant cardiac valve disease were observed in Parkinson's patients treated with pergolide and cabergoline, a finding that was thought to result from fibroblast simulation caused by the affinity of these drugs for 5HT-2b receptors on cardiac valves.[119,120] Ultimately, the discovery of a causal link between pergolide use and cardiac valve disease led the voluntary withdrawal of pergolide from the U.S. market and to its restricted use in Europe. An analysis of fibrotic reactions reported in the U.Ss Adverse Event Reporting System suggested increased odds of fibrosis with bromocriptine as well as cabergoline, but bromocriptine was not implicated in increased cardiac valve fibrosis in a nested case-control analysis using data from patients treated with DA using the United Kingdom General Practice Research Database.[121,119] A case of cardiac valve fibrosis was reported in a patient treated with up to 40 mg/d of bromocriptine for 5 years, indicating that at very high doses valve issues may be a concern.[122] Non-ergot dopamine agonists do not appear to be associated with valvular heart disease or other fibrosis.[119,120]

More serious side effects of ergot DA therapy including pleuropulmonary fibrosis and constrictive pericarditis have been reported but are largely associated with the higher therapeutic doses required to treat Parkinson's Disease.[52] [123,124] While valvular heart disease has been reported in some patients taking cabergoline for hyperprolactinemia at high doses (6mg/week), [125] the cardiac risks associated with standard treatment doses are thought to be modest.[126] In general, the doses used to treat prolactinomas are far lower than for Parkinson's, although the potential for similar cumulative dose exposure may exist due to the long treatment duration in some patients with prolactinomas. Of note, clinically relevant fibrotic reactions have not been observed at higher rates in patients on dopamine agonists at the doses classically prescribed for prolactinomas.[102] In an observational case-control study, Colao and colleagues described a higher rate of asymptomatic moderate tricuspid regurgitation in patients on cabergoline for prolactinoma therapy; the presence of moderate tricuspid regurgitation was associated not only with higher cabergoline doses but also with higher blood pressure in that cohort, and mild tricuspid regurgitation was observed more frequently in the control population.[113] In contrast to studies in Parkinson's, an increased incidence of mitral or aortic regurgitation was not observed. In a prospective 5-year single-arm study of 40 subjects with prolactinomas treated with cabergoline, no statistically or clinically significant increases in valvular regurgitation were observed .[126] Elenkova and colleagues used transthoracic echocardiograms to examine 334 patients and healthy controls on cabergoline (n=105), bromocriptine (n=57), or no DA (74 patients and 102 controls) in a case-control fashion, and did not identify an increase in clinically relevant valvular regurgitation.[127] Furthermore, in a prospective

multicenter study in the UK following 192 patients treated with cabergoline at cumulative doses ranging from 20-551mg over 2-3.5 years, there was no clinically significant association with valve disease.[128] The most recent meta-analysis examining the link between cabergoline use for hyperprolactinemia and clinically significant valvulopathy did identify an increased risk of tricuspid regurgitation in 836 cabergoline treated patients versus 1388 controls, but the clinical relevance of this finding remains unclear.[129]

Despite the absence of a definitive risk for valvular disease for prolactinoma patients treated with dopamine agonists, the FDA label for cabergoline recommends a pre-therapy echocardiogram and indicates medication use is contraindicated in individuals with a history of valvulopathy or pericardial, pulmonary, or retroperitoneal fibrosis. In the UK, cabergoline carries a similar label noting that patients with anticipated long treatment courses should have an echocardiogram prior to initiation of therapy. In contrast, the Endocrine Society's guidelines for the treatment of prolactinomas suggest echocardiography "may be necessary to assess for valvular abnormalities" in patients on high doses of dopamine agonists for prolonged periods, but do not recommend pre-treatment echocardiograms or regular echocardiographic screening for patients receiving typical doses of cabergoline (1–2 mg/week).[47] Regardless, patients should be counseled on the potential association between high dose cabergoline and valvular heart disease, and echocardiographic monitoring should be considered for prolactinoma patients treated with higher-than-standard doses or for those with concerning signs or symptoms.[59,130]

Impulse Control Disorders

The association between DAs and neuropsychiatric side effects, ranging from mood disorders to frank psychosis to impulse control disorders, is important to recognize, as proper counseling regarding these risks should be conducted by prescribing providers.[131] Impulse control disorders are of particular concern, and in recent years have been linked to the use of both ergot and non-ergot dopamine agonists. To date, the majority of extant data describing the association between dopamine agonists and these disorders has been in patients with Parkinson's in whom compulsive gambling, compulsive shopping, hypersexuality, and binge eating disorders have all been observed.[132,133] The data on impulse control disorders in patients with pituitary tumors treated with dopamine agonists has evolved over the last decade, beginning with case reports of impulse control disorders in treated patients with prolactinomas.[134] In a subsequent 12-month prospective evaluation of 25 DA treated patients with prolactinomas, 31 patients with non-functioning pituitary adenomas, and 32 healthy controls, two new cases of hypersexuality were diagnosed in DA-treated patients, both of which resolved upon discontinuation of the medication.[135] Additionally, a dose-related increase in some impulsivity

parameters as measured by psychometric tests was observed in 10 prolactinoma patients treated with DA, compared to untreated patients with either hyperprolactinemia or non-secreting pituitary tumors.[136] Similarly, in a case-control study examining impulse control disorders among 200 patients with prolactinomas and a history of current or prior DA use compared to 200 DA-naïve patients with non-functioning pituitary adenomas, a statistically significant difference in hypersexuality was observed among treated prolactinoma patients (12.99 vs 2.86%, P = 0.03).[137] Recently, it has been suggested that up to 25% of patients on DA may experience an impulse control disorder, most commonly hypersexuality or gambling, compared to 8% of the general population.[131] Larger prospective studies will be helpful for identifying associated risk factors and for determining if cumulative dopamine agonist exposure increases the risk for ICD in treated patients.

