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REVIEW

Managing Cushing's disease: the state of the art

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Abstract Cushing's disease is a rare chronic disease caused by a pituitary adenoma, which leads to excess secretion of adrenocorticotropic hormone (ACTH). The over-production of ACTH leads to hyperstimulation of the adrenal glands and a chronic excess of cortisol, resulting in the signs and symptoms of a severe clinical state (Cushing's syndrome) that leads to significant morbidity, negative impacts on the patient's quality of life, and, if untreated, increased mortality. The management of patients with Cushing's disease is complicated by the heterogeneity of the condition, with signs and symptoms that overlap with those of other diseases, and high subclinical incidence rates. Controversies surrounding the tests used for screening and identifying patients with Cushing's disease add to the challenge of patient management. Surgical intervention to remove the adenoma is the first-line treatment for patients with Cushing's disease, but medical therapies are useful in patients who relapse or are unsuitable for surgery. The recent introduction of pasireotide, the first pituitary-directed medical therapy, expands the number of treatment options available for patients with Cushing's disease. This state-of-the-art review aims to provide an overview of the most recent scientific research and clinical information regarding Cushing's disease. Continuing research into improving the diagnosis and treatment of Cushing's disease will help to optimize patient management.

Keywords Cushing's disease · ACTH · Cortisol · Pituitary · Management

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Introduction

Cushing's disease is a severe clinical condition caused by a pituitary adenoma hypersecreting adrenocorticotropic hormone (ACTH) [1]. The permanently high levels of ACTH lead to a chronic over-production of cortisol by the adrenal glands, known as Cushing's syndrome, with deleterious effects on most tissues of the body. Cushing's disease accounts for the majority of cases of endogenous chronic hypercortisolism; other causes include extrapituitary tumors that secrete ACTH or corticotropin-releasing hormone (CRH), adrenal adenoma or carcinoma, and adrenal hyperplasia or dysplasia [1, 2].

Cushing's disease is a rare condition, with an annual incidence reported of 1.2–1.7 cases per million population [3, 4] and a prevalence of 29.1 per million population [4]. However, the incidence of Cushing's disease is high and unfortunately still undiagnosed in some groups of patients, such as those with poorly controlled diabetes, osteoporotic

and relatively young women and men, and patients with hypertension resistant to treatment [5–7]. As such, the European Society of Endocrinology recommends investigation for Cushing's disease in patients presenting these features at an unusual (young) age [8].

The heterogeneity of Cushing's disease, the overlapping of signs and symptoms with those of other disorders, the need for differential diagnosis, the variety of biochemical tests and imaging techniques available for diagnosis, and questions surrounding how to better define response and remission all contribute to the challenges physicians face in optimizing patient management, despite ongoing advances in diagnosis and treatment. Thus, a multidisciplinary team of neurosurgeons, endocrinologists, and radiation oncologists, as well as an individualized patient approach, is recommended for the management of Cushing's disease [9–19].

The first-line treatment for Cushing's disease is transsphenoidal surgery (TSS) to remove the adenoma, but initial surgery frequently fails [2, 13]. Although radiotherapy is an option if initial TSS is unsuccessful, the effects of radiotherapy may only become apparent after many years [20] and the intervention may be followed by side effects, such as pituitary deficiency or failure, as well as damage to the optic nerve because of the frequent need of traditional approaches [21, 22]. Medical therapy can also be useful in cases of surgical failure, but some of the drugs in use have limited effects or are not approved for use in treating Cushing's disease [13, 23]. Pasireotide (Signifor®; Novartis AG, Basel, Switzerland), the first pituitary-directed medical therapy, was recently approved in the European Union and in the US for treating adult patients with Cushing's disease for whom surgery is not an option or for whom surgery has failed. Its long-term effectiveness in treating the symptoms of Cushing's disease has been shown in phase III trials [24, 25]. This state-of-the-art review aims to provide an overview of the most recent scientific research and clinical information regarding Cushing's syndrome, with an overall focus on Cushing's disease.

Pathophysiology and etiology of Cushing's disease

Corticotrophic adenomas secreting ACTH are the most common cause of endogenous Cushing's syndrome, accounting for approximately 70 % of cases [2]. The increased ACTH secreted by the tumor acts on the adrenal glands to stimulate increased cortisol production, which in turn leads to the variety of signs and symptoms of Cushing's disease (Fig. 1). In most cases, the tumors are benign and slow growing. Microadenomas (≤10 mm in diameter) are found in >90 % of cases, whereas macroadenomas

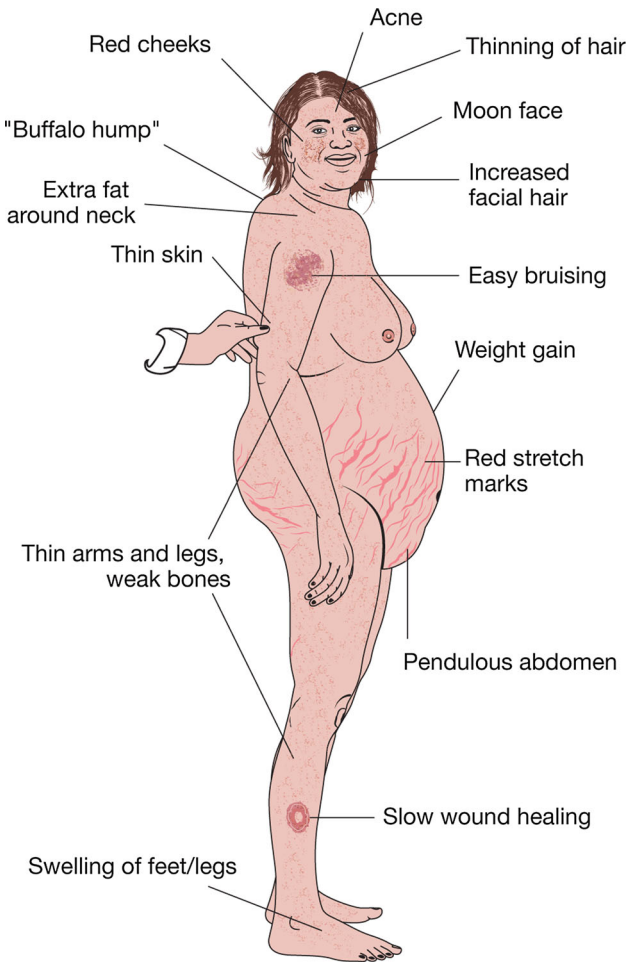

Fig. 1 Signs and symptoms of Cushing's disease

(>10 mm in diameter) are less common (<10 % of cases). As discussed below, the size of the tumor can influence treatment outcomes.

