Updates in the Medical Treatment of Pituitary Adenomas

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Key words
prolactinoma, somatostatin receptor ligands, non functioning pituitary adenomas, glucocorticoid receptor blockade, adrenal steroidogenesis inhibitors, Cushing's disease, acromegaly, pituitary adenoma

received 03.10.2019
accepted 13.11.2019

Bibliography
DOI https://doi.org/10.1055/a-1066-4592
Published online: 20.12.2019
Horm Metab Res 2020; 52: 8–24

ISSN 0018-5043

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ABSTRACT

Pituitary adenomas represent approximately 15 % of brain tumors; incidence is significantly on the increase due to widespread use of magnetic resonance imaging. Surgery remains the first-line treatment for most tumors overall. The role of dopaminergic agonists (DAs) and somatostatin receptor ligands (SRLs) in the treatment of pituitary adenomas is quite well established for prolactinomas and growth hormone (GH) excess. However, over the last decade new multi-receptor binding SRLs are increasingly used for treatment of acromegaly and Cushing's disease. SRLs/DA chimeric compounds seem to have enhanced potency and efficacy when compared to that of individual SRLs or DA receptor agonists according to preclinical data. However, following negative results, more research is needed to determine if this interesting mechanism will translate into positive clinical effects for acromegaly patients. Furthermore, new agents that block adrenal steroidogenesis have been developed in phase III clinical trials for Cushing's disease and several new compounds working at the pituitary level and/or blocking the glucocorticoid receptor are also in development. Combination therapy of drugs with similar or different mechanisms (possibly synergistic) are also on the increase. A growing awareness regarding all mechanisms involved in both control of pituitary secretion and cellular proliferation might allow for sole medical treatment of pituitary adenomas, especially macroadenomas, rather than surgery and/or radiation therapy, in the future. Moreover, the underlying decision on how to treat patients with pituitary adenomas should be individualized on a case-by-case basis with not only a goal of tumor shrinkage and biochemical control, but also of improving patients' quality of life.

Introduction

We have conducted a review of evidence regarding medical treatment of prolactinomas (lactotroph adenomas), acromegaly, Cushing's disease, and "non-secretory" pituitary adenomas. Updated information regarding efficacy and limitations of current treatments and recent developments (new drugs or combination treatments) are presented.

Medical treatment for aggressive pituitary adenomas will be discussed elsewhere in this special issue.

Discussion

Prolactinomas

Prolactinomas, hormone-secreting pituitary adenomas that secrete prolactin (PRL) [1, 2] represent approximately 40–45 % of pituitary tumors [3, 4]. Prevalence varies with both sex and age, occurring more frequently in women at a ratio of 10:1, and in those aged 20–50 years [5–8]. However, after the fifth decade of life, the female-to-male ratio radically changes to 1:1 [9]. Most prolactinomas are microadenomas (80 %), while macroadenomas are more rare and more commonly observed in males [7]. Hyperprolactinemia causes symptoms of amenorrhea/oligomenorrhea, galactor-

rhea and infertility in premenopausal females and erectile dysfunction, infertility and gynecomastia in males [7]. Headaches are also frequently noted in these patients, ranging from migraines (most common) to cluster headaches and other related headache subtypes [10]. Less common symptoms of prolactinomas can include visual field disturbances, due to large tumor size, which can compress the optic chiasm or other cranial nerve [1, 2, 7]. Although there is a clear prevalence of prolactinomas in women, men have shown to have more aggressive macroadenomas, which are more likely to be resistant to dopamine agonists (DAs) [11]. A retrospective study by Liu, et al., in 2018, analyzed outcomes of prolactinomas in men in comparison to a control group and found overall that men who required surgery had larger and more invasive tumors, as well as higher rates of DA resistance, similar to silent corticotroph adenomas, tumors that are known to be more clinically aggressive [12].

The primary treatment goal for prolactinomas is to normalize serum PRL levels [4]. First-line treatment for most patients is a DA [9, 13]. Dopamine typically regulates pituitary hormone secreted through the dopamine subtype 2 receptor, which is generally expressed in lactotrophs. After dopamine binds to D2R, on lactotroph cells, is inhibiting PRL secretion. Dopamine agonists non-selectively target and bind to the dopamine receptors, resulting in a decrease in PRL levels [1]. Bromocriptine (BRC) and cabergoline (CAB) are the two DAs that have been approved in the US as medical treatments. Quinagolide is also used outside the US [14, 15]. In most cases, treatment is long-term [16], although some studies have tried to predict, which patients will be able to withdraw from long-term treatment. While non-selective, it has been shown that BRC tends to bind to D2 receptors in the pituitary and also the D1 receptors in the gut. CAB is more specific to D2 receptors in the pituitary, which makes it more effective [1, 17]. Both BRC and CAB have been shown to bind to D3 receptors in the limbic system [14, 18]. The side effects of BRC can include: nausea, dizziness, which can make it less tolerated than CAB [19]. BRC has been shown to normalize PRL levels and reduce tumor size in 80–90 % of microprolactinoma and 70 % of macroprolactinoma cases [20]. CAB has better efficacy, normalizing PRL in up to 95 % of patients, is able to reduce tumor size in 50-90 % of patients, and controls the majority of symptoms [1, 21]. Typical dosing for BRC is approximately 2.5–15 mg/day, given the relatively short half-life [20]. CAB dosing ranges from 0.5–3.5 mg/week due to the longer half-life, which may indicate why CAB has higher patient adherence [20–22] (▶ **Table 1**). A recent study collected data from 3 tertiary care institutions looking at PRL secretion and tumor volume shrinkage following DA therapy. The study found evidence of plateaus in both the size regression of prolactinoma tumors, as well as the PRL level reduction. Both were found to have the greatest and most rapid reduction during the first 6 months of DA therapy, which then tapered off during the following 6 months, and diminished further thereafter [23].

Depending on definition of resistance, usually failure to achieve PRL normalization or a decrease by 50 % in PRL values and/or tumor shrinkage, 30 % of patients with prolactinomas encounter DA resistance at regular doses. It is estimated that 25 % of patients treated with BRC and 10–15 % of patients treated with CAB fail to reach normalized PRL levels [1, 24, 25]. Most DA-resistant patients can follow several lines of optimization in order to respond to treatment such as; switching to CAB if patient is being treated with BRC, escalating the CAB weekly dosage, transsphenoidal surgery, radiotherapy, or a combination of all lines of treatment optimization [24, 26]. The CAB titration scheme is variable; usually starting with 0.25 mg twice a week and increasing to 0.5 mg twice a week after 4–6 weeks; further increases are based on patient tolerance to DA and PRL prolactin values.

Of note, long-term CAB high dose may cause clinical valvular disease (as shown in patients with Parkinson's disease), and the risk should be taken into consideration for some patients [9, 21, 26]. Although occurrence of a clinically significant valvular disease was reassuringly low in large series of patients with prolactinomas treated with DAs [4, 9, 27], some groups recommend periodical follow-up of high risk patients, notably those taking high doses (e. g., > 3 mg/week) or high cumulative doses, with annual cardiovascular exam and, if necessary, echocardiogram (e. g., when a new cardiac murmur, edema, dyspnea, or cardiac failure occur) [28, 29].

