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THOUGHT LEADERS INVITED REVIEW

Medical therapy of pituitary adenomas

Mark E. Molitch[1]

The physiologic experiments of the 1950s and 1960s that established the hypothalamic regulation of pituitary function led to the biochemical characterization of the various release and inhibiting hormones and their receptors over the next two decades and ultimately to the development of medical therapies for the various pituitary adenoma types. The paradigm of medical therapy is the extremely successful use of dopamine agonists (DA) for the treatment of prolactinomas, which built upon the basic knowledge that dopamine is the physiologic prolactin (PRL) inhibitor factor. The discovery of somatostatin and its receptors led to the development of somatostatin receptor ligands (SRLs) for the treatment of acromegaly and thyrotropin (TSH)-secreting adenomas, Knowledge of how growth hormone (GH) interacts with its receptor led to the development of pegvisomant, which blocks the binding of GH to its receptor. Early clinical observations of patients with acromegaly have led to the use of estrogens and selective estrogen receptor modulators to aid in its treatment. DAs and SRLs have only modest activity in Cushing's disease and most therapies involve enzymatic blockade of the various steps in cortisol synthesis, the two most recent being osilodrostat and levoketoconazole. Blockade of the cortisol receptor by mifepristone was found accidentally but then was established as a good treatment for Cushing's syndrome. The finding that clinically nonfunctioning adenomas had dopamine receptors led to the use of DA in these patients as well. Finally, an understanding of some of the abnormal molecular pathways underlying the rare aggressiveness of some adenomas and carcinomas has led to the use of temozolomide and now other chemotherapies and immunotherapies in such patients.

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At the young age of 39, Seymour Reichlin, having studied under the "Father of Neuroendocrinology," Sir Geoffrey Harris at Oxford, wrote the definitive article "Neuroendocrinology" in the New England Journal of Medicine in 1963 (1). This review of the field strongly influenced me and many others to go into neuroendocrinology from both basic science and clinical medicine aspects. The regulation of the secretion of each of the pituitary hormones by the hypothalamus was explained in depth, including the concepts that there were specific hormonal releasing and inhibiting factors and that various neurotransmitters were involved in such regulation. These concepts were critical to the subsequent development of the various medical treatments of pituitary tumors (Table 1). In this paper, I review the development of these medical treatments from a historical perspective with the goal of providing insight into how they were developed and used clinically. However, a detailed description of exactly how and when to use them in specific clinical circumstances is beyond the scope of this paper.

Prolactinomas

Prolactinomas are the most common type of hormone-secreting adenoma, comprising close to 50% of cases (2). As Reichlin noted (1), prolactin (PRL) is tonically inhibited by the hypothalamus via a PRL inhibitory factor (PIF). Experiments in rats showed that tuberoinfundibular dopamine released into the hypothalamic-pituitary portal vessels in the median eminence was the physiologic PIF with direct action on the pituitary to inhibit PRL release (3). Studies with low-dose dopamine infusions in humans showed that dopamine blood concentrations similar to those found in rat and monkey hypothalamic-pituitary portal blood were able to suppress PRL secretion (4). Dopamine binds to the D2 class of dopamine receptors on the lactotroph cell membrane (3). Medical therapy using dopamine receptor agonists is the primary therapy for prolactinomas because of its very high efficacy but transsphenoidal surgery can also be done (2).

As experiments establishing dopamine as the physiologic PIF were taking place, other experiments showed that ergot derivatives could suppress PRL secretion. Shelesnyak *et al.* found that ergot derivatives could decrease luteotrophic hormone (prolactin) secretion in rats (5, 6). The ergot derivative, bromocriptine, was the first dopamine agonist (DA) introduced into clinical practice by Peter Lutterbeck (7, 8). Early studies showed that for microprolactinomas (tumors $<$ 10 mm in diameter), bromocriptine is successful in 80% to 90% of patients in normalizing serum PRL levels, restoring gonadal function, and shrinking tumor mass (9). For macroprolactinomas, normalization of serum PRL levels and tumor mass shrinkage occur in about 70% of patients treated with bromocriptine even when given at low doses (9). In most patients, headache and visual field defects improve dramatically within days after the first administration of bromocriptine, with gonadal and sexual function improving even before complete normalization of serum PRL levels. However, some patients have delayed responses. In the multicenter U.S. trial of patients with macroadenomas treated with bromocriptine, some patients had progressive decreases in size of their tumors even after 1 year of treatment (10). Reduction in PRL levels almost always precedes any detectable change in tumor size, and PRL nonresponders are also tumor size nonresponders. In some patients, normalization of PRL levels is accompanied by only modest changes in tumor size.

Cabergoline is now preferred to bromocriptine, as it has been found to have greater efficacy and tolerability than bromocriptine (9, 11, 12). With cabergoline, tumor size has been shown to reduce tumor size in 80% of patients and to restore normal PRL levels in 95% of patients (11). A systematic review and meta-analysis showed significant differences in favor of cabergoline versus bromocriptine with respect to clinical efficacy and adverse events (13). Cabergoline is effective in normalizing PRL levels in about 50% of patients unable to achieve this with bromocriptine (9).

Restoration of normal PRL levels by either drug restores fertility in most cases. Therefore, the drugs must be continued to allow ovulation to occur and then are stopped once pregnancy is confirmed. When given in this fashion, neither drug has been found to increase fetal malformations or other adverse fetal or maternal outcomes in a compilation of the literature (14). However, one study of 183 pregnancies found that compared with a control group, dopamine agonist exposure was associated with an increased risk of preterm birth and early pregnancy loss and an

[1]Emeritus Professor, Division of Endocrinology, Metabolism and Molecular Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
Corresponding Author: Mark E. Molitch, MD, 4942 Sevilla Shores Drive, Wimauma, FL 33598. Phone: 1 708-280-6848; E-mail: molitch@northwestern.edu
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Table 1. Medications used to treat pituitary adenomas

Target	Prolactinoma	Acromegaly	Cushing's Disease	TSHoma	CNFA	Aggressive Adenomas, Carcinomas
Pituitary	Dopamine Agonists	Somatostatin Receptor Ligands	Pasireotide	Somatostatin Receptor Ligands	Dopamine Agonists	Temozolomide
	Somatostatin Receptor Ligands	Dopamine Agonists	Dopamine Agonists		Somatostatin Receptor Ligands	Immune Checkpoint Inhibitors
						Everolimus Bevacizumab Lapatinib
Target Organ		Pegvisomant Estrogen SERMS	Metyrapone Ketoconazole Mitotane Etomidate Osilodrostat Levoketoconazole	PTU Methimazole		
Target Tissue			Mifepristone	Beta Blockers		

Abbreviations: CNFA – clinically nonfunctioning adenoma; PTU – propylthiouracil; SERM – selective estrogen receptor modulator; TSHoma – TSH secreting pituitary adenoma.

insignificant increase in fetal malformations (15). Because these drugs reduce tumor size, when they are stopped there is a risk for tumor enlargement during pregnancy. The risks of symptomatic (headaches, visual field defects) tumor enlargement are 2.5% in pregnant women with microprolactinomas, 18.1% for those with macroprolactinomas with no prior surgery or irradiation, and 4.7% for those with macroadenomas with prior surgery/irradiation (14).

As noted above, 10%–20% of patients are unable to achieve normoprolactinemia with conventional doses of DA (up to 7.5 mg/d for bromocriptine or 2.0 mg/wk for cabergoline) and are therefore deemed to be resistant to these drugs (16). Resistance with respect to tumor size reduction also occurs, but the precise definition of such is uncertain; most use a reduction in size of $<$50% as the definition. Such resistance is associated with a decrease in the number of D2 receptors on the cell membrane and a decrease in the G protein that couples the D2 receptor to adenyl cyclase (16). The underlying genetic underpinnings for this heterogeneity of response are not known (16). Several alternatives are available for such patients, including increasing the dose of the dopamine agonist, switching bromocriptine for cabergoline, transsphenoidal surgery, and adding other drugs such as somatostatin receptor ligands (SRLs; 17, 18) or metformin (19). About 50% of patients resistant to bromocriptine will then respond to cabergoline (9, 16). However, there are few data regarding the efficacy of bromocriptine in patients resistant to cabergoline, so this can be tried recognizing the uncertain benefit (16). Estrogen use may cause a decrease in the effectiveness of DA so that stopping exogenous estrogen may be helpful. A few studies have shown variable efficacy in reducing PRL levels with the use of selective estrogen receptor modulators (SERMs) on PRL secretion in women (20) and aromatase inhibitors in men (21). Rare patients with very aggressive tumors and the even rarer patients with PRL-secreting pituitary carcinomas that are resistant to cabergoline respond in about 40% of cases to temozolomide, an akylating agent (11, 12). There are also individual case reports of such patients responding to other medications, including immune checkpoint inhibitors, tyrosine kinase inhibitors, and mammalian target of rapamycin (mTOR) inhibitors (11, 12).