The biochemical relationships involved in the hypothalamus—pituitary—adrenal axis are such that hypercortisolism leading to Cushing's syndrome can also be caused by extrapituitary tumors that secrete ACTH or CRH, adrenal adenomas or carcinomas, and adrenal hyperplasia or dysplasia [2]. Furthermore, several genetic alterations have also been identified as contributing to sporadic corticotropinoma formation, including alterations to *PRKAR1A* (encoding a cAMP-dependent protein kinase A subunit), *PDE11A* (encoding a cyclic nucleotide signal transducer), and *PDE8B* (encoding a cyclic nucleotide phosphodiesterase) [26, 27]. Finally, aberrant stimulation of steroidogenesis in ACTH-independent macronodular adrenal hyperplasia and in some unilateral adenomas can be driven by ectopic receptors such as those for glucose-dependent insulinotropic peptide or gastric inhibitory polypeptide, β-adrenergic receptors, serotonin, and probably angiotensin II receptor. However, it can also result

from increased expression or altered activity of eutopic receptors such as those for vasopressin, luteinizing hormone/human chorionic gonadotropin [28].

Morbidity and mortality of Cushing's disease

Cushing's disease is a serious condition associated with significant morbidity and severe impacts on patients' quality of life [29–31]. Although the tumors causing the disease are slow growing, the efficient secretion of ACTH means that clinical features manifest before the tumor has grown large. These include easy bruising, peripheral edema, facial plethora, proximal myopathy, purple striae, weight gain, and growth retardation or delayed puberty in children [32]. In addition, due to the prolonged exposure to elevated cortisol levels, other features may manifest, including severe fatigue, hypokalemia, hypertension, depression and cognitive impairment, hyperpigmentation, sexual/menstrual dysfunction, hirsutism, acne, osteoporosis and bone fractures, kidney stones, and susceptibility to opportunistic infections (Fig. 1) [33–40]. Patients presenting pituitary adenomas frequently experience impairment of the gonadotropic axis resulting in impaired fertility [41]. Furthermore, the effects of Cushing's disease include cardiovascular complications [42–45], as well as metabolic disturbances that can result in fat tissue redistribution and obesity [42, 46–48]. In a recent population-based cohort study, patients with Cushing's syndrome have been found to be at increased risk of developing venous thromboembolism, stroke, and myocardial infarction [49]. Many of these are non-specific symptoms, and the manifestations of Cushing's disease overlap with many common conditions including obesity, depression, and hypertension [32, 50].

In addition to this significant morbidity, untreated Cushing's disease is associated with excess mortality [49, 51]. Overall mortality in Cushing's disease is double that of the general population [52], and up to four times higher than in age- and sex-matched controls [4, 49]. In addition, mortality in patients with Cushing's disease is more than twice that in patients with non-functioning pituitary macroadenomas even when these have been previously treated, implying that even transient cortisol over-exposure contributes to the increase in mortality [53].

Of note, even after successful treatment, the long-term effects of hypercortisolism mean that patients in remission can be affected by sustained deterioration of the cardiovascular system, bone remodeling, and cognitive function [54–59]. Thus, management plans for the patients in remission of Cushing's disease should include strategies to identify cognitive impairments and psychiatric disorders and to evaluate cardiovascular risk [60].

Diagnosis of Cushing's disease

Differential diagnosis is required for Cushing's disease because of the non-specific symptoms and manifestations common to other conditions. Hypercortisolemia may be the cause of cyclic Cushing's syndrome, a disease characterized by rhythmic fluctuations in glucocorticoid production; hypercortisolism secondary to a number of disorders, such as alcoholism and primary psychiatric disease, may also lead to the so-called pseudo-Cushing syndrome [61]. Patients with pseudo-Cushing syndrome might exhibit some of the clinical features of hypercortisolism; however, resolution of the underlying disease also results in disappearance of the symptoms. However, Cushing's disease is three to four-times more common in women than men [2, 62], and the disease usually manifests in adulthood, with the usual age at diagnosis 25–50 years [53]. Cushing's disease is rare in childhood [63].

Initially, testing to establish chronic hypercortisolism and diagnose Cushing's syndrome is recommended if features such as osteoporosis, hypertension, type 2 diabetes mellitus, or thin skin are present in patients younger than expected [32, 50]; other atypical features (e.g., resistant hypertension, osteoporosis without explanation despite comprehensive testing for secondary causes, and depression resistant to drugs) should also be tested to assess disease severity [8]. A diagnosis can be made if 24-h urinary free cortisol (UFC) or late-night salivary cortisol levels are elevated, if there is a loss of the circadian rhythm of cortisol levels, and if there is a positive response to a low-dose (1 mg) overnight dexamethasone suppression test [6, 8, 50]. Once the clinical diagnosis has been established, an etiological diagnosis is then required to determine Cushing's disease. This can be based on ACTH levels: if morning ACTH levels are normal/equivocal, but late-afternoon (after 16:00) plasma ACTH levels are higher than 10 pg/mL (2 pmol/L), then ACTH-dependent Cushing's disease can be suspected; in addition, if CRH-stimulated ACTH levels are elevated, then Cushing's disease can be also suspected [32, 50]. Similarly, blockade of cortisol in response to a high-dose dexamethasone test can assist in the differential diagnosis of Cushing's disease [32, 50].

A Cushing's disease diagnosis can then be confirmed using imaging, petrosal sinus sampling, or further biochemical tests [32, 50]. If pituitary magnetic resonance imaging reveals adenoma, or the inferior petrosal sinus ACTH:peripheral ACTH ratio is >3 following administration of CRH, then Cushing's disease can be confirmed. However, bilateral inferior petrosal sinus sampling is an invasive test, and non-invasive diagnostic tests may be preferred. A multidetector computed tomography scan, with a combination of unenhanced and dynamic scans, is