Over the last decade, increased impulse control disorders (ICD) in patients treated with DAs has been reported, initially in patients with Parkinson's disease (PD) [18]. ICD symptoms manifest as hypersexuality, compulsive shopping, eating and gambling, and punding [14, 30]. Most recently, retrospective studies and case reports have also described patients with prolactinomas developing ICDs. Prevalence varies between studies; Noronha, et al., reported an occurrence of 5 % [31], while a later cross-sectional observational study showed a higher prevalence, at 24.6 % in prolactinoma patients [32]. The rate of significant ICD in prolactinoma patients in clinical practice remains to be clarified by further studies. Impulse disorders can be detrimental to a person's personal and professional life [30]. Interestingly, there are no linked relationships between ICDs and DA type, duration of treatment, or dosing regime, so far [14, 32]. Although mechanisms are less clear, one hypothesis is that this ties into the D3 receptor signaling cascade. Since both CAB and BRC can bind to the D3 receptors in the limbic system, this can have an effect on impulsivity due to D3 receptor stimulation, with a higher prevalence of BRC binding to D3 than CAB [14, 20]. In a recent case-controlled study, males with prolactinomas who were treated with either DA were 9.9 times more likely than females to develop an ICD [32]. It is unclear whether there is a correlation between individuals with predisposing psychological traits or certain psychiatry disorders [14]. The exact treatment for DA-related ICD is not known, though stopping DAs seems to be the most effective approach in managing ICDs; reducing DA dosage can also improve or lead to symptoms eradication [14]. Other less common possible psychological effects of DAs can include mania, anxiety, depression, insomnia, psychosis, and paranoia [30]. Whenever possible, adding psychotherapy or psychiatric medication alongside reduced DAs dosing can be considered. Due to lack of clinical studies about this topic, it is important for physicians to routinely screen patients and their families about possible impulsive behaviors, as well as counsel all parties before DA prescription [30]. If psychosis (e. g., schizophrenia) and prolactinoma coexist, the treatment of one disease can exacerbate the symptoms of the other. While data are limited, reports of aripiprazole, clozapine, or quetiapine combined with BRC or quinagolide have shown effectiveness in these patients [33–35]. In other cases, prolactinoma surgery has been recommended if psychiatric disease coexisted with mass effect manifestations [12, 33].

▶ **Table 1** Medical treatment options for pituitary tumors directed to pituitary gland.

Medication	Family	Indication	Mechanism of action	Dose	Effectiveness	Side effects	Clinical development
Cabergoline	Ergot derivative (DR 2 agonist)	Prolactinoma	Decreases PRL secretion and tumor cell proliferation	0.5–3.5 mg/week, oral (usually 0.5–2 mg/week)	PRL normalization in 90–95 % of patients Tumor size decrease in 50–90 %	Nausea and dizziness (usually transient), hypotension Potential risk of valvular disease at high doses (rare) Compulsive behavior (rare) Cabergoline is better tolerated Acceptable in pregnancy (B), notably bromocriptine	Retrospective study Prospective study
		Acromegaly	Decreases GH secretion	1–4 mg/week, oral (mean 2.5 mg/week)	GH control in 30 % (notably in mixed GH-PRL tumors)		Retrospective study Prospective study
		Cushing's disease	Decreases ACTH secretion	0.5–7 mg/week, oral (mean 3.5 mg/week)	Normal UFC in 30–40 %		Retrospective study Prospective study Large retrospective multicenter
		Non-functioning adenomas	Decreases tumor cell proliferation	0.5–3.5 mg/week. oral (mean 1.5 mg/week)	Tumor shrinkage in 38 %, stable in 49 % (treated after surgery, with bromocriptine and/or cabergoline)		Retrospective study
Bromocriptine	Ergot Derivative (DR 2 agonist)	Prolactinoma Acromegaly Non-functioning adenomas	Decreases PRL and GH secretion Decreases tumor cell proliferation	2.5–10 mg/day, oral QD, BID	PRL normalization in 60–80 %; tumor size decrease; GH control in < 30 % (notably in mixed GH-PRL tumors)		Retrospective study
Octreotide	Somatostatin receptor ligand	Acromegaly	Decreases GH secretion and tumor cell proliferation	50–100 µg SC TID LAR: 10–40 mg IM/month	GH and IGF1 normalization in approx. 50–60 %; tumor shrinkage (of > 20 %) in 54–65 % (more in primary treatment) OCT SC may be added to LAR for acromegalic headache	N/V/D, constipation, abdominal pain, cholelithiasis/biliary sludge, bloating, bradycardia, fatigue, headache, alopecia, dysglycemia; subcutaneous nodules (for LAN) Pregnancy category: B (OCT), C (LAN)	Phase III Prospective studies
Lanreotide	Somatostatin receptor ligand	Acromegaly	Decreases GH secretion and tumor cell proliferation	Autogel 60–120 mg deep SC monthly			
Pasireotide (SOM-230)	Somatostatin receptor ligand (SSTR 5, 2, 3,1)	Acromegaly	Decreases GH secretion and tumor cell proliferation	LAR: 40–60 mg/month IM	IGF normalization in 20 % of patients resistant to 1st generation SRL	Transient diarrhea, nausea Cholelitiasis Hyperglycemia (frequent) QT prolongation Not approved for use during pregnancy (C)	Phase III Prospective studies
		Cushing's disease	Decreases ACTH secretion and tumor cell proliferation	600–900 µg SC BID. LAR: 10–30 mg/month IM	Hypercortisolism improvement in 34.5–50 % Tumor volume decrease 9.1–43.8 %		Phase III Pasireotide2305, G2304 Expanded pasireotide 2305-completed

▶ **Table 1** Continued

Medication	Family	Indication	Mechanism of action	Dose	Effectiveness	Side effects	Clinical development
Temozolomide	Alkylating agent	Aggressive tumors: Cushing's disease Prolactinoma Acromegaly Non-functioning adenomas	Metabolite MTIC causes DNA methylation	150–200 mg/m²/day for 5 days each month per cycle	Small studies: Tumor regression 40–50 % (less in NFA), decreased ACTH by 88 % and decreased UFC by 98 % (MGMT–MSH-6 + could be a predictive factor?)	Fatigue, hearing loss, phlegmone, UTI, liver enzyme increase Hematologycal (cytopenia) Pregnancy class: D	Case reports Retrospective studies Case Series
New drugs in development							
Oral octreotide	Somatostatin receptor ligand	Acromegaly	Decreases GH secretion and tumor cell proliferation	20–40 mg twice daily, oral	Maintenance of GH, IGF1 control in 85 % of patients previously normalized on Octreotide LAR	N/V/D, dyspepsia, cholelithiasis, headaches, dizziness, dysglycemia	A phase III completed and published Two Phase III studies ongoing
CRN00808	Oral selective nonpeptide SST2 biased agonists	Acromegaly	Clinical proof-of-concept in healthy volunteers-suppressed stimulated GH and baseline IGF-1		10 mg once daily reduced GHRH-induced GH release by 91 %		Ongoing phase II clinical trials
Lapatinib	Tyrosine kinase inhibitor for EGFR and HER2	Aggressive prolactinoma	Decreases PRL secretion and tumor cell proliferation	1250 mg/day	Stable tumor volume in approx. 50 % of patients	Fatigue, GI disturbances, acroparesthesias, insomnia	Case reports
R-roscovitine (CYC202, seliciclib)	Purin analogue (CDK2 antagonist)	Cushing's disease	Dissociates CDK2/Cyclin E complex, inducing cell senescence. Suppresses ACTH secretion and tumor growth	400 mg BID	Under study	Asthenia, nausea and hypokalemia Pregnancy class: NA	Ongoing Phase II Prospective NCT02160730
Gefitinib (ZD1839)	Tyrosine kinase inhibitor (EGFR antagonist)	Cushing's disease	Inhibits USP-8 mutation-induced EGFR overexpression	250 mg QD	Under study	Rash and diarrhea Pregnancy class: NA	Ongoing Phase II prospective for USP-8 mutated CD
Retinoic Acid	Vitamin A derivatives (agonist RAR and RXR)	Cushing's disease	Inhibits POMC transcription and ACTH secretion. Tumor cell apoptosis	RA: 10–80 mg QD Isotretinoin: 20–80 mg QD	Retinoic acid: Normal UFC 43 % Isotretinoin: Normal LNSC and UFC in 25 %	Conjunctival irritation, nausea, headache and arthralgia Do not use in pregnancy (X)	Prospective multicenter study Ongoing Phase II Prospective open-label