Once concern about using greater than standard doses of cabergoline has been the development of cardiac valve disorders. Large doses of cabergoline have been associated with leaflet and chordae tendinae thickening with incomplete valvular closing and regurgitation in patients with Parkinson's disease (22, 23). Histologically, there is fibroblast proliferation with deposition of a plaque-like process on the valve leaflet surfaces that may also encase the chordae tendinae (22, 24). Cabergoline, but not bromocriptine, has the ability to stimulate serotonin 2B receptors which results in activation of several mitogenic pathways, ultimately causing this overgrowth valve disorder (24). A meta-analysis of studies showed no increase in risk for clinically significant cardiac valve disease in patients treated with conventional doses of cabergoline, that is, up to 2 mg/wk, although there was a slight increase in mild tricuspid regurgitation (25). Because of the known increased risk of valvular disease with much higher doses, it is now recommended that patients treated with doses greater than 2 mg/wk undergo echocardiography at the time of instituting such doses and then yearly thereafter (9, 11, 12). Whether echocardiography should be done in patients receiving lower doses is controversial (9, 11, 12).

Both bromocriptine and cabergoline can cause nausea, vomiting, constipation, headache, fatigue, and dizziness; these symptoms tend to occur after the initial dose and with dosage increases but can be minimized by introducing the drugs at a low dosage and by gradual dose escalation (9, 12). Long-term, these adverse effects usually do not affect adherence. If these drugs cause significant tumor shrinkage of tumors located in the skull base, cerebrospinal fluid rhinorrhea may occur that will need surgical repair of the area of leakage (9, 12). Mental "fogginess" and psychosis have been rarely reported with both drugs (9, 11, 12). However, it has more recently become apparent that impulse control disorders (ICD) occur in frequencies in reported series varying from 0% to 60% depending upon the type of assessment used (26). Hypersexuality, compulsive shopping, gambling, compulsive eating, and punding were the most frequent types of ICD and symptoms improve with drug dose reduction or cessation (26). Because such ICD's may be hidden from family and friends and therefore can be potentially ruinous in the case of compulsive gambling, it is important to counsel patients and appropriate family members not only when initially prescribing the drugs but at all subsequent visits.

Some patients can be withdrawn from DA over time. In a meta-analysis of 24 studies of 1106 patients, with bromocriptine 15.1% of patients with macroadenomas and 25.9% of those with microadenomas could be successfully withdrawn and with cabergoline 33.5% of those with macroadenomas and 40.8% of those with microadenomas could be successfully withdrawn (27). Better numbers are seen if the duration of therapy is more than 2 years compared with 1 year (27). There are no studies of

outcomes of patients who remain on dopamine agonist therapy for many years.

Those women who were treated with dopamine agonists to restore menses can have the drugs withdrawn at the time of menopause, unless the drugs were used to control tumor size. For all hyperprolactinemic women not treated with DA, monitoring of PRL level every 6 to 12 months is important to detect any patient who might develop an enlarging tumor that might require treatment.

Acromegaly

Reichlin was one of the first to demonstrate the importance of the hypothalamus in regulating growth hormone (GH) secretion by showing that hypothalamic lesions could decrease pituitary GH content (28). It was not until 1982 that GH releasing hormone (GHRH) was characterized (29, 30). Reichlin did not recognize in 1963 that there is also a hypothalamic GH inhibiting factor, later called somatostatin. In 1968, Krulich *et al.* noted an inhibiting substance in hypothalamic extracts (31) and Brazeau *et al.* finally characterized the structure of somatostatin in 1978 (32). Over the ensuing decades, analogs of somatostatin have become the cornerstone of medical therapy for patients with acromegaly who are either not candidates for or who have not been cured by transsphenoidal surgery, which is the initial procedure of choice (33, 34). Of course, patients not controlled by an initial surgery may also be treated with a second surgery or radiotherapy (33, 34). Control of acromegaly is defined biochemically as a random GH level $<$2.5 ng/mL or $<$1.0 ng/mL, depending upon the study, and an insulin-like growth factor-1 (IGF-1) within the normal range (33, 34). When such control is achieved, often with multiple therapeutic modalities (surgery, medication, and sometimes irradiation), there is a reduction in the long-term outcome of mortality to normal, along with reductions in comorbidities such as diabetes and hypertension and improvements in symptoms and quality of life (33–37).

Because somatostatin is rapidly degraded enzymatically, synthetic SRLs were developed with longer half-lives (38). There are five receptor subtypes (SSTR1-5) (38, 39). Octreotide is highly selective for SSTR2 and less so for SSTR5 but has a 20- to 40-fold greater potency than somatostatin (38). Lamberts *et al.* were the first to report the beneficial effects of octreotide given subcutaneously three times daily (40). Subsequently, large, multicenter trials established the long-term efficacy of subcutaneous (41) and then long-acting release (LAR) forms of octreotide (42). A long-acting modification of another SRL, lanreotide, soon followed (43) and both long-acting drugs appear to be similarly efficacious (38, 44) with an ability to control elevated GH and IGF-1 levels in about 40% of patients. Tumor size can also be reduced in about two-thirds of patients (45). Octreotide LAR has to be given by deep intramuscular injection by a trained healthcare professional whereas lanreotide depot is given by deep subcutaneous injection and can be self-injected or injected by a family member/partner after instruction. This difference in administration as well as insurance issues generally dictates which preparation is chosen for a given patient and can affect adherence. Pasireotide is a second-generation SRL which has a higher affinity for SSTR3 and SSTR5 compared with octreotide and lanreotide (38). A head-to-head study showed that pasireotide LAR was more effective than octreotide (31.3% vs. 19.2% in controlling acromegaly) (GH $<$ 2.5 ng/mL and age-adjusted normal IGF-1 levels) (46). Other SRLs in the development pipeline include CAM2029 and Veldoreotide (38).

An oral octreotide formulation has also become available. It uses an enteric-coated capsule that is resistant to stomach acid and the octreotide is absorbed by using a permeability enhancer that allows for the transient opening of the connections between intestinal epithelial cells (47). Studies which involved switching participants with acromegaly who were controlled on injectable SRLs to this oral formulation showed that 65% (47) and 58% (48) maintained normal IGF-1 after 1 year. Another oral octreotide formulation, paltusotine, is in late clinical development with a phase III study showing that 83% of patients were able to maintain normal IGF-1 levels when switched from injectable SRLs (49).

All SRLs, including oral preparations, are generally well tolerated but commonly cause gastrointestinal side effects such as diarrhea, nausea, and flatulence (33). Cholelithiasis may occur but symptomatic gall bladder disease is rare (33). Because SRLs can inhibit insulin secretion, glucose tolerance can sometimes worsen (33). In addition, pasireotide inhibits incretins (38). In the head-to-head study of Colao *et al.*, 57.3% of those treated with pasireotide and 21.7% of those treated with octreotide had hyperglycemia adverse events (46) and this can affect adherence.

Dopamine agonists have also been used in acromegaly. Although early studies with bromocriptine showed only modest success (50), later studies using cabergoline showed that about one-third of patients were able to normalize IGF-1 levels (51). This effect of cabergoline was strongly affected by baseline IGF-1 levels (51). However, when cabergoline was added to SRL's in patients whose IGF-1 levels had remained elevated, 52% of the patients had their IGF-1 levels normalized (51). The Endocrine Society Acromegaly Guideline concluded that "cabergoline is most likely to be useful in patients with just modest elevations of GH and IGF-1 levels, with or without concomitant hyperprolactinemia" (33).

Pegvisomant is a modified GH that acts as a competitive inhibitor to GH for binding to the GH receptor; therefore, IGF-1 levels fall but GH levels do not and there is no anti-tumor effect (33). It is generally used as a second-line therapy singly or in combination in patients not controlled with SRLs (33, 34, 52). In the original trial, 95% of patients achieved normal IGF-1 levels (53) and in the 10-year surveillance follow-up study (ACROSTUDY), 73% of the 2090 treated patients achieved normal IGF-1 levels (54). The long-term study mentioned above did not show an excess number developing tumor enlargement and only 3% of patients developed significant transaminase abnormalities, which were usually transient (54). Pegvisomant use is associated with improved glucose tolerance (55).