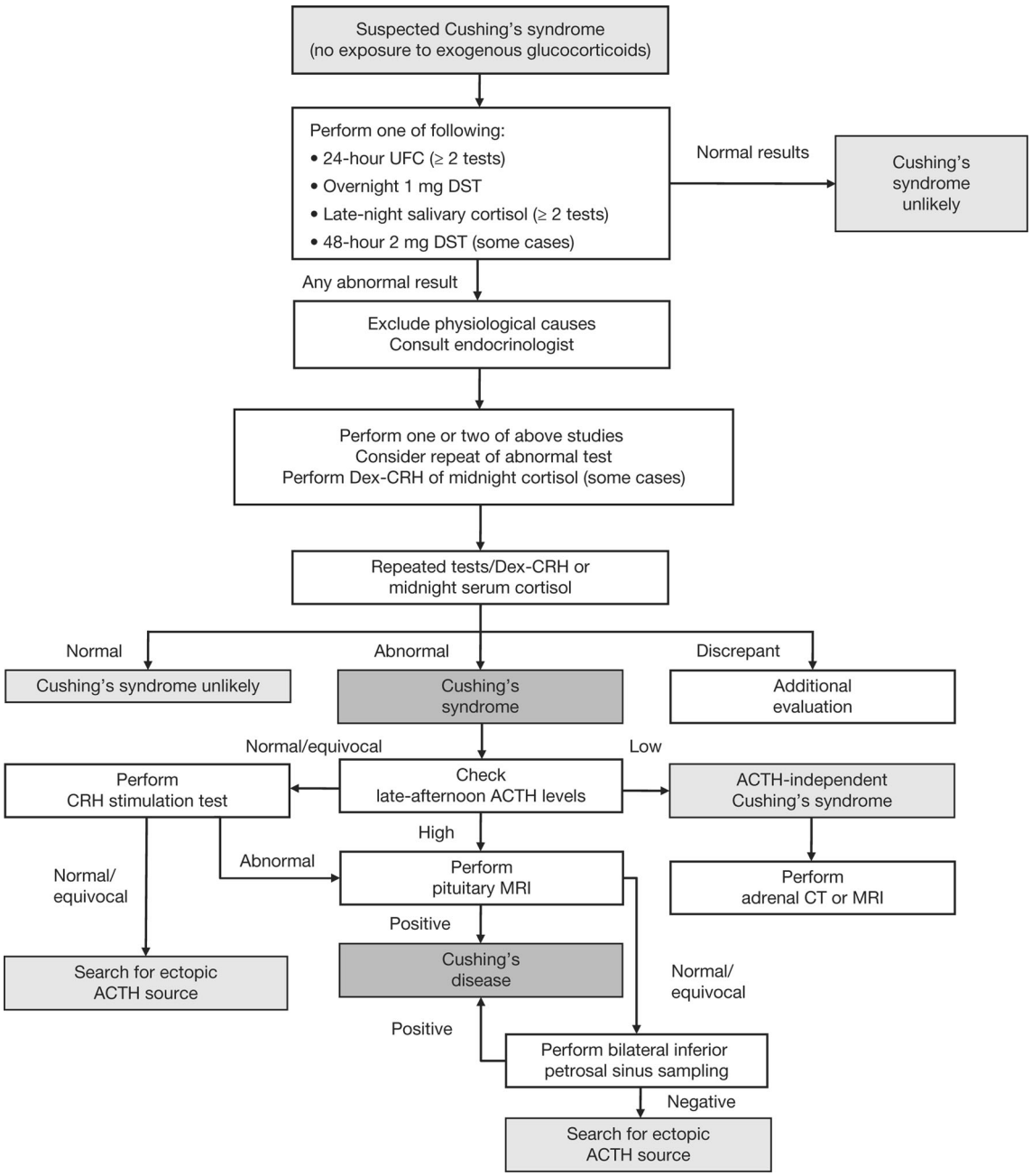

Fig. 2 Diagnostic algorithm for Cushing's disease [based on 32, 50]. *ACTH* adrenocorticotropic hormone, *CRH* corticotropin-releasing hormone, *CT* computed tomography, *Dex* dexamethasone, *DST* dexamethasone suppression test, *MRI* magnetic resonance imaging, *UFC* urinary free cortisol

useful to detect adrenal adenomas and thus assists in differential diagnosis [64]. A recommended diagnostic algorithm is available for Cushing's disease based on the results of biochemical tests for levels of cortisol (Fig. 2) [32, 50]. However, none of these tests is fully proven to be able to distinguish all cases of Cushing's disease from normal and/or obese individuals. In addition, there is no consensus regarding the diagnostic cut-offs related to these tests, which remain in debate; we would like to emphasize that cut-off values are always selected in an arbitrary manner and depend on the methods used for the different assays. The biochemical tests are, however, useful for identifying sub-clinical Cushing's disease in the absence of clinical manifestations [65].

Controversies in Cushing's disease diagnosis

The recommended tests for cortisol levels suffer from several general limitations. False-positive or false-negative results are common if single tests are used because cortisol

Table 1 Medications associated with iatrogenic Cushing's syndrome

Medication	Use
Glucocorticoids [67–69]	Chronic inflammatory disease
	Immunosuppression after organ transplant
Inhaled corticosteroids (especially in combination with ritonavir) [67, 69–71]	Asthma
	Allergic rhinitis
Corticosteroid creams [67, 73–75]	Atopic dermatitis
	Psoriasis
	Atopic eczema

levels fluctuate in a circadian pattern with intermittent release of corticotrophin. In addition, several steroid medications affect cortisol levels, which influence the accuracy of the results (Table 1) [66–76]. The common diagnostic tests have different sensitivities and specificities, and this, combined with the incidence of false-positives and false-negatives, means that repeat testing or use of several different tests is usually needed to provide a reliable diagnosis [77, 78]. With regard to test methodologies, multiple protocols and different cutoff criteria often exist for each test [79], and expertise is needed for accurate use of the tests; thus, in routine clinical practice their performance may be less than satisfactory [78, 80, 81]. However, night-time salivary cortisol measures offer several benefits over the 24-h UFC test for first-line screening [81, 82]. These include greater reproducibility and the non-invasive nature of the test compared with 24-h UFC measurement. Taking two samples rather than one increased the accuracy of the late-night test [83].

Recommendations for the diagnosis and treatment of Cushing's disease

Recommendations for early diagnosis

Cushing's syndrome is one of several disorders in which there may be considerable difficulty and delay in diagnosis [65]. In addition, the need for a differential diagnosis contributes to difficulties in identifying patients with Cushing's disease. As a result, the mean time-to-diagnosis interval for Cushing's disease has been estimated to be as high as 6 years [84]. However, early diagnosis can prompt timely intervention, decreasing patient morbidity and mortality [13], as well as a decrease in the rates of complications associated with treatment [85]. Different categories of patients should undergo screening for Cushing's syndrome, in particular those with visceral obesity, buffalo hump, diabetes mellitus, and hypertension, as well as those with obesity, vertebral fractures, and patients presenting with pituitary/adrenal incidentaloma. Salivary cortisol could be a suitable screening test once robust reference ranges are available. Another interesting screening test is the cortisol level in hair [86], but the usefulness of this method still needs to be confirmed in large populations. The development of educational programs for physicians (such as internists, cardiologists) aimed to meet patients with Cushing's disease, and new screening approaches with "easy-to-use" and cheaper tests are needed.

Recommendations for treatment

The treatment goals in Cushing's disease are the reversal of clinical features, normalization of cortisol levels with minimal morbidity, removal of the tumor mass, and/or stabilization of tumor growth, while preserving pituitary function and long-term control without recurrence [13]. Several interventions that can help achieve these goals are available. As mentioned above, the first-line treatment in Cushing's disease is TSS to remove the adenoma, but its success is dependent on surgeon experience and total removal of the tumor tissue [13, 87, 88]; thus, success is more likely in patients with microadenoma [89–95]. If the initial surgery fails, repeat surgery may be necessary; alternatively, radiotherapy is also an option if initial TSS is unsuccessful. However, none of the surgical or radiotherapeutic options is without risk (Table 2) [13, 21, 95, 96, 98]. Medical therapy can also be useful in cases when initial surgery has failed [102], whereas bilateral adrenalectomy—a highly invasive surgery that requires life-long maintenance hormone replacement therapy—is an intervention of last resort [13].