SRL: Somatostatin receptor ligand; SSTR's: Somatostatin receptors; DR: dopamine receptor; N/V/D: Nausea, vomiting, diarrhea ; SC: Subcutaneously; IM: Intramuscularly; QD: Once daily; BID: Twice daily; TID: Thrice daily; UFC: Urinary free cortisol; mgMT: *O*-6-Methylguanine-DNA methyltransferase; MSH-6: DNA mismatch protein 6; LFT: Liver function tests; RA: Retinoic acid; PRL: Prolactin; NFA: Non-functioning pituitary adenoma; DNA: Deoxyribonucleic acid; EGFR: Epidermal growth factor receptor; CDK2: Cyclin dependent kinase type 2; UTI: Urinary tract infection; RAR: Retinoic acid receptor; RXR: Retinoid X receptor; POMC: Pro-opiomelanocortin; GH: Growth hormone; IGF-1: Insulin-like growth factor 1; ACTH: Adrenocorticotropic hormone; SST: Somatostatin; MTIC: 3-Methyl(triazen-1-yl)imadazole-4-carboxamide; USP-8: Ubiquitin-specific protease 8; LAR: Long-acting repeatable; CD: Cushing's disease; GI: Gastrointestinal; LNSC: Late-night salivary cortisol; NA: Not assessed. Pregnancy categories: A (Generally acceptable. Controlled studies in pregnant women show no evidence of fetal risk), B (May be acceptable. Animal studies showed minor risks and human studies showed no risk), C (Use with caution if benefits outweigh risks. Either no studies available or only animal studies show risk and human studies not available), D (Positive evidence of human fetal risk. Use in last resort, as salvage therapy for emergencies when no safer drug is available), X (Do not use in pregnancy. Risks outweigh benefits, use alternatives).

Endoscopic transsphenoidal surgery (TSS) is considered the second-line treatment for prolactinomas [22]. A surgical option can be explored by the physician and patient on a case-by-case basis. Patients with DA resistance, where intensive treatment with CAB does not show lower serum PRL levels over a period of at least 3 months can opt for surgery to reduce hyperprolactinemia [1, 2, 22]. Also furthermore, surgery can be considered for patients with neurological signs from apoplexy or patients with giant or cystic macroprolactinomas who may exhibit neurological symptoms [4, 27]. Finally, patients that report DA intolerance can also opt for TSS [4]. With new advancements in technology and an increase in surgical experience and skill, TSS is considered minimally invasive, safe and efficacious, giving the surgeon a wider field of vision and increased working field [36]. Patients with microprolactinomas sometimes consider/prefer surgery in lieu of lifelong medical therapy. Considering this option, some clinical and economic results have shown that surgical resection costs mirror the costs of medical therapy over a 10-year period, after which TSS might be considered more cost effective for perhaps young patients with microadenomas [8, 37]. Complication rates with TSS are minimal [38], though surgical outcome is very dependent upon the skill and experience of the surgeon as well as the size of the tumor and baseline serum PRL levels, with gross total removal achieved in 18–75 % of patients [38, 39]. Patients with microprolactinomas are shown to have a higher rate of normalizing serum PRL levels post-surgery, at 75–90 % versus 33–50 % of patients with macroprolactinomas [1, 4, 9, 27]. However, recurrence rates of hyperprolactinemia can be observed if there was no gross total resection [39] or if patients had large tumors [25]. Recurrence of hyperprolactinemia may occur in 18–22 % of patients after initial normalization [4, 9, 27]. Tumor debulking can lead to DA responsiveness and potentially lower medication doses [40]. If surgery is not successful, further DA therapy, as well as radiation therapy can be explored [8, 20].

Radiation therapy is viewed as a third-line treatment for prolactinomas [1], increasingly given in a single high dose fraction [8]. Partial endocrine response ranges from 22–100 % while endocrine normalization ranges from 0–60 %, with a median of approximately 30 % [41, 42]. Due to high rates of hypopituitarism, radiation therapy is usually reserved when both medication and surgery (or surgeries) have failed [8].

Long-term follow-up is necessary for the treatment and management of prolactinomas [20]. Medical treatment can potentially last for an individual patient's lifespan and it is recommended that the patient's serum PRL levels should be monitored over the long term [27]. Furthermore, physicians prefer repeat magnetic resonance imaging (MRI) at 3-month intervals at the start of medical therapy, for patients with macroprolactinomas, high PRL levels post DA introduction, or new symptoms such as headaches, visual disturbances or other hormonal imbalances [1, 27]. For patients who choose to discontinue their DA due to sustained normal serum PRL levels following reduction of tumor, a 6-month MRI is recommended post withdrawal, followed by MRI annually [20, 43]. Higher remission rates after DA withdrawal are seen in patients who have no tumor visible on MRI, have a nadir PRL level < 1–2 ng/dl during drug treatment, and who have received drug treatment for > 5–6 years [7, 44]. Absence of cavernous sinus invasion and serum PRL levels < 132.7 ng/ml before treatment have been also deemed favorable predictive criteria [45]. If CAB treatment is withdrawn, monitoring for tumor regrowth after DA withdrawal includes periodic measurement of PRL levels and MRI, but size of the tumor at baseline and when treatment is discontinued, duration of PRL elevation, and other factors may influence MRI timeline.

Evidence is surfacing, however, that delineates a potential risk of too frequent MRIs. Gadolinium-based contrast agents (GBCAs) have been recognized to be retained throughout the brain in small amounts, which can grow in size with increased imaging [46]. In a recent survey assessing timing/frequency of pituitary MRI following medical, surgical or radiological treatment, most physicians agreed upon imaging every 6 months for the first year, then annually for several years [47]. Any follow-up management should be dependent upon the medical therapy used and the proximity of the tumor to the optic chiasm [1, 47]. Though intriguing, data on this subject is still limited, and the concern about long-term GBCA retention risks should be explored further in order to increase awareness of the potential risks of standard imaging care of pituitary tumors [47].

The treatment of aggressive pituitary tumors is discussed in detail in a separate paper in this issue. Temozolomide is an oral alkylating agent, which methylates DNA and has antitumor effects in aggressive prolactin secreting tumors but also in non-secreting, GH or ACTH-secreting adenomas and carcinomas (▶ **Table 1**). The response is variable; effects are counteracted by O6-methylguanine-DNA methyltransferase, a DNA repair enzyme [48].

Everolimus, a mammalian target of rapamycin (mTOR) inhibitor [49] and lapatinib, a tyrosine kinase inhibitor for EGFR and HER2 have also shown efficacy in some aggressive prolactinomas (▶ **Table 1**).

Acromegaly

Acromegaly is a rare, chronic condition with an incidence rate between 2–11 cases/million per year, and an estimated prevalence of 20–130/million [50, 51]. However, recent studies suggest a higher prevalence; and due to slow growth rate, a 10–11 year delay in diagnosis is very frequent [51]. Thus, patients can have many comorbidities and complications by the time of diagnosis [51–53].

The goal of acromegaly therapy is to reduce growth hormone (GH) and insulin-like growth factor 1 (IGF-1) levels and control tumor mass in order to improve morbidity, quality of life (QoL) and mortality [53–56]. Although primary therapy is TSS, there has been an increased trend of primary treatment with medication, as well as pre-surgical medical therapy [50, 54, 57]. In a study by Bex, et al., primary medical treatment increased 23–40 % [58]. Similarly, Maione, et al., published a French Registry describing the changes of primary medical therapy, which increased to 30–50 % [59]. Medical therapy is also suggested as first-line treatment for patients who will not benefit from surgery or are not surgical candidates [54, 60]. However, tumor debulking, even in patients not amenable to surgical cure, may result in an improved response to medical therapy (lower doses needed, higher rates of biochemical control) [50, 61, 62].