As noted above, not all patients achieve GH/IGF-1 targets with single-drug therapies and drugs may be switched within classes or between classes. The molecular basis for this heterogeneity of response to SRLs is poorly understood (52). In patients with IGF-1 levels $<$ twice the upper limit of normal, cabergoline is often tried initially, recognizing that only about one-third of patients will respond; however, it is oral, well tolerated and relatively inexpensive. If cabergoline is not effective or in patients with higher IGF-1 levels, either lanreotide depot or octreotide LAR is usually begun and the dose titrated based on IGF-1 levels (33, 34)). Cabergoline added to SRLs in patients whose IGF-1 levels had remained elevated resulted in the normalization of IGF-1 levels in 52% of patients (51). Another option in such patients is to switch to or add pegvisomant (33, 34). Pegvisomant given weekly to patients uncontrolled by SRLs was able to cause a normalization of IGF-1 levels in 94% of 34 patients (56). Yet another combination is pegvisomant plus pasireotide (57). Estrogens have long been known to decrease the generation of IGF-1 by GH in patients with acromegaly (58). A recent study showed that estrogens could normalize IGF-1 levels in 25% of acromegalic women uncontrolled by SRLs (59). Furthermore, when the SERMs clomiphene (60) and raloxifene (61) were added to the treatment of women uncontrolled by SRLs, over 40% had normalization of IGF-1 levels. The use of SERMs has not yet become routine.

Cushing's Disease

In his 1963 review, Reichlin discussed what was known then about the hypothalamic regulation of ACTH, including the accumulating data for a corticotropin releasing factor separate from vasopressin (1). ACTH-secreting pituitary adenomas comprise about 4% of clinically prevalent cases of pituitary tumors (2). In patients with acromegaly, about two-thirds of cases are macroadenomas (2, 33, 34) but in patients with Cushing's disease, about 90% of cases are microadenomas (2, 62, 63), making cure rates for transsphenoidal surgery much higher and the need for medical therapy much lower. Initial surgical cure rates are about 80% for patients with microadenomas and 60% for those with macroadenomas with recurrence rates as high as 35% being reported in some series (63). Those not cured by surgery and those with recurrence can be treated with second surgeries, irradiation, or medical therapy. Cushing's disease is associated with an increased long-term mortality and treatment that puts the patient into biochemical remission is associated with only a reduction in standardized mortality ratio from 5.7 to 2.3 (64). Similarly, complications of Cushing's disease, such as type 2 diabetes, osteoporosis with fractures, and cardiovascular disease all decrease substantially with treatment that puts

patients into remission but do not return entirely to normal (63). Several mutations have been discovered in patients with Cushing's disease, the most common being *USP8*, present in 36%–60% of adenomas (63). The USP8 mutation causes an overexpression of EGFR which results in an overproduction of ACTH (63). As yet, it is unknown whether the presence of any of these mutations alters the individual patient response to surgical or medical therapies.

Medical therapy can be directed at the pituitary to decrease ACTH secretion, at the adrenal cell to decrease cortisol synthesis, and at the cortisol receptor in various tissues to block glucocorticoid activity (63). In 1975, Krieger and colleagues first reported the successful use of cyproheptadine, an anti-serotonin agent, for the treatment of Cushing's disease, based on the concept of increased hypothalamic serontoninergic activity as being contributory to the development of the condition (65). Although subsequent studies showed much lower response rates and further trials were not done, the potential for successful medical treatment had now been demonstrated and this stimulated the development of many other medications over the years.

Octreotide and lanreotide are not very effective for the treatment of Cushing's disease. Corticotroph adenomas express substantial amounts of somatostatin receptor subtype 5 in addition to subtypes 1, 2, and 3 (66). Unlike octreotide and lanreotide, pasireotide has substantial action at subtype 5 (66). In a prospective, randomized study of 162 patients with Cushing's disease, pasireotide given in daily subcutaneous injections was able to normalize urinary free cortisol (UFC) at 12 months in 19.1% of patients, although many more had falls in UFC that did not reach normal (67). However, a worsening of glucose tolerance occurred in 73% (67). In a subsequent study of 150 patients treated with monthly pasireotide LAR, 62 (40%) patients were able to normalize UFC at 7 months (68). In a study in healthy volunteers, it was found that pasireotide reduced incretin (glucagon-like peptide 1 [GLP-1] and glucose insulinotropic peptide [GIP]) and insulin secretion, without affecting insulin sensitivity (69). The relatively low efficacy and the high rate of glycemic worsening have prevented substantial uptake of this treatment modality.

Dopamine D2 receptors have been found in 80% of corticotroph tumors (70). A multicenter study of 53 patients treated with a median cabergoline dose of 2·3 mg/wk (range 0·5–6·0) showed that normal UFC levels could be obtained in 40% of patients, but only 23% of those showed sustained UFC normalization after a 2.5-year follow-up (71).

A number of steroidogenesis inhibitors have been used to treat Cushing's syndrome of all types (72, 73). Mitotane (o,p'-DDD) is an adrenolytic agent that has been used at low doses, for the treatment of Cushing's disease. Although it is efficacious (48/67 [72%] normal UFC), it has substantial adverse effects (74) and because of the efficacy of other medications, mitotane is now rarely used for the treatment of Cushing's disease.

Metyrapone blocks the 11-hydroxylase enzyme that converts 11-deoxycortisol to cortisol and also inhibits aldosterone synthase (72). A large multicenter study from the United Kingdom of 164 patients with Cushing's syndrome 96 with Cushing's disease) treated with metyrapone monotherapy for up to 16 years showed that UFC normalized in 53% of patients (75). The increased ACTH stimulates other pathways resulting in increased androgen production with hirsutism in women and hypertension and hypokalemia from the increased 11-deoxycortisol levels (64, 72).

Ketoconazole is an imidazole derivative that has been the mainstay of medical treatment for Cushing's syndrome for many years. It blocks several steps in cortisol synthesis, including side chain cleavage, 17-hydroxylase, 17,20 lyase, 11β-hydroxylase, and aldosterone synthase (64, 73). A French series reported data on 200 patients treated with ketoconazole in doses ranging from 200 to 1200 mg/d, with 49% achieving a normal UFC (76). The drug was stopped in 26.8% of patients due to lack of efficacy and in 25.6% due to adverse effects. In this series, liver enzyme elevations were found as follows: $<$5x increase in 30 (15.8%), a 5–10x increase in 4 and a 40x increase in 1. Other side effects of ketoconazole include rash, gastrointestinal symptoms and hypogonadism in men. In 2013, the U.S. Food and Drug Administration (FDA) specified a "black box warning" regarding liver toxicity with ketoconazole use; ketoconazole had never had U.S. FDA approval for use in Cushing's syndrome (77). The European Medicines Agency recommended against prescribing ketoconazole in 2013 as well (78). Ketoconazole is no longer available for use in many countries as a result.

Levoketoconazole is an enantiomer of ketoconazole which has greater potency in inhibiting steroidogenesis enzymes while being potentially less hepatotoxic (72). A study of 94 patients with Cushing's syndrome (80 with Cushing's disease) showed that 31% of patients were able to achieve a normal UFC (79). The most common adverse events were nausea and headache but adverse events led to study discontinuation in 12 of the 94 patients. Alanine aminotransferase reversibly increased to more than three times the upper limit of normal in 10 patients (79). In a further 6-month extension of this study of 60 subjects, the number with normal UFC decreased from 33/54 (61%) to 18/44 (41%) 12 months later (80). Fluconazole is another oral imidazole derivative that has been shown to be effective in the treatment of patients with Cushing's disease in a few individual case reports (81) but there are no studies documenting efficacy in a large number of patients.

Etomidate is another imidazole that inhibits 11β-hydroxylase, aldosterone synthase, and side chain cleavage. It was originally used as an anesthetic agent but was found to cause adrenal insufficiency. Subsequently, it has been used for the treatment of severe hypercortisolemia in the critically ill patient, usually preoperatively to improve surgical risk (infection, wound dehiscence, hypercoagulability, hypertension, hyperglycemia). It must be given intravenously in the intensive care unit (ICU) in subhypnotic doses. It has a rapid onset of action with cortisol levels falling in 12–24 h. There is a need to monitor serum cortisol and potassium levels closely. It is often used in a "block and replace" strategy with higher doses and concomitant IV hydrocortisone (0.5–1 mg/h). Thus, it has a very limited but specific use (82).

Osilodrostat inhibits 11-β hydroxylase and aldosterone synthase, similar to metyrapone. In a study of 137 patients with Cushing's disease with active disease following surgery or who were not surgical candidates, 91 (66.4%) achieved a normal UFC after 48 wk of treatment (83). A long-term extension study showed that of these 91 patients, 86 maintained their complete response at wk 72 (84). The most common adverse effects were nausea, hirsutism, headache, and fatigue with 27/137 discontinuing the medication because of adverse effects over the entire 72-wk period (84). Hypocortisolism requiring a temporary cessation with dose reduction occurred in 54% of subjects with 22.6% requiring glucocorticoid therapy (84). Thirteen patients had tumor enlargement requiring discontinuation of treatment (84). Interestingly, 3 patients have been described who had persistent steroidogenesis blockade lasting from 6 wk to 9 months following cessation of osilodrostat (85). The mechanism for this prolonged blockade is unknown.