The state-of-the-art of medical therapy for Cushing's disease has recently advanced with the approval of pasireotide in Europe and the US to treat adult patients with Cushing's disease for whom surgery is not an option or for whom surgery has failed. Previously, the only medical therapies used for Cushing's disease were drugs inhibiting steroidogenesis, such as ketoconazole, metyrapone, mitotane, and etomidate [13, 23]. These are directed at the adrenal glands rather than at the primary cause of Cushing's disease, the ACTH-secreting pituitary adenoma, and may also be limited by a delayed onset of action and/or adverse events (Table 3) [13, 23, 103]. In contrast, pasireotide is the first medical therapy specifically designed and developed as a pituitary-targeted treatment for patients with Cushing's disease [104]. In the largest phase III trial performed in patients with Cushing's disease to date, pasireotide was beneficial with respect to clinical and patient quality-of-life outcomes over a period of 12 months [24]. In terms of safety, a high frequency of hyperglycemia was

Table 2 Surgical and radiotherapeutic treatment options for Cushing's disease

	TSS	Repeat surgery	Bilateral adrenalectomy	Conventional radiotherapy	Stereotactic radiosurgery	Fractionated stereotactic radiation therapy	Brachytherapy
Indication	Traditional first-line therapy	Following unsuccessful surgery	Non-response/ resistance to medical therapy/ radiotherapy [13, 100] Patients declining other therapy [2] or with low likelihood of successful pituitary surgery [100]	Option after unsuccessful TSS May eliminate tumors beyond the reach of TSS (invading the dura or cavernous sinus) [13]	Option after unsuccessful TSS A Gamma Knife can be used as a primary treatment in patients who are not good candidates for surgery [95]	Option after unsuccessful TSS	Option after unsuccessful TSS
Efficacy	65–90 % microadenoma [13]; <65 % macroadenoma [13]	37–73 % [96, 97]	Cortisol levels lowered immediately in almost all patients	Efficacy similar to surgery [13] Remission rate: 50–100 % [95, 99] The effects of radiotherapy may only become apparent after many years [20]	Remission rate: 63–100 % (Gamma Knife), 90–94 % (proton beam) [95]	Remission rate: 54–75 % [13]	Remission rate: 75–100 % [98] Induces remission faster than other forms of radiotherapy/ radiosurgery
Success factors	Experienced surgeon [13] Microadenoma [13] Long-term surveillance [14]	Confirmed remaining pituitary adenoma [101] Confirmation within 4–6 weeks of initial surgery [13]					
Failure factors/ risks	Younger age [13] Macroadenoma [13, 98]	Adenoma not located [96] Lower remission rates than after first surgery		May be followed by pituitary deficiency or failure [21]	Pituitary hormone deficiency develops in two-thirds of patients [95]	May be followed by pituitary hormone deficiency [95]	May be followed by pituitary hormone deficiency/ hypopituitarism [95]

TSS transsphenoidal surgery

observed with pasireotide; other adverse events were similar to those associated with other somatostatin analogs. Furthermore, with over 2 years of treatment with pasireotide, the normalization of UFC levels achieved in the first year was sustained, while the adverse event profile remained similar to that seen with 1 year of treatment [25].

Future directions and research

Despite the availability of diagnostic tests and recent progress in the treatments available for Cushing's disease, several challenges remain for those involved in patient care and management. The controversies associated with the

Table 3 Currently available medical treatment options for Cushing's disease [13, 23, 103]

Mode of action	Typical dose	Characteristics	Adverse events
Pituitary-directed somatostatin analog			
Pasireotide	0.3 mg b.i.d to 0.9 mg b.i.d (recommended starting dose is 0.6 mg b.i.d)	Enhanced activity at the principal receptor sub-type expressed in the target gland	Hyperglycemia; diabetes mellitus; diarrhea, abdominal pain, nausea; cholelithiasis; injection site reaction, fatigue
Steroidogenesis inhibitor			
Ketoconazole	200 mg b.i.d to 400 mg t.i.d	Several weeks needed to see full benefit	Antiandrogenic properties; gynecomastia and reduced libido in men
		Reduced total cholesterol and low-density lipoprotein cholesterol	Gastrointestinal upset and skin rashes
			Liver enzyme dysfunction in 10 % of cases
Metyrapone	250 mg q.i.d to 1,500 mg q.i.d	Potent; rapid onset of action	Nausea, abdominal pain
		Serum cortisol levels fall within 4 h of initial dose	Accumulation of cortisol precursors results in elevated androgens, leading to hirsutism and acne in women
		Care needed to avoid over-treatment	
Mitotane	500 mg t.i.d to 3,000 mg t.i.d	Slow onset of action	At doses >2,000 mg/day, nausea, anorexia, and diarrhea
		Sustained action maintained after discontinuation in up to 33 % of patients	At highest doses, adrenal insufficiency and neurological adverse events, abnormal liver enzymes, hypercholesterolemia, skin rash, hypouricaemia, gynecomastia
		Needs gradual uptitration and to be taken with food	

The glucocorticoid-receptor antagonist mifepristone has been recently approved by the Food and Drug Administration in the US for the management of hyperglycemia in patients with Cushing's disease

b.i.d. twice daily, *q.i.d.* four times daily, *t.i.d.* three times daily

currently available diagnostic tests mean that screening and early identification of patients with Cushing's disease remains complex. Thus, simpler, more accurate diagnostic tests are required to optimize differential diagnosis. Some promising recent developments include the use of combined quantification of UFC/cortisone and detection of synthetic glucocorticoids [105]. Steroid treatment has been reported as a cause of Cushing's syndrome in some cases [67], and thus the use of a liquid chromatography-tandem mass spectrometry method to detect commonly prescribed steroid drugs simultaneously with measurement of 24-h UFC and cortisone could assist in the accurate diagnosis of Cushing's disease [106, 107]. As discussed above, the use of salivary cortisol tests offers advantages over the 24-h UFC test, and successful methods for automating analysis of salivary cortisol levels have recently been reported, increasing the clinical utility of this diagnostic test [108, 109].

The recent introduction of pasireotide has expanded the range of therapeutic options available for the management of patients with Cushing's disease, allowing lowering of ACTH secretion, normalization of cortisol production by the adrenal glands, restoration of normal secretory dynamics to the hypothalamic—pituitary—adrenal axis, and inhibition of tumor growth [31]. Several other therapies (directed to the pituitary as a target and steroidogenesis inhibitor therapies) have been investigated or are in development for use in Cushing's disease. However, these have either not been extensively studied clinically or the initial promise shown has not been fulfilled in further investigations (Table 4) [110–119]. A promising product currently in development is LCI699, a potent 11β-hydroxylase inhibitor [118]. Preliminary results were presented at the 2012 Congress of the European NeuroEndocrine Association showing the efficacy and a satisfactory safety profile in patients with Cushing's disease treated with this new compound [118]. In small-scale studies, cabergoline monotherapy has shown efficacy in selected patients with Cushing's disease, but close follow-up was required for dose adjustments [111, 112, 119]. In these studies, the use of cabergoline was effective in the control of cortisol secretion, measured via changes in UFC excretion. However, additional large-scale prospective studies are needed to establish cabergoline therapy in these patients. Despite a response to bromocriptine in some cases of Cushing's disease, there is generally no reduction of hypercortisolism seen in patients with Cushing's disease treated with this investigative agent [114, 120]. A molecule with initially encouraging experimental results in Cushing's disease models or theoretical advantages over existing therapies is BIM-23A760. The chimeric BIM-23A760 molecule was investigated as a possible therapy on the basis of its theoretically increased inhibition of ACTH secretion from Cushing's-causing corticotroph tumors