Somatostatin receptor ligands (SRLs) are considered first-line medical therapy options in many patients [52, 54, 56]. SRLs include octreotide (OCT), lanreotide (LAN) and the more recently approved pasireotide (PAS) [63]; a main effect is suppression of GH and IGF-1 levels. SRLs interact with specific G-protein couple recep-

tors on somatotroph cells, which exist as five isoforms (somatostatin receptor SSTR types 1–5) [7, 56]. This leads to a signaling cascade which ultimately inhibits endocrine and exocrine hormone secretion [52]. By suppressing GH secretion, secondary suppression of IGF-1 is achieved, which can lead to improvement of acromegaly symptoms such as headache, tissue swelling, and fatigue [52]. SRLs are viewed as safe and efficacious, with minimal gastrointestinal side effects and injection site reactions [64]. Biochemical control of GH and IGF-1 by SRLs is achieved in approximately 50 % of patients (17–80 %) [56, 65]. This apparently low biochemical response, as well as the response variance, varies in function of clinical parameters, molecular mechanisms, previous surgeries, or dosing/duration differences, and with different study designs [7, 56, 65, 66]. GH and IGF-1 normalization is higher in patients with prior SRL therapy compared with patients naïve to SRL therapy [56, 66]. OCT and LAN, first-generation SRLs, have high SSTR2 affinity, and dosing/duration of drug administration can vary in order to achieve biochemical control [55, 56, 67]. Dose up-titration even after the maximum approved doses has been shown to improve efficacy with limited increase in side effects. OCT is administered at 40 mg every 4 weeks while LAN can be administered every 4 weeks in 180 mg doses, or every 3 weeks in 120 mg doses [55, 67, 68]. This escalation in dose therapy is sometimes used in order to achieve optimal biochemical control of GH and IGF-1 levels [7, 62]. Sparsely granulated tumors [69], T2-weighted MRI hyperintense tumors [70], SST receptor2A-negative adenomas and patients harboring aryl hydrocarbon receptor interacting protein [AIP] mutations seem to have a lower response to SRLs [71]. SRLs have important effects on tumor shrinkage. A recent study in patients treated with LAN as a primary treatment showed that approximately half (54.1 %) had clinically significant tumor shrinkage (of > 20 %) in 3 months [72] (▶ **Table 1**).

PAS is a second-generation SRL, and targets 4 of 5 SSTR isomers (1,2,3 and 5), with a long-acting form; PAS-LAR, developed and administered via intramuscular injection [52, 56]. An initial 40 mg/28 days PAS-LAR dose can be increased to 60 mg/28 days to reach optimal results [56]. PAS-LAR is associated with hyperglycemia in 57–63 % of patients, requiring close monitoring in patients and, if necessary, treatment, preferably initiated with metformin and/or incretin-related therapies (dipeptidyl peptidase-4 inhibitors or glucagon-like peptide-1 agonists) [7, 73, 74] (▶ **Table 1**).

Pegvisomant (PEG), a GH-receptor antagonist, is now considered one of the most effective treatments available for acromegaly therapy [51], with 76 % of patient achieving normal IGF-1 levels after 24 months [75]. Patients that are resistant or intolerant to maximal SRL doses may benefit from PEG, and IGF-1 levels normalize with a higher success rate [52]. Furthermore, PEG can be used in conjunction with SRL therapy or CAB to achieve maximum biochemical balance, with rates of normalized IGF-1 levels reaching up to 90 % [51, 52, 76, 77] with effectiveness continuing after SRL discontinuation [76]. These results, however, may be reduced in real-world settings, due to lower standard doses in everyday practice, as compared to higher administrated doses in clinical trials [54, 55] (▶ **Table 2**). Increased use of combination therapy at initiation of PEG in the ACROSTUDY, led to an increase in IGF-1 normalization rates when compared to monotherapy [55]. PEG is very well tolerated and efficacious, making it a preferred medication for acromegaly therapy. However, high cost and route of administration can produce practical limitations [78]. The cost of treatment for patients taking PEG is high [79]; exceeding that of SRLs by 3–4 times [79, 80]. A combination of PEG and other medications, however, might allow for cost-effective therapy, due to a reduced PEG dose [7, 20, 77, 81–90] (▶ **Table 3**).

A new study on a combination of PEG and PAS-LAR showed that switching to PAS-LAR, either as mono or PEG combination, can control IGF-1 levels in most patients and also decrease the dose of PEG by 66 % compared with the combination of first generation SRLs. However, hyperglycemia was still frequent and PEG did not have sparing effect on hyperglycemia [87]. Switching from a combination therapy with 1st generation SRL and PEG or CAB, monotherapy with PAS-LAR controlled IGF-1 (≤ 1.3 ULN) with an acceptable tolerance in almost half (8/15) patients, with large variability of the response, while the combination therapy had to be resumed in 7/15 patients due to inefficacy or intolerance (frequent hyperglycemia) [91].

Side effects of PEG can include mild elevation of liver enzymes, which should be monitored regularly, and treatment should be discontinued if transaminases increase by 5 times the upper normal limit (ULN) [7, 76, 81]. Improvement in glucose metabolism can also be significant, as PEG in monotherapy or in SRL combination seems to improve glucose metabolism, reducing fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), fasting plasma insulin (FPI), and homeostasis model assessment (HOMA-1) independently of disease control [92].

DAs suppress the D2 receptor in GH-secreting pituitary adenomas, inhibiting GH secretion in patients with acromegaly [93]. However, with CAB approximately 30 % of patients obtained biochemical control that decreased with time [94, 95]. CAB can also be added to SRLs in conjunction, to enhance GH suppression and increase SRL efficacy [7, 96]. During treatment adding CAB to PEG is also an effective option when elevated liver enzymes are present, allowing for a PEG dose reduction [84, 87, 97]. CAB effects in GH decrease are modest and as such CAB can be used as a treatment option in patients with moderate elevated IGF-1 levels and mild symptoms of GH excess, as well as in conjunction with higher-efficacy drugs [7, 50, 54]. In a meta-analysis, mean CAB dose was 2.5 mg/week, which is higher than the usual recommended dose for hyperprolactinemia, with no adverse effects [95].

The role of preoperative medical therapy (i. e., SRL) in acromegaly has been studied with conflicting results over the years. However, it seems that although SRLs could play a role in carefully selected patients, data is insufficient to support the general use of a SRL prior to surgery in order to improve post-surgery biochemical outcomes [98]. Primary medical therapy with an SRL may be considered in patients with macroadenomas without local mass effects on the optic chiasm, as SRLs have been shown to reduce tumor size and control GH hypersecretion [98].

Medical therapies currently in development (phase II or III studies) but not yet available on the market include (▶ **Tables 1** and ▶ **2**): oral octreotide, shown to maintain GH and IGF-1 control in 85 % of patients previously normalized on octreotide LAR or lanreotide [99], CRN00808, an orally bioavailable sst2-selective, non-peptide somatostatin biased agonist ([100], (ACROBAT EDGE and EVOLVE trials), other SRL formulations have been tested such as, long-acting lanreotide up to 3 months interval, subcutaneous oc-

▶ **Table 2** Medical treatment options with receptor blockers for acromegaly and Cushing's disease.