Mifepristone, a glucocorticoid receptor antagonist was first demonstrated to be able to successfully treat a patient with Cushing's syndrome due to the ectopic secretion of ACTH by Nieman *et al*. (86). In a literature review in 2010, it was noted that only 37 patients had been treated with mifepristone for various types of Cushing's syndrome (87). Its affinity for the glucocorticoid receptor is more than 10-fold greater than that of cortisol. Mifepristone levels rise within a few hours after dosing, but because it is highly protein bound, it has a long half-life of elimination of 85 h and can appear in the circulation up to 2 wk after being stopped (88).

A study of 50 patients with Cushing's syndrome, including 43 with Cushing's disease, showed that after 24 wk, 60% of 25 treated patients with a concurrent diagnosis of type 2 diabetes or impaired glucose tolerance had a significant reduction of at least 25% from baseline in area under the curve for glucose during an oral glucose tolerance test, and 38% of 21 patients with hypertension showed a significant reduction of at least 5 mm Hg in diastolic blood pressure (DBP) (88). Insulin resistance, weight, waist circumference, and quality of life also improved (84). Adverse effects include adrenal insufficiency (this diagnosis was difficult, as it was based solely on symptoms, as blood cortisol and ACTH levels are high, not low), hypokalemia due to activity of these higher cortisol levels acting at the mineralocorticoid receptor, and menorrhagia in women because it causes an endometrial condition termed progesterone receptor modulator-associated endometrial changes (PAEC), which is not a premalignant lesion (88). One potential concern with mifepristone use was the enlargement of corticotroph adenomas (Nelson's syndrome) but this

turned out to not be a major concern (89), although tumor size does need to be followed in treated patients with Cushing's disease.

To reduce the adverse effects of mifepristone, relacorilant has been developed that binds to the glucocorticoid but not the progesterone receptor (90). A phase II study over 12–16 wk in patients with Cushing's syndrome showed that a dose of 400 mg/d achieved the DBP response (≥5 mm Hg decrease) in 64% and a glycemic response in 50% (91). Adverse effects noted included back pain, headache, edema, nausea, diarrhea, and dizziness but no vaginal bleeding or hypokalemia (91). Phase III clinical trials are now ongoing.

Because of the increased morbidity and mortality when remission is not achieved with surgery, medical therapy is usually initiated quickly. Cabergoline is often tried initially as it is well tolerated and relatively inexpensive but it is successful in less than one-third of patients; however, if it is not successful other medications will be needed. Osilodrostat has more recently become the primary medical therapy because of its high efficacy and relatively low rate of adverse effects compared with the other medications. Mifepristone is often used for severe cases because of its high efficacy in reducing the morbidity of Cushing's syndrome; however, it is difficult to use because of the inability to monitor therapy biochemically and this limits wider usage. Ketoconazole is very cheap and is still used in many countries worldwide but its liver toxicity precludes its use for most patients in the United States, Europe, and many other countries. Newer drugs on the horizon include relacorilant (91) and seliciclib (92), which are in clinical trials. There are also individual case reports of patients treated with immune checkpoint inhibitors, vascular endothelial growth factor (VEGF) antibodies, and mTOR inhibitors. Because of the need to continue medical therapy for many years, pituitary irradiation, usually stereotactic, is often given concomitantly to induce long-term remission without medication.

TSH-Secreting Adenomas

Thyrotropin (TSH) releasing factor (TRF) as a regulator of pituitary thyroid stimulating hormone (TSH) was discussed by Reichlin but the concept that somatostatin could suppress TSH from normal thyrotroph cells and TSH-secreting tumors was not then known (1). TSH-secreting adenomas are the least common of the hormone-secreting pituitary adenomas, comprising about 1% (2, 93). Almost three-quarters secrete TSH alone, but 19% cosecrete GH and 13% cosecrete PRL with three-quarters being macroadenomas and only one-quarter being microadenomas (94). Surgery is the primary treatment modality with medical therapy being reserved for those failing surgical cure (93, 95).

SRLs are the major medical therapies when surgery fails to cure or if a patient is not a candidate for surgery (93–95). There is high expression of SSTR2 in almost all patients as well as SSTR5 (96). SRLs are able to normalize thyroid hormone levels in over 90% of cases and reduce tumor volume by ≥20% in 50% or more of cases (93–95). Escape from control by or failure to respond to SRLs have been reported in a small number of cases (94). Dopamine receptors are also present in these tumors and dopamine agonists have been used in small numbers of patients with variable results (93).

Clinically Nonfunctioning Pituitary Adenomas

Clinically nonfunctioning adenomas (CNFA) range from being completely asymptomatic, and therefore being found either at autopsy or incidentally on imaging, to causing significant symptoms due to mass effects, such as headaches, visual disturbance or hypothalamic/pituitary dysfunction (97). Symptomatic CNFAs are usually treated by surgery but asymptomatic CNFAs are usually followed with serial imaging and only operated if there is significant enlargement over time (97). Overall, CNFAs comprise about one-third of pituitary tumors seen clinically (2). For those tumors that undergo surgery, postoperative imaging over time may show regrowth and the regrowth rate varies depending upon whether routine radiotherapy was given. If there is no tumor visible on MRI postoperatively, regrowth of tumor occurs in 7% of those routinely treated with radiotherapy and in 14.0% of those not treated with radiotherapy (97). If tumor is still visible on MRI postoperatively, regrowth of tumor occurs in 11.2% if those treated with radiotherapy and 50.1% of those not treated with radiotherapy (97). With tumor regrowth, therapeutic options include repeat surgery, radiotherapy, and medical therapy.

Dopamine D2 and somatostatin SSTR2 and SSTR5 receptors are expressed on most CNFAs (98) and thus dopamine agonists and SRLs have been tried as therapy. Greenman *et al.* studied three groups of patients, finding that bromocriptine given to patients with CNFAs who had residual tumor on MRI following surgery caused the tumor mass to decrease or remain stable in 48/55 (87%), that when bromocriptine was started when tumor remnant growth became evident the growth stabilized or decreased in 14/24 (58%) patients, and tumor size decreased or remained stable in 32/60 (53%) of subjects who had neither bromocriptine nor radiotherapy (99). Batista *et al.* performed a prospective, randomized open-label trial in patients with CNFAs following surgery, finding that in 59 patients randomized to cabergoline tumor shrinkage, stabilization, and enlargement occurred in 28.8%, 66.1%, and 5.1% respectively while in the 57 randomized to nonintervention, these proportions were 10.5%, 73.7%, and 15.8% (100). Botelho *et al.* found that the proportion of CNFAs that reduced in size cabergoline was 19%, the number that were stable was 50% and 14% required additional intervention (101). In their review of 11 studies which examined the effects of SRLs on CNFAs, Colao *et al.* found that visual fields improved in 27/84 patients (32.1%) but the changes in tumor volume were much less impressive, with tumor reduction occurring in only 5/100 patients, tumor increase occurring in 12/100 patients and no size change in the remainder (102). Although these studies suggest that cabergoline should be given to patients with tumor visible on MRI postoperatively, such use has not gained wide acceptance. However, radiotherapy is now reserved for patients with growth of a tumor postoperatively documented on serial surveillance MRI scans, even with tumor visible on the initial postoperative scan. However, radiotherapy may be given earlier when the tumor residual is substantial.

Aggressive Pituitary Adenomas and Carcinomas

Less than 1% of pituitary adenomas show progression of tumor growth despite conventional, maximal treatment that includes repeat surgery, radiotherapy, and medical therapy with dopamine agonists or SRLs (103, 104). The diagnosis of carcinoma can be made only if local (within the CNS) or distant metastases can be demonstrated (103, 104). In a cohort of 171 patients from 15 European countries, 121 were aggressive adenomas and 50 were carcinomas, about two-thirds were male, and the origins of the aggressive tumors and carcinomas, respectively were prolactinoma (31.4% and 32.0%), ACTH-secreting (26.4% and 38.0%, GH-secreting (9.9% and 6.0%), nonsecreting (27.3% and 24.0%), and FSH/TSH/unknown (5.0% and 0%) (105). At the time of the initial surgeries, the median Ki67 indices were 6% in the aggressive tumors and 10% in the carcinomas (105).