Table 4 Medical therapies in development for Cushing's disease

Compound	Class	Rationale	Available evidence
Pituitary-directed therapies			
Cabergoline	Dopamine receptor agonist	D_2 receptor expressed in >75 % of corticotrophic pituitary adenomas and associated with inhibitory function [111] May not be greatly downregulated in the presence of glucocorticoids [112]	Small, short-term study: cabergoline may be effective in a subset of patients with Cushing's disease [111] Small study ($n = 20$): cabergoline controls UFC levels in post-surgical patients [112]
Bromocriptine	Dopamine receptor agonist	D_2 receptor expressed in >75 % of corticotrophic pituitary adenomas and associated with inhibitory function [112] May not be greatly downregulated in the presence of glucocorticoids [113]	ACTH secretion inhibited in vitro [113] No reduction of hypercortisolism seen in patients with Cushing's disease [114]
BIM-23A760	Chimeric D_2-and $sst_{2,5}$-preferring agonist	D_2 receptor expressed in >75 % of corticotrophic pituitary adenomas and associated with inhibitory function [111] May not be greatly downregulated in the presence of glucocorticoids [112]	In theory, greater inhibitory effect due to possible D_2 and somatostatin receptor dimer formation [115, 116]
Steroidogenesis inhibitor			
LCI699	11β-hydroxylase inhibitor	11β-hydroxylase catalyzes the final step of cortisol synthesis	Proof-of-concept study: 12 patients were enrolled and completed the study. The primary endpoint (UFC $\leq$ ULN or a $\geq$50 % decrease from baseline at day 70) was achieved in 12 patients. No serious drug-related adverse events were reported [118]

PPAR-γ peroxisome proliferator-activated receptor gamma, *UFC* urinary free cortisol, *ULN*, upper limit of normal

relative to that of other molecules, thought to be due to its dual action on somatostatin and dopamine receptors [121]. However, a metabolite of BIM-23A760 with dopaminergic activity gradually accumulates in vivo and interferes with the activity of the parent compound [116]. In terms of novel therapies, recently, long-term treatment with retinoic acid was shown to be beneficial and well-tolerated in 5 of 7 patients with Cushing's disease [122]. Further research into pituitary-directed treatments for patients with Cushing's disease may yield additional medicinal therapies to extend the clinical armamentarium available to physicians.

In addition to these pituitary-directed molecules, the glucocorticoid receptor has been targeted in research aimed at identifying novel therapies for Cushing's disease. Mifepristone is a glucocorticoid-receptor antagonist shown to produce clinical and metabolic benefits in patients with Cushing's disease over 6 months [123]. However, a lack of available biological monitoring data during treatment and a risk of worsening of hypokalemia and blood pressure levels mean that its clinical utility is limited to the management of hyperglycemia in patients with Cushing's disease [124–126]. Mifepristone has been recently approved by the Food and Drug Administration in the US for the treatment of hyperglycemia in patients with Cushing's disease.

Combination treatments with cabergoline and ketoconazole have also been reported; however, larger studies are needed to determine the efficacy and safety of these therapies.

Conclusions

In summary, Cushing's disease is the most common cause of endogenous Cushing's syndrome, and is caused by ACTH-secreting pituitary adenomas. It is associated with significant complications and reduced quality of life, and is a fatal condition in the absence of adequate treatment. The diagnosis and treatment of patients with Cushing's disease are complex and require both a multidisciplinary and individualized approach to patient management. Currently, the first-line therapy in Cushing's disease is TSS to remove the adenoma. The recent approval of pasireotide, the first medical therapy to directly target the cause of Cushing's disease, provides a new therapeutic option for patients in whom initial TSS is unsuccessful or for those patients who are ineligible for surgery.

Greater awareness of Cushing's disease is required among primary physicians because there is a high rate of subclinical disease. The lack of awareness coupled with signs and symptoms common to other conditions means that more accurate diagnostic tests to screen for and diagnose Cushing's disease in its earliest stages are required.

Future research into Cushing's disease diagnosis and an expanding number of treatment options will improve clinical outcomes for patients with Cushing's disease and optimize their management.