Medication	Family	Indication	Mechanism of action	Dose	Effectiveness	Side effects	Clinical development
Pegvisomant	Antagonist GH receptor	Acromegaly	Blocks GHR, preventing activation despite high GH levels	10–40 mg SC daily	Normal IGF-1 in 76% Highly effective Improves insulin resistance	LFT elevation, lipodystrophy, arthralgias Not recommended in pregnancy (risk unknown, case reports with normal pregnancies)	Phase III
Mifepristone (RU486)	Antagonist progestogen and glucocorticoid receptor	Cushing's syndrome FDA approval for adults with CS with diabetes or glucose intolerance who are not surgical candidates	Blocks PR and GR, preventing activation despite high cortisol levels	300–1200 mg daily, oral	Glucose improvement in 60%. Hypertension improvement in 38%.	Nausea, fatigue, headache, hypokalemia, arthralgia, peripheral edema, endometrial thickening, vaginal bleeding, miscarriage AI (necessitates supraphysiological dexamethasone doses as replacement) Do not use in pregnancy (X)	Phase III SEISMIC
New drugs in clinical trials							
Relacorilant (CORT125134)	Antagonist glucocorticoid receptor	Cushing's syndrome	Blocks GR, preventing activation despite high cortisol levels	100–400 mg QD, oral	Glucose improvement in 81.8% Hypertension improvement in 45.5%	Musculoskeletal (back pain) and gastrointestinal AI Pregnancy class: NA	Phase I prospective Phase II prospective completed Ongoing Phase III
ATL1103	Antisense oligonucleotide inhibitor of the GH receptor	Acromegaly	Inhibits translation of human GH receptor mRNA and consequently its synthesis	200 mg SC once or twice weekly	27.8% reduction of IGF-1 at week 14 2 of 13 (15%) achieved normal IGF-1	Injection site reaction, LFT elevation, headache	Phase II Prospective completed
ISIS 766720	Antisense oligonucleotide inhibitor of the GH receptor, in liver	Acromegaly	Inhibits selectively the translation of human GH receptor mRNA in the liver	60–80 mg SC every 4 weeks	TBD	TBD	Ongoing Phase II Prospective

GH: Growth hormone; IGF-1: Iinsulin-like growth factor 1; GHR: Growth hormone receptor; PR: Progesterone receptor; GR: Glucocorticoid receptor; SC: Subcutaneously, QD: Once daily; LFT: Liver function tests; AI: Adrenal insufficiency; FDA: Food and Drug Administration; CS: Cushing's syndrome; TBD: To be determined; NA: Not assessed; Pregnancy categories: A (Generally acceptable. Controlled studies in pregnant women show no evidence of fetal risk), B (May be acceptable. Animal studies showed minor risks and human studies showed no risk), C (Use with caution if benefits outweigh risks. Either no studies available or only animal studies show risk and human studies not available), D (Positive evidence of human fetal risk. Use in last resort, as salvage therapy for emergencies when no safer drug available), X (Do not use in pregnancy. Risks outweigh benefits, use alternatives).

▶ **Table 3** Medical treatment combinations for pituitary tumors.

Medication	Indication	Mechanism of action	Dose	Effectiveness	Side effects
Ketoconazole and Metyrapone	CD	Adrenal steroidogenesis inhibition, decrease cortisol	Ketoconazole 300–1200 mg/day Metyrapone 750–1000 mg	Normal UFC in 52 % in 4 months in preoperative untreated CD patients	No new safety issues
Ketoconazole, Metyrapone, and Mitotane	CD	Adrenal steroidogenesis inhibition + adrenolytic action, decrease cortisol	Ketoconazole 400–1200 mg/day Metyrapone 3.0–4.5 g/day Mitotane 3.0–5.0 g/day	Rapid clinical improvement with normalization of UFC, in severe ACTH dependent CS	High frequency of side effects: Acute AI in 36 % Elevated liver enzymes in > 80 %
Cabergoline and Ketoconazole	CD	Decrease pituitary secretion and adrenal steroidogenesis	CAB 0.5– 3.5 mg/week Ketoconazole 50–200 mg QD, in progressive doses	Improved UFC response in long-term, irrespective of which drug was started first	No new safety issues
Pasireotide and cabergoline	Acromegaly	Decrease GH secretion and tumor cell proliferation	PAS-LAR: 40–60 mg/month i. m. CAB: 0.5–3 mg/wk	Used combination but not specifically studied	
	CD	Decrease ACTH secretion and tumor cell proliferation.	CAB 0.5–1 mg/day daily Pasireotide SC 0.6–0.9 mg BID	Control rate in 38 % of 66 patients at week 35	Side-effects not increased during the combination
Pasireotide, Cabergoline, and Ketoconazole	CD	Decrease ACTH secretion, tumor cell proliferation and adrenal steroidogenesis.	Pasireotide SC 0.6–0.9 mg BID CAB 0.5–1 mg/ day from day 28 Ketoconazole 200 mg TID from day 60	Added in this order, in patients not controlled on the previous drug. At the end of 80 days, efficacy rate was 29 % with pasireotide, 53 % after cabergoline and 88 % after addition of ketoconazole	No new safety issues
First generation SRL (octreotide, lanreotide) and Cabergoline	Acromegaly	Decrease GH (+ PRL) secretion and tumor cell proliferation	SRL: usual doses CAB 1–7 mg/week (mean 2.5)	IGF-1 normalized in 52 %, inversely proportional with baseline IGF1 levels	No new safety issues
First generation SRL (octreotide, lanreotide) and Pegvisomant	Acromegaly	Decrease GH secretion and block GH receptor	SRL: usual doses Pegvisomant SC: 10–40 mg/day; has been also used twice/week (40–120 mg/week)	IGF1 normalization in up to 90 % of patients not controlled on SRL	Lower doses of SRL and PEG may be better tolerated than maximal dose of monotherapy
Pegvisomant and Cabergoline	Acromegaly	Decrease GH secretion and block GH receptor	CAB: 1–3.5 mg/week Pegvisomant SC: 10 mg/day	IGF1 normalization in 68 % of patients	Well tolerated, no new safety issues
Pasireotide and Pegvisomant	Acromegaly	Decrease GH secretion and block GH receptor	Pasireotide LAR 60 mg/mth Pegvisomant: 44–78 mg/wk (mean 61)	Switching from 1st-generation SRLs + PEG to pasireotide allowed for a reduction in pegvisomant dose by 66 %; IGF1 normalization in 73.8 %	PEG had no sparing effect on PAS –induced hyperglycemia (diabetes increased from 32.8 % at baseline to 68.9 %)
SRL and Estrogen or SERM	Acromegaly	Decrease GH and GH signaling (Estradiol inhibition of liver GHR expression, upregulation of suppressors of cytokine signalling-2)	SRL: usual dose Raloxifene 60 mg BID Tamoxifen 20–40 mg/day Clomiphene 50 mg/day	In men and post-menopausal women with uncontrolled acromegaly (more studies needed) IGF1 normalization in 41–45 %	Flushing (+ usual side-effects of SRLs)

GH: Growth hormone; GHR: Growth hormone receptor; IGF-1: Insulin-like growth factor 1; ACTH: Adrenocorticotropic hormone; PRL: Prolactin; SRL: Somatostatin receptor ligand; CD: Cushing's disease; CS: Cushing's syndrome; SC: Subcutaneously; IM: Intramuscularly; QD: Once daily; BID: Twice daily; TID: Thrice daily; UFC: Urinary free cortisol; CAB: Cabergoline; PAS: Pasireotide, LAR: Long-acting release; PEG: Pegvisomant; SERM: Selective estrogen receptor modulator; AI: Adrenal insufficiency;

treotide implant or depot formulation, somatoprim (SRL with SSTR type 2,4 and 5 affinity) [9, 21]. Antisense synthetic oligonucleotides can inhibit the translation of human GH receptor mRNA and consequently its synthesis. In a phase II study, a second-generation antisense oligomer targeting the translation of GH receptor mRNA, 200 mg administered twice weekly subcutaneously (s.c.) demonstrated a 27.8 % reduction of IGF-1 at week 14, with 2 (15 %) of 13 patients achieving normal IGF-1 levels. It was generally well tolerated, but with frequent mild-to-moderate injection-site reactions (in 85 % of patients) [101]. A newer generation antisense oligonucleotide targeting hepatic expression of GH receptor, is currently being investigated in a phase II trial (https://clinicaltrials.gov/ct2/show/NCT03548415) (▶ **Table 2**).