Use of DA for the Treatment of Pituitary tumors in Patients on Anti-psychotics

The use of dopamine agonists to treat prolactinomas or other pituitary tumors in patients who are taking anti-psychotics requires careful consideration given anti-psychotics often are designed to antagonize dopamine receptors. Options for medical treatment of pituitary tumors in this setting include the use of higher doses of a DA, consideration of an alternate antipsychotic with reduced D2 antagonism, or the addition of aripiprazole.[138] In the case of prolactinomas, consideration may also be given to avoiding dopamine agonist entirely and treating prolactin induced hypogonadism with appropriate hormone replacement.[139] When dopamine agonists are used, the psychiatric diagnosis or symptoms being treated by the D2-blocker must be closely monitored. Fortunately, reports of psychosis in psychiatric patients treated with DA are rare.[139] One multicenter retrospective study of 18 patients found worsened psychotic symptoms only in patients with more severe psychoses at baseline. While a causative relationship between exacerbations in psychosis and DA could not be identified since relapses also occurred in patients not on DA during the study period,[140] providers should be vigilant about the possibility of worsening psychosis.

Novel developments

The concomitant use of dopamine and somatostatin agonists for the treatment of pituitary tumors, and the potential for more-than-additive effects by receptor hybridization, have driven interest in the clinical development of dopastatins-- chimeric molecules that bind both D2 and somatostatin subtype 2 and/or 5 receptors. *In vitro* studies of the effects of these chimeric molecules on non-functional, TSH-secreting, and GH-secreting adenoma cells have shown efficacy, but in vivo studies have not demonstrated prolonged effects. Of the first generation dopastatins, BIM 23A760 (also known as TBR-760) initially showed the most promise. In early *in vitro* studies, the anti-proliferative effects of BIM

23A760 on non-functioning pituitary adenoma cells were comparable to those of cabergoline.[141] *In vivo*, in a POMC knockout mouse model that spontaneously developed aggressive non-functional pituitary adenomas, suppression of tumor growth was seen and tumor volume reduction was observed in 20% of treated mice compared to placebo.[142] When tested *in vitro* for the treatment of TSHomas, BIM 23A760 and another dopastatin, BIM-23A387, inhibited the growth of tumors cells to a greater degree than either octreotide or somatostatin, and both chimeric compounds reduced TSH secretion although to a lesser degree than observed with octreotide.[143] BIM23A760 also demonstrated *in vitro* activity in cells from GH-secreting adenomas, apparently associated with SSTR2 affinity, in some cases demonstrating more GH suppression and in all cases demonstrating greater prolactin suppression than octreotide.[144] [145] Additional studies suggested that BIM23A760, also known as TBR-760, was more effective at suppressing GH from acromegaly tumor cells than octreotide and cabergoline together, and a phase 2 randomized clinical trial was planned. However, in human studies the compound was only found to be effective following a single dose; chronic administration was associated with the production of a metabolite that interfered with efficacy of the compound for GH secretion, and clinical development of the compound for the treatment of acromegaly was terminated[146].

Later-generation compounds have been met with greater success. The second-generation somatostatin-dopamine chimeric molecule TBR-065 (BIM-23B065), a full D2R and SST2R agonist and partial SST5R agonist[146], decreased cell viability in human somatotroph and corticotroph cells,[147] and demonstrated greater suppression of GH secretion from human pituitary somatotroph tumor cell lines than its predecessor TBR-760 (BIM237A60).[148] Furthermore, the main metabolite associated with TBR-065 does not bind to SST receptors nor interfere with the parent compound's efficacy.[148] A phase 1 clinical trial in 63 healthy male volunteers treated with subcutaneous TBR-065 found reduced GH and IGF-1 levels in response to GHRH stimulation in treated versus untreated subjects. [149] The medication was mostly well-tolerated, although orthostatic hypotension led to dose limits, and a separate study of the compound's cardiovascular effects concluded that blood pressure and heart rate should be monitored during use of BIM23B065.[149,150] Further studies are needed to determine the full clinical potential of TBR-065 and other chimeric dopamine/somatostatin molecules, to better meet the pharmacologic needs of patients who don't respond well to SSA or DA alone.

Conclusion

More than forty years since the first clinical application of bromocriptine for the treatment of pituitary tumors in humans, dopamine agonists remain the preferred therapy for prolactin-secreting tumors. Although numerous clinical studies have explored the potential role of DAs in the treatment of other

pituitary tumor subtypes, the prominence of DAs in the therapeutic algorithm for non-prolactinoma tumors has been tempered by variable efficacy and by a dearth of large-scale randomized double-blind placebo controlled trials. Consequently, DAs are used only as adjuvant therapy in non-prolactinoma pituitary tumors, when surgery is contraindicated or not curative, and -- with the notable exception of bromocriptine for the treatment of acromegaly -- their use remains off-label. The class of chimeric compounds targeting both dopamine and somatostatin receptors highlights the existing opportunity to treat other pituitary tumors pharmacologically, potentially achieving desired clinical outcomes while minimizing surgical risks and the associated healthcare costs.

Acknowledgements

Funding for this publication was supported by a generous donation from the Winberg Foundation.

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