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References

1. S.S. Praw, A.P. Heaney, Medical treatment of Cushing's disease: overview and recent findings. Int. J. Gen. Med. **29**, 209–217 (2009)
2. J. Newell-Price, X. Bertagna, A.B. Grossman et al., Cushing's syndrome. Lancet **367**, 1605–1617 (2006)
3. J. Lindholm, S. Juul, J.O. Jørgensen et al., Incidence and late prognosis of Cushing's syndrome: a population-based study. J. Clin. Endocrinol. Metab. **86**, 117–123 (2001)
4. J. Etxabe, J.A. Vazquez, Morbidity and mortality in Cushing's disease: an epidemiological approach. Clin. Endocrinol. (Oxf) **40**, 479–484 (1994)
5. R. Pivonello, M.C. De Martino, M. De Leo et al., Cushing's syndrome. Endocrinol. Metab. Clin. North Am. **37**, 135–149 (2008)
6. M. Boscaro, G. Arnaldi, Approach to the patient with possible Cushing's syndrome. J. Clin. Endocrinol. Metab. **94**, 3121–3131 (2009)
7. C. Steffensen, A.M. Bak, K.Z. Rubeck et al., Epidemiology of Cushing's syndrome. Neuroendocrinology **92**, 1–5 (2010)
8. L. Guignat, J. Bertherat, The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline: commentary from a European perspective. Eur. J. Endocrinol. **163**, 9–13 (2010)
9. J. Kreutzer, R. Fahlbusch, Diagnosis and treatment of pituitary tumors. Curr. Opin. Neurol. **17**, 693–703 (2004)
10. A.S. Kanter, A.O. Diallo, J.A. Jane Jr et al., Single-center experience with pediatric Cushing's disease. J. Neurosurg. **103**, 413–420 (2005)
11. D.F. Kelly, Transsphenoidal surgery for Cushing's disease: a review of success rates, remission predictors, management of failed surgery, and Nelson's Syndrome. Neurosurg. Focus **23**, E5 (2007)
12. J. Newell-Price, A.B. Grossman, Differential diagnosis of Cushing's syndrome. Arq. Bras. Endocrinol. Metabol. **51**, 1199–1206 (2007)
13. B.M. Biller, A.B. Grossman, P.M. Stewart et al., Treatment of adrenocorticotropin-dependent Cushing's syndrome: a consensus statement. J. Clin. Endocrinol. Metab. **93**, 2454–2462 (2008)
14. D.M. Prevedello, N. Pouratian, J. Sherman et al., Management of Cushing's disease: outcome in patients with microadenoma detected on pituitary magnetic resonance imaging. J. Neurosurg. **109**, 751–759 (2008)
15. G. Arnaldi, M. Boscaro, New treatment guidelines on Cushing's disease. F1000 Med. Rep. **1**, 64 (2009)
16. L.S. Blevins Jr, N. Sanai, S. Kunwar et al., An approach to the management of patients with residual Cushing's disease. J. Neurooncol. **94**, 313–319 (2009)
17. B.M. Biller, A. Colao, S. Petersenn et al., Prolactinomas, Cushing's disease and acromegaly: debating the role of medical therapy for secretory pituitary adenomas. BMC Endocr. Disord. **10**, 10 (2010)
18. N. Sonino, F. Fallo, G.A. Fava, Psychosomatic aspects of Cushing's syndrome. Rev. Endocr. Metab. Disord. **11**, 95–104 (2010)
19. A. Rizk, J. Honegger, M. Milian et al., Treatment options in Cushing's disease. Clin. Med. Insights. Oncol. **6**, 75–84 (2012)
20. F. Castinetti, M. Nagai, H. Dufour et al., Gamma knife radiosurgery is a successful adjunctive treatment in Cushing's disease. Eur. J. Endocrinol. **156**, 91–98 (2007)
21. J.K. Devin, G.S. Allen, A.J. Cmelak et al., The efficacy of linear accelerator radiosurgery in the management of patients with Cushing's disease. Stereotact. Funct. Neurosurg. **82**, 254–262 (2004)
22. M. Boschetti, M. De Lucchi, M. Giusti et al., Partial visual recovery from radiation-induced optic neuropathy after hyperbaric oxygen therapy in a patient with Cushing disease. Eur. J. Endocrinol. **154**, 813–818 (2006)
23. C.N. Dang, P. Trainer, Pharmacological management of Cushing's syndrome: an update. Arq. Bras. Endocrinol. Metabol. **51**, 1339–1348 (2007)
24. A. Colao, S. Petersenn, J. Newell-Price et al., A 12-month phase 3 study of pasireotide in Cushing's disease. N. Engl. J. Med. **366**, 914–924 (2012)
25. J. Bertherat, W. Ludlam, R. Pivonello et al., Long-term use of pasireotide in Cushing's disease: 24-month safety results from a randomized Phase III study. Endocr. Abstr. **27**, P1405 (2012)
26. M. Yaneva, S. Vandeva, S. Zacharieva et al., Genetics of Cushing's syndrome. Neuroendocrinology **92**, 6–10 (2010)
27. Genetics Home Reference. http://ghr.nlm.nih.gov/ (2013). Accessed 5 July 2013
28. A. Lacroix, ACTH-independent macronodular adrenal hiperplasia. Best practice and research. Clin. Endocrinol. Metab. **23**, 245–259 (2009)
29. S.M. Webb, X. Badia, M.J. Barahona et al., Evaluation of health-related quality of life in patients with Cushing's syndrome with a new questionnaire. Eur. J. Endocrinol. **158**, 623–630 (2008)
30. A. Santos, E. Resmini, M.A. Martínez et al., Quality of life in patients with pituitary tumors. Curr. Opin. Endocrinol. Diabetes Obes. **16**, 299–303 (2009)
31. A. Colao, A. Cozzolino, R. Pivonello, Quality of life in patients with Cushing's disease: a modern approach. Clin. Endocrinol. **76**, 776–777 (2012)
32. L.K. Nieman, B.M. Biller, J.W. Findling et al., The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. J. Clin. Endocrinol. Metab. **93**, 1526–1540 (2008)
33. L. Katznelson, J.S. Bogan, J.R. Trob et al., Biochemical assessment of Cushing's disease in patients with corticotroph macroadenomas. J. Clin. Endocrinol. Metab. **83**, 1619–1623 (1998)
34. R.C. Bakker, P.R. Gallas, J.A. Romijn et al., Cushing's syndrome complicated by multiple opportunistic infections. J. Endocrinol. Invest. **21**, 329–333 (1998)
35. A. Faggiano, R. Pivonello, D. Melis et al., Nephrolithiasis in Cushing's disease: prevalence, etiopathogenesis, and modification after disease cure. J. Clin. Endocrinol. Metab. **88**, 2076–2080 (2003)
36. L. Tauchmanovà, R. Pivonello, M.C. De Martino et al., Effects of sex steroids on bone in women with subclinical or overt endogenous hypercortisolism. Eur. J. Endocrinol. **157**, 359–366 (2007)