Improving the QoL of acromegaly patients is also increasingly recognized as a health outcome goal [102]. Despite long-term biochemical balance, QoL remains low for many patients [103]. Clinical manifestations and symptoms, such as physical changes and multisystem comorbidities can lead to reduced QoL [54, 104, 105]. Many factors can contribute to QoL, which may differ due to the different stages of disease management. Factors during the untreated phase can be different from factors during initial treatment, as well as during remission. General depression and body mass index (BMI) factors have a significant negative impact on QoL in both active and non-active patients [102]. Treatment with SRLs and GH-receptor antagonists has shown to have a positive impact on QoL, while third-line therapies such as radiotherapy have been associated with lower QoL [102]. Improvement in QoL has also been shown to correlate with improvements in symptoms such as loss of body weight and soft tissue swelling [106]. Patients who performed an exercise program through therapist-oriented home rehabilitation (TOHR) demonstrated improvements in general fatigue, body composition, and overall QoL, which remained higher than baseline levels after the washout period [107]. Specific interventions should be established to increase QoL, focusing on comorbidities treatment as well as depression and obesity targeted therapy [102].

In a study comparing patients with acromegaly with those with nonfunctioning pituitary adenomas (NFA), patients with active acromegaly reported a greater prevalence and severity of dysfunction with respect to concentration/distractibility and the ability to learn, while patients with controlled acromegaly reported the greatest improvement in health over the previous year [108]. Further research may be useful regarding patient QoL, patient functionality during normal daily activities, and perceived dysfunction despite biological disease control.

Cushing's disease

Cushing's syndrome (CS) is a multisystem disorder from chronic excessive levels of endogenous or exogenous glucocorticoids (GCs) [109]. The overall incidence of endogenous CS is 0.7–3.2/million/year [110, 111] with only approximately 10 % of new cases/year in children [112]. While traditionally Cushing's disease (CD) represented 75–80 % of ACTH-dependent CS cases [110], a study in 2019 reported CD in approximately 65 % of ACTH-dependent CS cases, with a higher proportion of ectopic ACTH-producing tumors (24 % in the whole CS series) [111]. Benign or malignant adrenal tumors and micro- or macronodular adrenal hyperplasia are the ACTH-independent causes of endogenous CS.

CD has significant morbidity and mortality, mainly through cardiovascular, metabolic and infectious complications [109, 113]. It occurs more frequently in women (3:1 ratio) and over 90 % of the patients harbor microadenomas, from which 20–58 % are not visible on MRI; of note, pituitary microincidentalomas, occurring in about 10 % of the general population, may be misleading [113–115]. Aggressive corticotroph macroadenomas do occur occasionally and will be discussed in a separate paper in this issue.

The primary treatment of CD is TSS [109]. Remission rates after endoscopic TSS are better than after microscopic surgery (88 % versus 56 %) in some reports [116], but not all [117, 118]. However, depending on tumor size, location, dural, or local invasion and notably by the surgeon expertise, 20–40 % of patients will not be cured by TSS [109]. Moreover, up to 35 % of patients in apparent remission will relapse within 10 years or more [119, 120]. For patients with persistent disease there are several options [109]: repeat surgery (with lower efficacy of around 60 % of cases), radiotherapy (adenoma-targeted or whole sellar stereotactic radiosurgery), with a 54–75 % efficacy at 5 years and a 20–30 % recurrence rate [41, 121], medical treatment [85], a combination of the above or bilateral adrenalectomy (the latter having a 10–30 % risk of inducing Nelson's syndrome) [122].

Medical therapy for CD is mainly used in patients with persistent or recurrent hypercortisolism after pituitary surgery or while awaiting the effects of radiation therapy. It can also be used to control hypercortisolism, hence to alleviate the related morbidity before surgery, and in patients who decline surgery or who have no clear tumor localization [109, 123, 124]. Size and tumor invasion, disease severity, sex, patient's comorbidities and related therapy, drug's mechanism of action, potential side-effects, interaction with other drugs, availability, cost and patient's preferences (which may increase the adherence to a usually long-term therapy), balanced with efficacy and side effects of bilateral adrenalectomy [7, 123] are all important for therapy selection.

Pituitary directed drugs

Pasireotide is a SRL that binds SSTR5 with a potency that is 40 times higher than that of OCT, decreases ACTH release and may decrease the tumor volume. PAS is approved for CD in s.c. administration twice a day at doses of 0.3–0.9 mg, or LAR once a month in doses of 10 or 30 mg intramuscular (i.m.) [125, 126] (▶ **Table 1**). PAS-LAR achieved median urinary free cortisol (UFC) normalization in 40 % of patients at 7 months, and > 20 % of tumor reduction in 43–47 % of patients [125]. In an extension study, a controlled response was maintained in 51.9, 65.5, and 72.2 % at months 12, 24, and 36, respectively, with tumor volume reduction ≥ 20 % observed in approximately 65 % of patients with a pituitary macroadenoma at 24 and 36 months, respectively [127]. However, a large dropout rate of more than 50 % of cases was also recorded in the extension trial. Approximately 6 % of patients discontinued treatment because of hyperglycemia-related adverse events (AEs). Patients with mild Cushing's (UFC < 1.5 ULN) had better biochemical response, approximately 50 % with both subcutaneous pasireotide and long acting pasireotide LAR, interestingly, in either doses, 10 or 30 mg per month. [125, 126]. If a patient does not respond in the first 2 months of treatment, it would very likely be a non-responder [124–126]. Not all patients with UFC normalization at 6 months maintai-

ned the response at 12 months, and a lack of response may occur after treatment interruption and re-administration [128]. Both PAS s.c. and LAR improve clinical signs and symptoms and QoL in selected patients with CD.

The most common AEs, similarly in PAS s.c. and LAR, are gastrointestinal (usually transient diarrhea, nausea), cholelithiasis, and hyperglycemia-related, the latter occurring in > 70 % of patients [125, 126] and in nearly all those followed for 5 years [129]. Hyperglycemia may develop in about 1/3 of those with normal glucose tolerance at baseline, while diabetes mellitus type 2 may occur in approximately 50 % and in > 75 % of those patients with prediabetes at baseline. Hyperglycemia is reversible after PAS withdrawal [73]; close check-up of glycemic levels are recommended after PAS initiation.

Cabergoline is not approved for treatment of CD, but has been used with various results (30–50 %) at 1.5–7 mg/week (usually 2–3.5 mg), especially in patients with mild or moderate disease, [130–134] but less than 20–25 % patients maintain response at 2–3 years [131]. Usual side effects include orthostatic hypotension, nausea, headache, and dizziness. CAB in CD is mostly used in combination with other drugs or in women planning pregnancy, because it has relatively no side effects upon the fetus [135, 136]. In severe aggressive cases, temozolomide could be considered [48] (▶ **Table 1**).

Novel pituitary-directed agents for CD in clinical trials

Several drugs are in development for CD (▶ **Table 1**), including **Roscovitine**, a cyclin-dependent kinase inhibitor that suppresses 2/cyclin E on corticotroph tumor cells, which leads to inhibition of proopiomelanocortin (POMC) and a subsequent decrease of ACTH production [137].

Gefitinib, an epidermal growth factor receptor (EGFR) inhibitor [138], reduces the EGF-induced ACTH synthesis in corticotroph tumors of patients with USP8 mutation [139, 140] (▶ **Table 1**). In aggressive corticotroph tumors, temozolomide, bevacizumab, a vascular endothelial growth factor receptor [VEGF] monoclonal antibody, and everolimus have been used with partial efficacy [49].

Adrenal steroidogenesis inhibitors

Adrenal steroidogenesis inhibitors reduce/normalize serum cortisol levels in ACTH dependent or independent CS by inhibiting cytochrome P450 enzymes involved in steroidogenesis (▶ **Table 4**). All members of this drug class may induce adrenal insufficiency, which may be prevented by block and replace therapy with add-on glucocorticoids [7, 85, 109].

Ketoconazole, a mixture of two *cis*-enantiomers, is an antifungal imidazole licensed for CS syndrome in Europe and is used off-label in the USA. Efficacy of ketoconazole in CS, is for the most part retrospectively reported, at doses of 400–1200 mg/day, orally, divided into 2–4 doses, in 30–90 % of patients [141, 142]. About 15 % of patients escape control after 2 years of treatment [141]. Adverse reactions are common, notably hepatotoxicity, which may vary from mild liver enzyme elevation (frequent) to the rare severe liver toxicity (black box warning); due to the inhibition of androgen synthesis, hypogonadism and gynecomastia may occur in men; the drug is not recommended during pregnancy; it also increases the risk of QT prolongation and interacts with various drugs [143].