Temozolomide is the major drug used for treatment of these conditions (103–106) and was used in 91% of the European cohort patients (105). Temozolomide is an oral alkylating agent that causes DNA damage by adding methyl groups to guanine residues, which disrupts DNA transcription (106). The gene *methyl guanine methyltransferase (MGMT)* encodes the MGMT enzyme which catalyzes the removal of these methyl groups (106); therefore, the presence of MGMT may limit the effectiveness of temozolomide but the literature is inconsistent in this effect in clinical practice (106). Of the 156 patients in the European cohort, 9.6% had a complete response, 30.1% a partial response, 28.1% stable disease, and 32.2% progressive disease (100); the mean durations of the complete and partial responses were 6.4 years and 3.3 years, respectively but only 1.4 years in the stable disease group (106). Thirty-one of these received a second temozolomide dose. Halevy and Whitelaw compared different tumor types in a literature summary, finding the following responses: ACTH-secreting adenomas – 56%, prolactinomas – 44%, GH-secreting adenomas – 38%, and CNFAs – 22% (106). The most common adverse effects of temozolomide are fatigue, rash, transaminitis, constipation, nausea, and vomiting (98).

The management of patients who do not respond to or who later fail to continue to respond to temozolomide is not clear and the use of individual other agents has been limited to individual case reports and small case series. Cytotoxic chemotherapy has included cisplatin/etoposide,

lomustine/5-fluorouracil, and 5-fluorouracil/cyclophosphamide/doxorubicin but has had limited success (103, 104). Other therapeutic agents that have shown benefits in small numbers of cases include Lapatinib, a tyrosine kinase inhibitor that inhibits epidermal growth factor receptor (EGFR) and ErbB2 (HER2), bevacizumab, a VEGF inhibitor, the mTOR inhibitor, everolimus, and immune checkpoint inhibitors (103, 104, 107). Peptide receptor radionuclide therapy uses radiolabled somatostatin receptor binding moieties has also been shown to be effective in a small number of cases in whom somatostatin receptors could be demonstrated on their tumors (103, 104, 107). In summary, none of these treatments stand out as being better than another in patients failing temozolomide based on the small numbers of patients treated. Therefore, the best treatment might be one in which a trial for it is being undertaken at the nearest center experienced in the treatment of such patients.

Conclusions

The extensive and detailed physiologic experiments of the 1950s and 1960s that established the hypothalamic regulation of pituitary function, so succinctly summarized by Reichlin (1), led to the biochemical characterization of the various release and inhibiting hormones (no longer factors) and their receptors over the next two decades. This allowed the development of medical therapies for the various tumor types. Over the past two decades, knowledge of the molecular pathways involved in hormone secretion and tumor pathogenesis is allowing the development of even newer treatments that may ultimately be more specific and efficacious.

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References

1. Reichlin S. Neuroendocrinology. N Engl J Med. 1963;269:1182–91. DOI: 10.1056/NEJM196311282692206. PMID: 14061128
2. Molitch ME. Diagnosis and treatment of pituitary adenomas. JAMA. 2017; 317:516–24. DOI: 10.1001/jama.2016.19699. PMID: 28170483
3. Ben-Jonathan N, Hnasko R. Dopamine as a prolactin (PRL) inhibitor. Endocr Rev. 2001;22:724–63. DOI: 10.1210/edrv.22.6.0451. PMID: 11739329
4. Levinson PD, Goldstein DS, Munson PJ, Gill JR Jr, Keiser HR. Endocrine, renal, and hemodynamic responses to graded dopamine infusions in normal men. J Clin Endocrinol Metab. 1985;60:821–6. DOI: 10.1210/jcem-60-5-821. PMID: 3920231
5. Shelesnyak MC. Ergotoxine inhibition of deciduoma formation and its reversal by progesterone. Am J Physiol. 1954;179:301–4. DOI: 10.1152/ajplegacy.1954.179.2.301. PMID: 13218163
6. Lobel BL, Shelesnyak MC, Tic L. Studies on the mechanism of nidation. XIX. Histochemical changes in the ovaries of pregnant rats following ergocornine. J Reprod Fertil. 1966;11:339–48. DOI: 10.1530/jrf.0.0110339. PMID: 4287335
7. Lutterbeck PM, Pryor JS, Varga L, Wenner R. Treatment of non-puerperal galactorrhoea with an ergot alkaloid. Br Med J. 1971;3:228. DOI: 10.1136/bmj.3.5768.228. PMID: 5105219; PMCID: PMC1798547
8. Varga L, Lutterbeck PM, Pryor JS, Wenner R, Erb H. Suppression of puerperal lactation with an ergot alkaloid: a double-blind study. Br Med J. 1972;2:745. DOI: 10.1136/bmj.3.5768.228. PMID: 5105219; PMCID: PMC1798547
9. Gillam MP, Molitch ME, Lombardi G, Colao A. Advances in the treatment of prolactinomas. Endocrine Revs. 2006;27:485–534. DOI: 10.1210/er.2005-9998. PMID: 16705142
10. Molitch ME, Elton RL, Blackwell RE, Caldwell B, Chang RJ, Jaffe R, et al. Bromocriptine as primary therapy for prolactin-secreting macroadenomas: results of a prospective multicenter study. J Clin Endocrinol Metab. 1985;60: 698–705. DOI: 10.1210/jcem-60-4-698. PMID: 3882737
11. Auriemma RS, Pirchio R, Pivonello C, Garifalos F, Colao A, Pivonello R. Approach to the patient with prolactinoma. J Clin Endocrinol Metab. 2023;108:2400–23. DOI: 10.1210/clinem/dgad174. PMID: 36974474
12. Petersenn S, Fleseriu M, Casaneuva FF, Giustina A, Biermasz N, Biller B, et al. Diagnosis and management of prolactin-secreting pituitary adenomas. Pituitary Society International Consensus Guidelines. Nat Rev Endocrinol. 2023; 19(12):722–40. DOI: 10.1016/S2213-8587(21)00235-7. PMID: 37670148
13. Dos Santos Nunes V, El Dib R, Boguszewski CL, Nogueria CR. Cabergoline versus bromocriptine in the treatment of hyperprolactinemia: a systematic review of randomized controlled trials and meta-analysis. Pituitary. 2011;14(3):259–65. DOI: 10.1007/s11102-010-0290-z. PMID: 21221817
14. Huang W, Molitch ME. Pituitary tumors in pregnancy. Endocrine Metab Clin North Am. 2019;48(3):569–81. DOI: 10.1016/j.ecl.2019.05.004. PMID: 31345524
15. Hurault-Delarue C, Montastruc JL, Beau AB, Lacroix I, Damase-Michel C. Pregnancy outcome in women exposed to dopamine agonists during pregnancy: a pharmacoepidemiology study in EFEMERIS database. Arch Gynecol Obstet. 2014;290:263–70. DOI: 10.1007/s00404-014-3210-z. PMID: 24664257
16. Molitch ME. Management of medically refractory prolactinoma. J Neurooncol. 2014;117:421–8. DOI: 10.1007/s11060-013-1270-8. PMID: 24146188
17. Sosa-Eroza E, Espinosa E, Ramírez-Rentería C, Mendoza V, Arreola R, Mercado M. Treatment of multiresistant prolactinomas with a combination of cabergoline and octreotide LAR. Endocrine. 2018;61(2):343–8. DOI: 10.1007/s12020-018-1638-9. PMID: 29948930
18. Coopmans EC, van Meyel SWF, Pieterman KJ, van Ipenburg JA, Hofland LJ, Donga E, et al. Excellent response to pasireotide therapy in an aggressive and dopamine-resistant prolactinoma. Eur J Endocrinol. 2019;181(2):K21–7. DOI: 10.1530/EJE-19-0279. PMID: 31167168
19. Liu X, Liu Y, Gao J, Feng M, Bao X, Deng K, et al. Combination treatment with bromocriptine and metformin in patients with bromocriptine-resistant prolactinomas: pilot study. World Neurosurg. 2018;115:94–8. DOI: 10.1016/j.wneu.2018.02.188. PMID: 29530699
20. Lasco A, Cannavo' S, Gaudio A, Morabito N, Basile G, Nicita-Mauro V, et al. Effects of long-lasting raloxifene treatment on serum prolactin and gonadotropin levels in postmenopausal women. Eur J Endocrinol. 2002;147(4): 461–5. DOI: 10.1530/eje.0.1470461. PMID: 12370106
21. Gillam MP, Middler S, Freed DJ, Molitch ME. The novel use of very high doses of cabergoline and a combination of testosterone and an aromatase inhibitor in the treatment of a giant prolactinoma. J Clin Endocrinol Metab. 2002;87(10): 4447–51. DOI: 10.1210/jc.2002-020426. PMID: 12364416
22. Antonini A, Poewe W. Fibrotic heart-valve reactions to dopamine-agonist treatment in Parkinson's disease. Lancet Neurol. 2007(9);6:826–9 DOI: 10.1016/S1474-4422(07)70218-1. PMID: 17706566
23. Trifirò G, Mokhles MM, Dieleman JP, van Soest EM, Verhamme K, Mazzaglia G, et al. Risk of cardiac valve regurgitation with dopamine agonist use in Parkinson's disease and hyperprolactinemia. A multi-country, nested case-control study. Drug Saf. 2012;35(2):159–71. DOI: 10.2165/11594940-000000000-00000. PMID: 22204718
24. Roth BL. Drugs and valvular heart disease. N Engl J Med. 2007;356(1):6–9. DOI: 10.1056/NEJMp068265. PMID: 17202450
25. Stiles CE, Tetteh-Wayoe ET, Bestwick JP, Steeds RP, Drake WM. A meta-analysis of the prevalence of cardiac valvulopathy in patients with hyperprolactinemia treated with cabergoline. J Clin Endocrinol Metab. 2019;104(2):523–38. DOI: 10.1210/jc.2018-01071. PMID: 30215804
26. Hamblin R, Karavitaki N. Impulse control disorders in patients with pituitary tumors treated with dopamine agonists: a systematic review. Arch Med Res. 2023;54:102910. DOI: 10.1016/j.arcmed.2023.102910. PMID: 37985276
27. Xia MY, Lou XH2, Lin SJ, Wu ZB. Optimal timing of dopamine agonist withdrawal in patients with hyperprolactinemia: a systematic review and meta-analysis. Endocrine. 2018;59(1):50–61. DOI: 10.1007/s12020-017-1444-9. PMID: 29043560
28. Reichlin S. Growth hormone content of pituitaries from rats with hypothalamic lesions. Endocrinology. 1960;67(8):225–230. DOI: 10.1210/endo-69-2-225. PMID: 13740467
29. Rivier J, Spiess J, Thorner M, Vale W. Characterization of a growth hormone-releasing factor from a human pancreatic islet tumour. Nature. 1982;300:276–8. DOI: 10.1038/300276a0. PMID: 6292724
30. Guillemin R, Brazeau P, Bohlen F, Esch F, Ling N, Wehrenberg WB. Growth hormone releasing factor from a human pancreatic tumor that caused acromegaly. Science. 1982;218:585–7. DOI: 10.1126/science.6812220. PMID: 6812220
31. Krulich L, Dhariwal AP, McCann SM. Stimulatory and inhibitory effects of purified hypothalamic extracts on growth hormone release from rat pituitary in vitro. Endocrinology. 1968;83:783–90. DOI: 10.1210/endo-83-4-783. PMID: 4879544
32. Brazeau P, Vale W, Burgus R, Ling N, Butcher M, Rivier J, et al. Hypothalamic polypeptide that inhibits the secretion of immunoreactive pituitary growth hormone. Science. 1973;179:77–9. DOI: 10.1126/science.179.4068.77. PMID: 4682131