37. S.G. Kosseifi, D.N. Nassour, M.A. Shaikh et al., Nodular pulmonary histoplasmosis in Cushing's disease: a case report and literature review. Tenn. Med. **100**, 44–46 (2007)
38. A.W. van der Eerden, M. den Heijer, W.J. Oyen et al., Cushing's syndrome and bone mineral density: lowest Z scores in young patients. Neth. J. Med. **65**, 137–141 (2007)
39. G. Kaltsas, P. Makras, Skeletal diseases in Cushing's syndrome: osteoporosis versus arthropathy. Neuroendocrinology **92**, 60–64 (2010)
40. R.A. Feelders, S.J. Pulgar, A. Kempel, A.M. Pereira, The burden of Cushing's disease: clinical and health-related quality of life aspects. Eur. J. Endocrinol. **167**, 311–2620 (2012)
41. M.D. Bronstein, L.R. Salgado, N.R. de Castro Musolino, Medical management of pituitary adenomas: the special case of management of the pregnant woman. Pituitary **5**, 99–107 (2002)
42. L. Tauchmanovà, R. Rossi, B. Biondi et al., Patients with subclinical Cushing's syndrome due to adrenal adenoma have increased cardiovascular risk. J. Clin. Endocrinol. Metab. **87**, 4872–4878 (2002)
43. R. Pivonello, A. Faggiano, G. Lombardi et al., The metabolic syndrome and cardiovascular risk in Cushing's syndrome. Endocrinol. Metab. Clin. North Am. **34**, 327–339 (2005)
44. M. De Leo, R. Pivonello, R.S. Auriemma et al., Cardiovascular disease in Cushing's syndrome: heart versus vasculature. Neuroendocrinology **92**, 50–54 (2010)
45. F. Fallo, G. Famoso, D. Capizzi et al., Coronary microvascular function in patients with Cushing's syndrome. Endocrine **43**, 206–213 (2013)
46. S. Savastano, R. Pivonello, A. Colao, Bariatric surgery for obesity and hidden Cushing syndrome. Surg. Obes. Relat. Dis. **5**, 121–122 (2009)
47. P. Chanson, S. Salenave, Metabolic syndrome in Cushing's syndrome. Neuroendocrinology **92**, 96–101 (2010)
48. E.B. Geer, W. Shen, D. Gallagher et al., MRI assessment of lean and adipose tissue distribution in female patients with Cushing's disease. Clin. Endocrinol. **73**, 469–475 (2010)
49. O.M. Dekkers, E. Horváth-Puhó, J.O. Jørgensen et al., Multisystem morbidity and mortality in Cushing's syndrome: a cohort study. J. Clin. Endocrinol. Metab. **98**, 2277–2284 (2013)
50. G. Arnaldi, A. Angeli, A.B. Atkinson et al., Diagnosis and complications of Cushing's syndrome: a consensus statement. J. Clin. Endocrinol. Metab. **88**, 5593–5602 (2003)
51. D. Graversen, P. Vestergaard, K. Stochholm et al., Mortality in Cushing's syndrome: a systematic review and meta-analysis. Eur. J. Intern. Med. **23**, 278–282 (2012)
52. R.N. Clayton, D. Raskauskiene, R.C. Reulen et al., Mortality and morbidity in Cushing's disease over 50 years in Stoke-on-Trent, UK: audit and meta-analysis of literature. J. Clin. Endocrinol. Metab. **96**, 632–642 (2011)
53. O.M. Dekkers, N.R. Biermasz, A.M. Pereira et al., Mortality in patients treated for Cushing's disease is increased, compared with patients treated for nonfunctioning pituitary macroadenoma. J. Clin. Endocrinol. Metab. **92**, 976–981 (2007)
54. E. Valassi, I. Crespo, A. Santos, S.M. Webb, Clinical consequences of Cushing's syndrome. Pituitary **15**, 319–329 (2012)
55. R. Pivonello, M.C. De Martino, M. De Leo et al., Cushing's syndrome: aftermath of the cure. Arq. Bras. Endocrinol. Metabol. **51**, 1381–1391 (2007)
56. A. Faggiano, R. Pivonello, S. Spiezia et al., Cardiovascular risk factors and common carotid artery caliber and stiffness in patients with Cushing's disease during active disease and 1 year after disease remission. J. Clin. Endocrinol. Metab. **88**, 2527–2533 (2003)
57. A. Colao, R. Pivonello, S. Spiezia et al., Persistence of increased cardiovascular risk in patients with Cushing's disease after five years of successful cure. J. Clin. Endocrinol. Metab. **84**, 2664–2672 (1999)
58. C. Di Somma, R. Pivonello, S. Loche et al., Effect of 2 years of cortisol normalization on the impaired bone mass and turnover in adolescent and adult patients with Cushing's disease: a prospective study. Clin Endocrinol (Oxf). **58**, 302–308 (2003)
59. A. Faggiano, R. Pivonello, M. Filippella et al., Spine abnormalities and damage in patients cured from Cushing's disease. Pituitary **4**, 153–161 (2001)
60. O. Ragnarsson, G. Johannsson, Management of endocrine disease: Cushing's syndrome: a structured short- and long-term management plan for patients in remission. Eur. J. Endocrinol. **169**, R139–R152 (2013)
61. C. Garcia, B.M. Biller, A. Klibanski, The role of the clinical laboratory in the diagnosis of Cushing syndrome. Am. J. Clin. Pathol. **120**, S38–S45 (2003)
62. J. Newell-Price, P. Trainer, M. Besser et al., The diagnosis and differential diagnosis of Cushing's syndrome and pseudo-Cushing's states. Endocr. Rev. **19**, 647–672 (1998)
63. L.F. Chan, H.L. Storr, A.B. Grossman et al., Pediatric Cushing's syndrome: clinical features, diagnosis, and treatment. Arq. Bras. Endocrinol. Metabol. **51**, 1261–1271 (2007)
64. F. Lumachi, P. Marchesi, D. Miotto et al., CT and MR imaging of the adrenal glands in cortisol-secreting tumors. Anticancer Res. **31**, 2923–2926 (2011)
65. D.C. Aron, Cushing's syndrome: why is diagnosis so difficult? Rev. Endocr. Metab. Disord. **11**, 105–116 (2010)
66. S. Hasinski, Assessment of adrenal glucocorticoid function. Which tests are appropriate for screening? Postgrad. Med. **104**(61–64), 69–72 (1998)
67. D. Vassiliadi, S. Tsagarakis, Unusual causes of Cushing's syndrome. Arq. Bras. Endocrinol. Metabol. **51**, 1245–1252 (2007)
68. T.B. Carroll, J.W. Findling, Cushing's syndrome of nonpituitary causes. Curr. Opin. Endocrinol. Diabetes Obes. **16**, 308–315 (2009)
69. M.M. Foisy, E.M. Yakiwchuk, I. Chiu et al., Adrenal suppression and Cushing's syndrome secondary to an interaction between ritonavir and fluticasone: a review of the literature. HIV Med. **9**, 389–396 (2008)
70. J. Lo, S.K. Grinspoon, Adrenal function in HIV infection. Curr. Opin. Endocrinol. Diabetes Obes. **17**, 205–209 (2010)
71. C. Bernecker, T.B. West, G. Mansmann et al., Hypercortisolism caused by ritonavir associated inhibition of CYP 3A4 under inhalative glucocorticoid therapy. 2 case reports and a review of the literature. Exp. Clin. Endocrinol. Diabetes **120**, 125–127 (2012)
72. C. Levin, H.I. Maibach, Topical corticosteroid-induced adrenocortical insufficiency: clinical implications. Am. J. Clin. Dermatol. **3**, 141–147 (2002)
73. B. Coureau, J.F. Bussières, S. Tremblay, Cushing's syndrome induced by misuse of moderate- to high-potency topical corticosteroids. Ann. Pharmacother. **42**, 1903–1907 (2008)
74. T. Tempark, V. Phatarakijnirund, S. Chatproedprai et al., Exogenous Cushing's syndrome due to topical corticosteroid application: case report and review literature. Endocrine **38**, 328–334 (2010)
75. E. Castela, E. Archier, S. Devaux et al., Topical corticosteroids in plaque psoriasis: a systematic review of risk of adrenal axis suppression and skin atrophy. J. Eur. Acad. Dermatol. Venereol. **26**, 47–51 (2012)
76. L. Vilar, Mda C. Freitas, M. Faria et al., Pitfalls in the diagnosis of Cushing's syndrome. Arq. Bras. Endocrinol. Metabol. **51**, 1207–1216 (2007)
77. F. Pecori Giraldi, Recent challenges in the diagnosis of Cushing's syndrome. Horm. Res. **71**, 123–127 (2009)