Metyrapone is an inhibitor of steroid 11β-monooxygenase with rapid onset of action (within 2 hours of a first dose). In divided doses of 500 mg up to 6 g/day taken after a meal, metyrapone lowers cortisol in 43–76 % of patients with CS. The effect is usually long-lasting, with escapes described in 9–19 % of cases [144, 145]. Blockade of 11β-hydroxylase leads to an increase of mineralocorticoid and androgen precursors producing hypertension, hypokalemia, edema, and in women hirsutism and acne. Mild gastrointestinal symptoms are common. Metyrapone has been used during pregnancy in some cases, with apparently no teratogenic effect [146]. There are no major interactions with other drugs.

Mitotane, an insecticide derivative, is rarely used for CS with the exception of adrenal cancer [147].

Etomidate is an intravenous anesthetic imidazole, which at subhypnotic doses rapidly inhibits cortisol production (within hours) by blocking several steroidogenic enzymes. It may be used in patients with very severe CS and life-threatening hypercortisolism, or preoperatively, but requires permission for admission to an intensive care unit [148].

Novel steroidogenesis inhibitors currently evaluated in clinical trials

Phase III trials

Levoketoconazole, the 2*S*,4*R*-enantiomer of ketoconazole, was studied in a recently published phase III, multicenter, open-label, non-randomized, single-arm study [149]. The primary end point of the study, UFC normalization without dose increase and without imputing any missing data was achieved in 31 % of patients; when missing data was computed, similar with other studies for comparison, 42 % of patients had normal UFC. Clinical signs and symptoms of CS and biochemical markers for cardiovascular risk improved. Common side-effects were nausea (30 %) and headache. An increase in transaminases of more than 3 × ULN was recorded in 11 %, and AEs led to study discontinuation in only 13 % of patients, indicating an acceptable safety and tolerability profile [149]. Interestingly, the drug did not induce a significant lowering of serum testosterone in men.

Osilodrostat (formerly LCI699) is an oral nonsteroidal inhibitor of 11β-hydroxylase and also of aldosterone synthase [119]. Preliminary results from a randomized double-blind placebo-controlled phase III study (LINC-3, https://clinicaltrials.gov/ct2/show/NCT02180217) revealed that 86 % on the maintained dose had a median UFC ≤ ULN compared to 29 % taking placebo, and 66 % of the patients had median UFC ≤ ULN at week 48. The most common side effects were adrenal insufficiency, increased mineralocorticoids and testosterone precursors, nausea, headache, and fatigue; 18 % of the patients discontinued the drug, mostly because of side effects [150].

Glucocorticoid receptor blockade

Mifepristone is an oral glucocorticoid receptor (GR) antagonist approved in USA for CS in patients with diabetes mellitus or glucose intolerance. Mifepristone, at a dose of 300–1200 mg/day significantly improved CS clinical manifestations (including glucose metabolism, hypertension and weight gain) in up to 87 % of patients [151]. It often increases ACTH and cortisol, therefore the disease management relies only on clinical status [152]. Side effects are

▶ **Table 4** Medical treatment options for Cushing's disease directed to adrenal glands[a]

Medication	Mechanism of action	Dose	Effectiveness	Side effects	Clinical development
Ketoconazole	Inhibits StAR, CYP11A1 CYP11B1, CYP17	400–1200 mg daily (BID)	Normal UFC in 48.7–50 % Escape phenomenon in 23 %	GI disturbance Liver enzyme increase AI Not approved for use during pregnancy (C)	Large retrospective FReSKO EMA approved for CS
Fluconazole	Inhibits CYP17	200 mg QD	No studies	Liver enzyme increase	Case Reports
Etomidate	Inhibits StAR, CYP11A1, CYP11B1, CYP17	Bolus 5 mg once Followed by 0.02 up to 0.3 mg/kg/h	Median serum cortisol reduction by 80 %, after median time of 38 hours	Sedation/Anesthesia AI Not approved for use during pregnancy (C)	Case Reports Retrospective studies
Metyrapone (SU4885)	Potent inhibitor of CYP11B1 Weaker CYP17, CYP11B2, CYP19	0.5–4.5 mg daily in multiple doses (TID or QID)	Response rate in 43–76 % Escape phenomenon in 19 % of responders FDA approved only as diagnostic test	"Pseudohyperaldosteronism" due to aldosterone precursors (hypertension, hypokalemia) Hirsutism AI Not approved for use during pregnancy (C)	Retrospective studies Phase III PROMPT Case reports treated in pregnancy
Mitotane	Insecticide derivative (*o*,*p*′-DDT) Inhibits StAR, CYP11A1, CYP11B1, CYP11B2, 3β-HSD Adrenolytic	2–5 g daily (BID or TID)	Remission rates of 72 % Approved for treatment of adrenal cancer	GI disturbance, dizziness Cognitive alterations AI (necessitates supraphysiological glucocorticoid doses as replacement) Teratogenic (not recommended during pregnancy D)	Retrospective studies
Novel drugs in clinical trials					
Levoketoconazole (COR-003)	Inhibits StAR, CYP11A1, CYP21A2, CYP11B1, CYP17	150–600 mg BID	Phase III: UFC normalized in 31–42 %	Nausea, headache, edema Liver enzyme increase AI Not approved for use during pregnancy (C)	Ongoing Phase III SONICS and LOGICS
Osilodrostat (LCI-699)	Potent inhibitor of CYP11B1	LINC 2 2–50 mg BID LINC 3 2–30 mg po BID	Phase II: UFC normalized in 79.8 % at 22 weeks Phase III: 66.0 % maintained normal mUFC levels for at least 6 months after first mUFC normalization	Nausea, diarrea, astenia "Pseudohyperaldosteronism" due to aldo precursors (hypertension, hypokalemia) Hirsutism Hyperkaliemia AI Not approved for use during pregnancy (C)	Phase I LINC1 Phase II LINC2 Ongoing Phase III LINC3 and LINC4
Abiraterone Acetate	Androgen biosynthesis inhibitor Inhibits CYP17, CYP21A2, CYP11B1	250–500 mg BID	Under study	"Pseudohyperaldosteronism" (hypertension, hypokalemia) AI Pregnancy class: NA	Phase II NCT03145285

ACAT1: Cholesterol acyltransferase type 1; StAR: Steroidogenic acute regulatory protein; CYP11A1: 20,22 Desmolase ; CYB11B1: 11β-Hydroxylase; CYP17: 17α-Hydroxylase/17,20 lyase; CYP11B2: Aldosterone synthase (18-hydroxylase); CYP19:0 Aromatase (19-hydroxylase); 3β-HSD: 3β-Hydroxysteroid dehydrogenase; CYP21A2: 21-Hydroxylase; QD: Once daily; BID: Twice daily; TID: Thrice daily; QID: Four times daily; UFC: Urinary free cortisol; mUFC: Median urinary free cortisol; GI: Gastrointestinal; AI: Adrenal insufficiency; FDA: Food and Drug Administration; EMA: European Medicines Agency NA: Not assessed. Pregnancy categories: A (Generally acceptable. Controlled studies in pregnant women show no evidence of fetal risk), B (May be acceptable. Animal studies showed minor risks and human studies showed no risk), C (Use with caution if benefits outweigh risks. Either no studies available or only animal studies show risk and human studies not available), D (Positive evidence of human fetal risk. Use in last resort, as salvage therapy for emergencies when no safer drug is available), X (Do not use in pregnancy. Risks outweigh benefits, use alternatives). [a] Adapted from ref. [85].