33. Katznelson L, Laws ER Jr, Murad MH, Melmed S, Molitch ME, Utz A, et al. Acromegaly: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014;99(11):3933–51. DOI: 10.1210/jc.2014-2700. PMID: 25356808
34. Fleseriu M, Biller BMK, Freda PU, Gadelha MR, Giustina A, Katznelson L, et al. A pituitary society update to acromegaly management guidelines. Pituitary. 2021;24:1–13. DOI: 10.1007/s11102-020-01091-7. PMID: 33079318; PMCID: PMC7864830
35. Mercado M, Gonzalez B, Vargas G, Ramirez C, Espinosa de los Monteros AL, Sosa E, et al. Successful mortality reduction and control of comorbidities in patients with acromegaly followed at a highly specialized multidisciplinary clinic. J Clin Endocrinol Metab. 2014;99:4438–46. DOI: 10.1210/jc.2014-2670. PMID: 25210882
36. Bolfi F, Neves AF, Boguszewski CL, Nunes-Nogueira VS. Mortality in acromegaly decreased in the last decade: a systematic review and meta-analysis. Eur J Endocrinology. 2018;179:59–61. DOI:10.1530/EJE-18-0255. PMID: 29764907
37. Broersen LHA, Najafabadi AHZ, Pereira AM, Dekkers OM, van Furth WR, Biermasz NR. Improvement in symptoms and health-related quality of life in acromegaly patients: a systematic review and meta-analysis. J Clin Endocrinol Metab. 2021;106:577–87. DOI: 10.1210/clinem/dgaa868. PMID: 33245343
38. Gadelha MR, Wildemberg LE, Kasuki L. The future of somatostatin receptor ligands in acromegaly. J Clin Endocrinol Metab. 2022;107:297–308. DOI: 10.1210/clinem/dgab726. PMID: 34618894; PMCID: PMC8764337
39. Patel YC. Somatostatin and its receptor family. Front Neuroendocrinol. 1999;20(3):157–98. DOI: 10.1006/frne.1999.0183. PMID: 10433861
40. Lamberts SWU, Uitterlinden P, Verschoor L, van Dongen KJ, del Pozo E. Long-term treatment of acromegaly with the somatostatin analogue SMS 201-995. N Engl J Med. 1985;313:1576–80. DOI: 10.1056/NEJM198512193132504. PMID: 2866445
41. Ezzat S, Snyder PJ, Young WF, Boyajy LD, Newman C, Klibanski A, et al. Octreotide treatment of acromegaly. A randomized, multicenter study. Ann Intern Med. 1992;117:711–8. DOI: 10.7326/0003-4819-117-9-711. PMID: 1416572
42. Fløgstad AK, Halse J, Bakke S, Lancranjan I, Marbach P, Bruns C, et al. Sandostatin LAR in acromegalic patients: long-term treatment. J Clin Endocrinol Metab. 1997;82(1):23–8. DOI: 10.1210/jcem.82.1.3572. PMID: 8989226
43. Caron P, Beckers A, Cullen DR, Goth MI, Gutt B, Laurberg P, et al. Efficacy of the new long-acting formulation of lanreotide (lanreotide Autogel) in the management of acromegaly. J Clin Endocrinol Metab. 2002;87(1):99–104. DOI: 10.1210/jcem.87.1.8153. PMID: 11788630
44. Murray RD, Melmed S. A critical analysis of clinically available somatostatin analog formulations for therapy of acromegaly. J Clin Endocrinol Metab. 2008;93:2957–68. DOI: 10.1210/jc.2008-0027. PMID: 18477663
45. Bevan JS, Atkin SL, Atkinson AB, Bouloux P-M, Hanna F, Harris PE, et al. Primary medical therapy for acromegaly: an open, prospective, multicenter study of the effects of subcutaneous and intramuscular slow-release octreotide on growth hormone, insulin-like growth factor-I, and tumor size. J Clin Endocrinol Metab. 2002;87(10):4554–63. DOI: 10.1210/jc.2001-012012. PMID: 12364434
46. Colao A, Bronstein MD, Freda P, Gu F, Shen CC, Gadelha M, et al. Pasireotide C2305 study group. Pasireotide versus octreotide in acromegaly: a head-to-head superiority study. J Clin Endocrinol Metab. 2014;99(3):791–9. DOI: 10.1210/jc.2013-2480. PMID: 24423324; PMCID: PMC3965714
47. Melmed S, Popovic V, Bidlingmaier M, Mercado M, van der Lely AJ, Biermasz N, et al. Safety and efficacy of oral octreotide in acromegaly: results of a multicenter phase III trial. J Clin Endocrinol Metab. 2015;100(4):1699–7. DOI: 10.1210/jc.2014-4113. PMID: 25664604
48. Samson SL, Nachtigall LB, Fleseriu M, Gordon MB, Bolanowski M, Labadzhyan A, et al. Maintenance of acromegaly control in patients switching from injectable somatostatin receptor ligands to oral octreotide therapy. J Clin Endocrinol Metab. 2020;105(10):e3785–97. DOI: 10.1210/clinem/dgaa526. PMID: 32882036; PMCID: PMC7470473
49. Gadelha MR, Casagrande A, Strasburger CJ, Bidlingmaier M, Snyder PJ, Guitelman MA, et al. Acromegaly disease control maintained after switching from injected somatostatin receptor ligands to oral paltusotine. J Clin Endocrinol Metab. 2024:dgae385. DOI: 10.1210/clinem/dgae385. PMID: 38828555
50. Moses AC, Molitch ME, Sawin CT, Jackson IM, Biller BJ, Furlanetto R, et al. Bromocriptine therapy in acromegaly: use in patients resistant to conventional therapy and effect on serum levels of somatomedin-C. J Clin Endocrinol Metab. 1981;53(4):752–8. DOI: 10.1210/jcem-53-4-752. PMID: 6793607
51. Sandret L, Maison P, Chanson P. Place of cabergoline in acromegaly: a meta-analysis. J Clin Endocrinol Metab. 2011;96(5):1327–35. DOI: 10.1210/jc.2010-2443. PMID: 21325455
52. Coopmans EC, van der Lely AJ, Neggers SJCMM. Approach to the patient with treatment-resistant acromegaly. J Clin Endocrinol Metab. 2022;107:1759–76. DOI: 10.1210/clinem/dgac037. PMID: 35090028; PMCID: PMC9315163