▶ **Table 5** Important considerations when choosing medical treatment for Cushing's disease.[a]

Factors	Considerations
Tumor size	If macroadenoma or growing tumor, pasireotide may produce tumor shrinkage or prevent tumor growth Cabergoline may control the disease, but effect on tumor shrinkage is limited
Disease severity: - Very severe, life-threatening - Severe (UFC > 5 × ULN) - Mild disease	- Etomidate i. v., rapid onset, patient should be hospitalized in ICU - May consider drugs with rapid onset of the effect (metyrapone, ketoconazole, or combination) - Lower rate of UFC normalization with pasireotide in patients with severe disease, though patients with high UFC have been shown to be responders, too Cabergoline alone or in combination with pasireotide or Ketoconazole might be beneficial in selected cases For all drugs, start with low doses to reduce risk of adrenal insufficiency
Sex - Male - Female	 Prefer to avoid drugs producing hypogonadism (ketoconazole), prefer drugs inducing androgen excess (metyrapone) In selected cases of premenopausal women, drugs producing androgen excess (hirsutism, acne) as metyrapone should be 2nd line
Pregnancy desired/ongoing	Prefer cabergoline Mifepristone is contraindicated (miscarriage, vaginal bleeding, endometrial hyperplasia) Avoid medication with teratogenic effect (mitotane) or combinations with fetal risk (Ketoconazole + metyrapone)
Pre-existing hyperglycemia Severe hyperglycemia	Pasireotide may worsen glycemic control even in normoglycemic patients; regular control of blood glucose and HbA1c is needed; introduce or adjust the antidiabetic medication if needed (metformin, GLP1 agonist, DPP4 inhibitor are preferred) Consider mifepristone; need to adjust medications for diabetes as doses requirements can change very rapidly
Uncontrolled hypertension	Drugs that may increase the mineralocorticoid precursors may worsen the blood pressure control (ketoconazole, mitotane, metyrapone); consider adding spironolactone, especially if hypokaliemia present
Hypokalemia	Drugs that may increase the mineralocorticoid precursors may worsen the blood pressure control (ketoconazole, mitotane, metyrapone); consider adding spironolactone or K supplement
Elevated liver enzymes	Avoid drugs with hepatotoxicity (ketoconazole, mitotane); closely monitor the liver tests; avoid association with other drug known for hepatotoxicity
Biliary lithiasis or gallbladder discomfort	Pasireotide may induce biliary lithiasis in up to 35 % of patients; some will need surgery if symptomatic; nausea, gastrointestinal tract discomfort may occur or exacerbate with almost all the drugs used for Cushing's disease.
QT interval prolongation (or predisposing cardiac medication)	Caution in using drugs that may prolong QT interval (ketoconazole, pasireotide, metyrapone, mifepristone) Caution in combining therapies that prolong QTc
Concomitant medication for comorbidities	Always check the list of drug interactions to avoid major adverse effects (ketoconazole, mitotane and mifepristone interfere with CYP450 3A4 metabolized drugs – e. g., for ketoconazole: selected statins, benzodiazepines, cyclosporine)
Adrenal insufficiency on therapy	Closely follow patients for clinical and biochemical evidence of adrenal insufficiency; block and replacement therapy is sometimes used If patient takes mitotane, etomidate or mifepristone, higher (supraphysiological) doses of glucocorticoids should be used, dexamethasone in case of receptor blockage with mifepristone
Uncontrolled disease on monotherapy	Progressive dosage increase or combination with other drug/s. Lower doses of 2 drugs may be more efficacious and/or better tolerated than maximal doses of monotherapy. Studied combinations: ketoconazole and metyrapone; pasireotide and cabergoline; cabergoline and ketoconazole; ketoconazole, metyrapone and mitotane; ketoconazole, pasireotide, and cabergoline Consider repeat pituitary surgery, radiotherapy or bilateral adrenalectomy (balance the benefits and side effects)
Criteria for treatment monitoring	Clinical status (not always concordant with UFC) UFC – individual intravariability of 52 %, variability increases when baseline values are high LNSC – repeated assessments are useful if baseline value was high; may be more convenient than UFC collection; lack of concordance between UFC and LNSC in many cases Serum cortisol, ACTH – highly variable; during treatment with mifepristone ACTH and cortisol evaluation are not relevant, only clinical monitoring is available Biochemistry evaluation should correspond to the drug mechanism and potential side-effects

UFC: 24 h-Urinary free cortisol; LNSC: Late-night salivary cortisol; ACTH: Adrenocorticotrophic hormone; CD: Cushing's disease. [a] Adapted from ref [85].

hypokalemia, edema, and worsening hypertension, due to the unopposed mineralocorticoid effects of high cortisol levels, for which spironolactone may be used; macroadenomas should be monitored for tumor progression [152]. If adrenal insufficiency occurs, usually high doses of dexamethasone (2–10 mg daily) are needed to overcome the receptor blockade [152].

Relacorilant (CORT125134) is a selective antiglucocorticoid receptor antagonist (not inhibiting the progesterone receptor), currently studied in a phase III trial, https://clinicaltrials.gov/ct2/show/NCT03697109.

Combination of drug therapies in Cushing's disease

Several drug combinations have been studied [82, 83, 86, 88–90] and clinicians should aim to obtain additional or synergistic efficacy (considering the mechanisms of action) and to avoid synergistic side effects (▶ **Table 3**) [7, 20, 77, 81–90].

Medical therapy monitoring (▶ **Table 5**)

Besides clinical status, UFC and late night salivary cortisol (LNSC) are the markers of choice for disease monitoring (mostly UFC), although there is not always a correlation between UFC or LNSC, and response to treatment [153]. Of note, when mifepristone is used, these markers are not informative and therapeutic decisions should not rely on them. At least two repeated tests are necessary to confirm biochemical control, as it is known that UFC has a within-patient variability of 52 % [154]. Glycemic control and serum potassium levels should be regularly checked. The patient should be thoroughly instructed in recognizing and reporting signs of adrenal insufficiency and administration of replacement therapy with glucocorticoids if needed.

Non-functioning pituitary adenomas (NFA)

The treatment of a NFA remains mostly surgical and in patients with large residual tumors or recurrence, radiation therapy also plays a role. As some of these tumors have D2 receptors, a role for DA, especially CAB has been envisioned [155, 156]. However, data is limited to retrospective studies [157, 158]. In a historical cohort analysis undertaken at two pituitary centers with different practices for postoperative management of NFA, tumor decreased, remained stable, or enlarged, in 38, 49, and 13 % of patients, respectively in the group treated preventively after surgery with BRC (mean daily doses 6.8 ± 2.6 mg, range 2.5–10 mg) and/or CAB (mean weekly dose 1.5 ± 0.7 mg, range 0.5–3.5 mg) [158]. Interestingly, outcome measures were not related to the D2R numbers. The authors suggested that D2R polymorphisms, nerve growth factor receptor expression, and decreased levels of $G_{\alpha i}$ inhibitory G protein subunit might play a role in the lack of correlation of D2R with response [158].

At this time, in the absence of long-term prospective randomized trials, treatment with DA post- surgery cannot be recommended in all NFA patients, but research is needed to determine if a subgroup of patients will respond the most.

Conclusion

Medical treatment plays an increasing role in the management of pituitary adenomas, either as first-line or adjuvant treatment. Knowledge of possible AEs is, however, expanding and data on lifelong safety of medications and repeat imaging are needed. Treatment needs to be individualized to achieve tumor control, normalization of hormonal hypersecretion, but also to decrease complications and improve patients' QoL. New drugs targeting new and novel mechanisms are currently in clinical trials and will help inform evidence-based medicine and hopefully improve patient outcomes.

Acknowledgements

The authors thank Shirley McCartney, Ph.D., for editorial assistance.

Conflict of Interest

Monica Gheorghiu has received speaker's fee from Novartis, Ipsen and Pfizer. Maria Fleseriu, Principal investigator with research funding to OHSU from Chiasma, Crinetics, Ionis, Novartis, and Strongbridge, has received occasional scientific consulting fees from Chiasma, Crinetics, Ionis, Ipsen, Novartis, Strongbridge, and Pfizer. Francesca Negreanu has no disclosures.

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