53. Trainer PJ, Drake WM, Katznelson L, Freda PU, Herman-Bonert V, van der Lely AJ, Dimaraki EV, et al. Treatment of acromegaly with the growth hormone-receptor antagonist pegvisomant. N Engl J Med. 2000;342(16):1171–7. DOI: 10.1056/NEJM200004203421604. PMID: 10770982
54. Buchfelder M, van der Lely AJ, Biller BMK, Webb SM, Brue T, Strasburger CJ, et al. Long-term treatment with pegvisomant: observations from 2090 acromegaly patients in ACROSTUDY. Eur J Endocrinol. 2018;179(6):419–27. DOI: 10.1530/EJE-18-0616. PMID: 30325178
55. Feola T, Cozzolino A, Simonelli I, Sbardella E, Pozza C, Giannetta E, et al. Pegvisomant Improves glucose metabolism in acromegaly: a meta-analysis of prospective interventional studies. J Clin Endocrinol Metab. 2019;104(7):2892–902. DOI: 10.1210/jc.2018-02281. PMID: 30869797
56. Bonert V, Mirocha J, Carmichael J, Yuen KCJ, Araki T, Melmed S. Cost-effectiveness and efficacy of a novel combination regimen in acromegaly: a prospective, randomized trial. J Clin Endocrinol Metab. 2020;105(9):3236–45. DOI: 10.1210/clinem/dgaa444. PMID: 32754748
57. Muhammad A, van der Lely AJ, Delhanty PJD, Dallenga AHG, Haitsma IK, Janssen J, et al. Efficacy and safety of switching to pasireotide in patients with acromegaly controlled with pegvisomant and first-generation somatostatin analogues (PAPE study). J Clin Endocrinol Metab. 2018;103(2):586–95. DOI: 10.1210/jc.2017-02017. PMID: 29155991
58. Clemmons DR, Underwood LE, Ridgway EC, Kliman B, Kjellberg RN, Van Wyk JJ. Estradiol treatment of acromegaly: reduction of immunoreactive somatomedin-C and improvement in metabolic status. Am J Med. 1980;69(4):571–5. DOI: 10.1016/0002-9343(80)90470-2. PMID: 7424946
59. Magalhães J, Ventura N, Lamback EB, Da Silva D, Camacho AH, Chimelli L, et al. A prospective study on the efficacy of oral estrogen in female patients with acromegaly. Pituitary. 2022;25(3):433–43. DOI: 10.1007/s11102-021-01204-w. PMID: 35088193
60. Duarte FH, Jallad RS, Bronstein MD. Clomiphene citrate for treatment of acromegaly not controlled by conventional therapies. J Clin Endocrinol Metab. 2015;100(5):1863–9. DOI: 10.1210/jc.2014-3913. PMID: 25738590
61. Imani M, Khamseh ME, Asadi P, Ghorbani M, Akbari H, Alaei-Shahmiri F, et al. Comparison of cabergoline versus raloxifene add-on therapy to long-acting somatostatin analogue in patients with inadequately controlled acromegaly: a randomized open label clinical trial. Endocr Pract. 2018;24(6):542–7. DOI: 10.4158/EP-2017-0195. PMID: 29949429
62. Reincke M, Fleseriu M. Cushing syndrome. A review. JAMA. 2023;330;170–81. DOI: 10.1001/jama.2023.11305. PMID: 37432427
63. Fleseriu M, Auchus R, Bancos I, Ben-Shlomo A, Bertherat J, Biermasz N, et al. Consensus on diagnosis and management of cushing's disease: a guideline update. Lancet Endocrinol Diabetes. 2021;9(12):847–75. DOI: 10.1016/S2213-8587(21)00235-7. PMID: 34687601; PMCID: PMC8743006
64. Limumpornpetch P, Morgan AW, Tiganescu A, Baxter PD, Nyaga VN, Pujades-Rodriguez M, et al. The effect of endogenous Cushing syndrome on all-cause and cause-specific mortality. J Clin Endocrinol Metab. 2022;107:2377–88. DOI: 10.1210/clinem/dgac265. PMID: 35486378; PMCID: PMC9282270
65. Krieger DT, Amorosa L, Linick F. Cyproheptadine-induced remission of Cushing's disease. N Engl J Med. 1975;293:893–6. DOI: 10.1056/NEJM197510302931802. PMID: 1177986
66. Hofland LJ, Lamberts SW. The pathophysiological consequences of somatostatin receptor internalization and resistance. Endocr Rev. 2003;24(1):28–47. DOI: 10.1210/er.2000-0001. PMID: 12588807
67. Colao A, Petersenn S, Newell-Price J, Findling JW, Gu F, Maldonado M, et al. A 12-month phase 3 study of pasireotide in Cushing's disease. N Engl J Med. 2012;366(10) 914–24. DOI: 10.1056/NEJMoa1105743. PMID: 22397653
68. Lacroix A, Gu F, Gallardo W, Pivonello R, Yu Y, Witek P, et al. Pasireotide G2304 Study Group. Efficacy and safety of once-monthly pasireotide in Cushing's disease: a 12 month clinical trial. Lancet Diabetes Endocrinol. 2018;6:17–26. DOI: 10.1016/S2213-8587(17)30326-1. PMID: 29032078
69. Henry RR, Ciaraldi TP, Armstrong D, Burke P, Ligueros-Sayfari M, Mudaliar S. Hyperglycemia associated with pasireotide: results from a mechanistic study in healthy volunteers. J Clin Endocrinol Metab. 2013;98(8):3446–53. DOI: 10.1210/jc.2013-1771. PMID: 23733372
70. Pivonello R, Ferone D, de Herder WW, Kros JM, de Caro MLDB, Arvigo M, et al. Dopamine receptor expression and function in corticotroph pituitary tumors. J Clin Endocrinol Metab. 2004;89:2452–62. DOI: 10.1210/jc.2003-030837. PMID: 15126577
71. Ferriere A, Cortet C, Chanson P, Delemer B, Caron P, Chabre O, et al. Cabergoline for Cushing's disease: a large retrospective multicenter study. Eur J Endocrinol. 2017;176:305–14. DOI: 10.1530/EJE-16-0662. PMID: 28007845
72. Tritos NA. Adrenally directed medical therapies for Cushing syndrome. J Clin Endocrinol Metab. 2021;106(1):16–25. DOI: 10.1210/clinem/dgaa778. PMID: 33118025

73. Castinetti F, Nieman LK, Reincke M, Newell-Price J. Approach to the patient treated with steroidogenesis inhibitors. J Clin Endocrinol Metab. 2021; 106(7):2114–23. DOI: 10.1210/clinem/dgab122. PMID: 33675650; PMCID: PMC8427736
74. Baudry C, Coste J, Khalil RB, Silvera S, Guignat L, Guibourdenche J, et al. Efficiency and tolerance of mitotane in Cushing's disease in 76 patients from a single center. Eur J Endocrinol. 2012;167(4):473–81. DOI: 10.1530/EJE-12-0358. PMID: 22815335
75. Daniel E, Aylwin S, Mustafa O, Ball S, Munir A, Boelaert K, et al. Effectiveness of metyrapone in treating Cushing's syndrome: a retrospective multicenter study in 195 patients. J Clin Endocrinol Metab. 2015;100(11):4146–54. DOI: 10.1210/jc.2015-2616. PMID: 26353009; PMCID: PMC5393433
76. Castinetti F, Guignat L, Giraud P, Muller M, Kamenicky P, Drui D, et al. Ketoconazole in Cushing's disease: is it worth a try? J Clin Endocrinol Metab. 2014;99(5): 1623–30. DOI: 10.1210/jc.2013-3628. PMID: 24471573
77. United States Food and Drug Administration. FDA drug safety communication: FDA limits usage of Nizoral (ketoconazole) oral tablets due to potentially fatal livery injury and risk of drug interactions and adrenal gland problems. 2016; 1–6.
78. European Medicines Agency. 2013. European Medicines Agency recommends suspension of marketing authorisations for oral ketoconazole. EMA/ 458028/2013.
79. Fleseriu M, Pivonello R, Elenkova A, Salvatori R, Auchus RJ, Feelders RA, et al. Efficacy and safety of levoketoconazole in the treatment of endogenous Cushing's syndrome (SONICS): a phase 3, multicentre, open-label, single-arm trial. Lancet Diabetes Endocrinol. 2019;7(11):855–65. DOI: 10.1016/S2213-8587(19)30313-4. PMID: 31542384
80. Fleseriu M, Auchus RJ, Greenman Y, Zacharieva S, Geer EB, Salvatori R, et al. Levoketoconazole treatment in endogenous Cushing's syndrome: extended evaluation of clinical, biochemical, and radiologic outcomes. Eur J Endocrinol. 2022;187(6):859–71. DOI: 10.1530/EJE-22-0506. PMID: 36251618; PMCID: PMC9716395
81. Burns K, Christie-David D, Gunton JE. Fluconazole in the treatment of Cushing's disease. Endocrinol Diabetes Metab Case Rep. 2016:2016:150115. DOI: 10.1530/EDM-15-0115. PMID: 26858837; PMCID: PMC4744941
82. Preda VA, Sen J, Karavitaki N, Grossman AB. Etomidate in the management of hypercortisolaemia in Cushing's syndrome: a review. Eur J Endocrinol. 2012;167(2):137–43. DOI: 10.1530/EJE-12-0274. PMID: 22577107
83. Pivonello R, Fleseriu M, Newell-Price J, Bertagna X, Findling J, Shimatsu A, et al. Efficacy and safety of osilodrostat in patients with Cushing's disease (LINC 3): a multicentre phase III study with a double-blind, randomised withdrawal phase. Lancet Diabetes Endocrinol. 2020;8:748–61. DOI: 10.1016/S2213-8587(20)30240-0. PMID: 32730798
84. Fleseriu M, Newell-Price J, Pivonello R, Shimatsu A, Auchus RJ, Scaroni C, et al. Long-term outcomes of osilodrostat in Cushing's disease: LINC 3 study extension. Eur J Endocrinol. 2022;187(4):531–41. DOI: 10.1530/EJE-22-0317. PMID: 35980235; PMCID: PMC9513654
85. Poirier J, Bonnet-Serrano F, Thomeret L, Bouys L, Bertherat J. Prolonged adrenocortical blockade following discontinuation of osilodrostat. Eur J Endocrinol. 2023;188(6):K29–32. DOI: 10.1093/ejendo/lvad060. PMID: 37300549
86. Nieman LK, Chrousos GP, Kellner C, Spitz IM, Nisula BC, Cutler GB, et al. Successful treatment of Cushing's syndrome with the glucocorticoid antagonist RU 486. J Clin Endocrinol Metab. 1985;61(3):536–40. DOI: 10.1210/jcem-61-3-536. PMID: 2991327
87. Castinetti F, Conte-Devolx B, Brue T. Medical treatment of Cushing's syndrome: glucocorticoid receptor antagonists and mifepristone. Neuroendocrinol. 2010; 92:125–30. DOI: 10.1159/000314224. PMID: 20829633
88. Fleseriu M, Biller BMK, Findling JW, Molitch ME, Schteingart DE, Gross C. Mifepristone, a glucocorticoid receptor antagonist, produces clinical and metabolic benefits in patients with Cushing's syndrome. J Clin Endocrinol Metab. 2012;97(6):2039–49. DOI: 10.1210/jc.2011-3350. PMID: 22466348
89. Fleseriu M, Findling JW, Koch CA, Schlaffer S-M, Buchfelder M, Gross C. Changes in plasma ACTH levels and corticotroph tumor size in patients with Cushing's disease during long-term treatment with the glucocorticoid receptor antagonist mifepristone. J Clin Endocrinol Metab. 2014;99(10):3718–27. DOI: 10.1210/jc.2014-1843. PMID: 25013998; PMCID: PMC4399272
90. Hunt H, Donaldson K, Strem M, Zann V, Leung P, Sweet S, et al. Assessment of safety, tolerability, pharmacokinetics, and pharmacological effect of orally administered CORT125134: an adaptive, double-blind, randomized , placebo-controlled Phase I clinical study. Clin Pharmacol Drug Dev. 2018;7(4):408–21. DOI: 10.1002/cpdd.389. PMID: 28967708; PMCID: PMC5947602
91. Pivonello R, Bancos I, Feelders RA, Kargi AY, Kerr JM, Gordon MB, et al. Relacorilant, a selective glucocorticoid receptor modulator, induces clinical improvements in patients with Cushing syndrome: results from a prospective, open-label Phase 2 study. Front Endocrinol. 2021;12:662865. DOI: 10.3389/fendo.2021.662865. PMID: 34335465; PMCID: PMC8317576
92. Liu NA, Ben-Shlomo A, Carmichael JD, Wang C, Swerdloff RS, Heaney AP, et al. Treatment of Cushing disease with pituitary-targeting seliciclib. J Clin Endocrinol Metab. 2023;108(3):726–35. DOI: 10.1210/clinem/dgac588. PMID: 36214832; PMCID: PMC10210614
93. Amlashi FG, Tritos NA. Thyrotropin-secreting pituitary adenomas: epidemiology, diagnosis, and management. Endocrine. 2016;52(3):427–40. DOI: 10.1007/s12020-016-0863-3. PMID: 26792794
94. Beck-Peccoz P, Lania A, Beckers A, Chatterjee K, Wemeau J-L. 2013 European thyroid association guidelines for the diagnosis and treatment of thyrotropin-secreting pituitary tumors. Eur Thyroid J. 2013;2(2):76–82. DOI: 10.1159/000351007. PMID: 24783044; PMCID: PMC3821512
95. De Herdt C, Philipse E, De Block C. Endocrine tumours: Thyrotropin-secreting pituitary adenoma: a structured review of 535 adult cases. Eur J Endocrinol. 2021;185(2):R65–74. DOI: 10.1530/EJE-21-0162. PMID: 34132199
96. Gatto F, Arvigo M, Ferone D. Somatostatin receptor expression and patients' response to targeted medical treatment in pituitary tumors: evidences and controversies. J Endocrinol Invest. 2020;43(11):1543–53. DOI: 10.1007/s40618-020-01335-0. PMID: 32557353
97. Molitch ME. Non-functioning pituitary tumors. Handb Clin Neurol. 2014;124: 167–84. DOI: 10.1016/B978-0-444-59602-4.00012-5. PMID: 25248587
98. Yavropoulou MP, Tsoli M, Barkas K, Kaltsas G, Grossman A. The natural history and treatment of non-functioning pituitary adenomas (non-functioning PitNETs). Endocr Relat Cancer. 2020;27(10):R375–90. DOI: 10.1530/ERC-20-0136. PMID: 32674070
99. Greenman Y, Cooper O, Yaish I, Robenshtok W, Sagiv N, Jonas-Kimchi R, et al. Treatment of clinically nonfunctioning pituitary adenomas with dopamine agonists. Eur J Endocrinol. 2016;175(1):63–72. DOI: 10.1530/EJE-16-0206. PMID: 27150495
100. Batista RL, Musolino NRC, Cescato VAS, da Silva GO, Medeiros RSS, Herkenhoff CGB, et al. Cabergoline in the management of residual nonfunctioning pituitary adenoma: a single-center, open-label, 2-year randomized clinical trial. Am J Clin Oncol. 2019;42(2):221–7. DOI: 10.1097/COC.0000000000000505. PMID: 30540568
101. Botelho MS, Franzini ÍA, Nunes-Nogueira VDS, Boguszewski CL. Treatment of non-functioning pituitary adenoma with cabergoline: a systematic review and meta-analysis. Pituitary. 2022;25(6):810–8. DOI: 10.1007/s11102-022-01257-5. PMID: 35902444
102. Colao A, DiSomma C, Pivonello R, Faggiano A, Lombardi G, Savastano S. Medical therapy for clinically non-functioning pituitary adenomas. Endocrine-Related Cancer. 2008;15:905–15. DOI: 10.1677/ERC-08-0181. PMID: 18780796
103. Lin AL, Donoghue MTA, Wardlaw SL, Yang TJ, Bodei L, Tabar V, et al. Approach to the treatment of a patient with an aggressive pituitary tumor. J Clin Endocrinol Metab. 2020;105(12):3807–20. DOI: 10.1210/clinem/dgaa649. PMID: 32930787; PMCID: PMC7566322
104. Burman P, Casar-Borota O, Perez-Rivas LG, Dekkers OM. Aggressive pituitary tumors and pituitary carcinomas: from pathology to treatment. J Clin Endocrinol Metab. 2023;108(7):1585–601. DOI: 10.1210/clinem/dgad098. PMID: 36856733; PMCID: PMC10271233
105. Burman P, Trouillas J, Losa M, McCormack A, Petersenn S, Popovic V, et al. Aggressive pituitary tumours and carcinomas, characteristics and management of 171 patients. Eur J Endocrinol. 2022;187(4):593–605. DOI: 10.1530/EJE-22-0440. PMID: 36018781; PMCID: PMC9513638
106. Halevy C, Whitelaw BC. How effective is temozolomide for treating pituitary tumours and when should it be used? Pituitary. 2017;20(2):261–6. DOI: 10.1007/s11102-016-0745-y. PMID: 27581836
107. Ilie MD, Lasolle H, Raverot G. Emerging and novel treatments for pituitary tumors. J Clin Med. 2019;8(8):1107. DOI: 10.3390/jcm8081107. PMID: 31349718; PMCID: PMC6723109