78. D.G. Morris, A.B. Grossman, Dynamic tests in the diagnosis and differential diagnosis of Cushing's syndrome. J. Endocrinol. Invest. **26**, 64–73 (2003)
79. M.B. Elamin, M.H. Murad, R. Mullan et al., Accuracy of diagnostic tests for Cushing's syndrome: a systematic review and metaanalyses. J. Clin. Endocrinol. Metab. **93**, 1553–1562 (2008)
80. H. Raff, Update on late-night salivary cortisol for the diagnosis of Cushing's syndrome: methodological considerations. Endocrine. Epub ahead of print (2013)
81. A. Viardot, P. Huber, J.J. Puder et al., Reproducibility of nighttime salivary cortisol and its use in the diagnosis of hypercortisolism compared with urinary free cortisol and overnight dexamethasone suppression test. J. Clin. Endocrinol. Metab. **90**, 5730–5736 (2005)
82. S.A. Doi, J. Clark, A.W. Russell, Concordance of the late night salivary cortisol in patients with Cushing's syndrome and elevated urine-free cortisol. Endocrine **43**, 327–333 (2013)
83. C.A. Carrasco, M. García, M. Goycoolea et al., Reproducibility and performance of one or two samples of salivary cortisol in the diagnosis of Cushing's syndrome using an automated immunoassay system. Endocrine **41**, 487–493 (2012)
84. T. Psaras, M. Milian, V. Hattermann et al., Demographic factors and the presence of comorbidities do not promote early detection of Cushing's disease and acromegaly. Exp. Clin. Endocrinol. Diabetes **119**, 21–25 (2011)
85. A. Meyer, M. Behrend, Cushing's syndrome: adrenalectomy and long-term results. Dig. Surg. **21**, 363–370 (2004)
86. L. Manenschijn, J.W. Koper, E.L. van den Akker et al., A novel tool in the diagnosis and follow-up of (cyclic) Cushing's syndrome: measurement of long-term cortisol in scalp hair. J. Clin. Endocrinol. Metab. **97**, E1836–E1843 (2012)
87. P. Leach, A.H. Abou-Zeid, T. Kearney et al., Endoscopic transsphenoidal pituitary surgery: evidence of an operative learning curve. Neurosurgery. **67**, 1205–1212 (2010)
88. X. Bertagna, L. Guignat, Approach to the Cushing's disease patient with persistent/recurrent hypercortisolism after pituitary surgery. J. Clin. Endocrinol. Metab. **98**, 1307–1318 (2013)
89. D.A. Rees, F.W. Hanna, J.S. Davies et al., Long-term follow-up results of transsphenoidal surgery for Cushing's disease in a single centre using strict criteria for remission. Clin. Endocrinol. (Oxf) **56**, 541–551 (2002)
90. I. Shimon, Z. Ram, Z.R. Cohen et al., Transsphenoidal surgery for Cushing's disease: endocrinological follow-up monitoring of 82 patients. Neurosurgery. **51**, 57–61 (2002)
91. G.D. Hammer, J.B. Tyrrell, K.R. Lamborn et al., Transsphenoidal microsurgery for Cushing's disease: initial outcome and long-term results. J. Clin. Endocrinol. Metab. **89**, 6348–6357 (2004)
92. A.B. Atkinson, A. Kennedy, M.I. Wiggam et al., Long-term remission rates after pituitary surgery for Cushing's disease: the need for long-term surveillance. Clin. Endocrinol. (Oxf) **63**, 549–559 (2005)
93. G. Rollin, N.P. Ferreira, M.A. Czepielewski, Prospective evaluation of transsphenoidal pituitary surgery in 108 patients with Cushing's disease. Arq. Bras. Endocrinol. Metabol. **51**, 1355–1361 (2007)
94. B.M. Hofmann, M. Hlavac, R. Martinez et al., Long-term results after microsurgery for Cushing disease: experience with 426 primary operations over 35 years. J. Neurosurg. **108**, 9–18 (2008)
95. A.S. Mahmoud-Ahmed, J.H. Suh, Radiation therapy for Cushing's disease: a review. Pituitary. **5**, 175–180 (2002)
96. R.B. Friedman, E.H. Oldfield, L.K. Nieman et al., Repeat transsphenoidal surgery for Cushing's disease. J. Neurosurg. **71**, 520–527 (1989)
97. R.J. Benveniste, W.A. King, J. Walsh et al., Repeated transsphenoidal surgery to treat recurrent or residual pituitary adenoma. J. Neurosurg. **102**, 1004–1012 (2005)
98. L.S. Blevins Jr, J.H. Christy, M. Khajavi et al., Outcomes of therapy for Cushing's disease due to adrenocorticotropin-secreting pituitary macroadenomas. J. Clin. Endocrinol. Metab. **83**, 63–67 (1998)
99. N. Sonino, M. Zielezny, G.A. Fava et al., Risk factors and long-term outcome in pituitary-dependent Cushing's disease. J. Clin. Endocrinol. Metab. **81**, 2647–2652 (1996)
100. G. Assié, H. Bahurel, J. Coste et al., Corticotroph tumor progression after adrenalectomy in Cushing's Disease: a reappraisal of Nelson's Syndrome. J. Clin. Endocrinol. Metab. **92**, 172–179 (2007)
101. M. Boscaro, L. Barzon, F. Fallo et al., Cushing's syndrome. Lancet **357**, 783–791 (2001)
102. R.A. Feelders, L.J. Hofland, Medical treatment of Cushing's disease. J. Clin. Endocrinol. Metab. **98**, 425–438 (2013)
103. Pasireotide Summary of Product Characteristics: http://www.medicines.org.uk/emc/medicine/26746/SPC#INDICATIONS (2013). Accessed in 5 July 2013
104. H.A. Schmid, Pasireotide (SOM230): development, mechanism of action and potential applications. Mol. Cell. Endocrinol. **286**, 69–74 (2008)
105. N.K. Djedovic, S.J. Rainbow, Detection of synthetic glucocorticoids by liquid chromatography–tandem mass spectrometry in patients being investigated for Cushing's syndrome. Ann. Clin. Biochem. **48**, 542–549 (2011)
106. A.E. Kulle, M. Welzel, P.M. Holterhus, F.G. Riepe, Principles and clinical applications of liquid chromatography–tandem mass spectrometry for the determination of adrenal and gonadal steroid hormones. J. Endocrinol. Invest. **34**, 702–708 (2011)
107. B.M. Fong, S. Tam, K.S. Leung, Improved liquid chromatography-tandem mass spectrometry method in clinical utility for the diagnosis of Cushing's syndrome. Anal. Bioanal. Chem. **396**, 783–790 (2010)
108. T. Deutschbein, M. Broecker-Preuss, J. Flitsch et al., Salivary cortisol as a diagnostic tool for Cushing's syndrome and adrenal insufficiency: improved screening by an automatic immunoassay. Eur. J. Endocrinol. **166**, 613–618 (2012)
109. H. Raff, Cushing's syndrome: diagnosis and surveillance using salivary cortisol. Pituitary. **15**, 64–70 (2012)
110. R. Pivonello, D. Ferone, W.W. de Herder et al., Dopamine receptor expression and function in corticotroph pituitary tumors. J. Clin. Endocrinol. Metab. **89**, 2452–2462 (2004)
111. C. de Bruin, R.A. Feelders, A.M. Waaijers et al., Differential regulation of human dopamine D2 and somatostatin receptor subtype expression by glucocorticoids in vitro. J. Mol. Endocrinol. **42**, 47–56 (2009)
112. R. Pivonello, M.C. De Martino, P. Cappabianca et al., The medical treatment of Cushing's disease: effectiveness of chronic treatment with the dopamine agonist cabergoline in patients unsuccessfully treated by surgery. J. Clin. Endocrinol. Metab. **94**, 223–230 (2009)
113. E.F. Adams, M.J. Ashby, S.M. Brown et al., Bromocriptine suppresses ACTH secretion from human pituitary tumour cells in culture by a dopaminergic mechanism. Clin. Endocrinol. (Oxf) **15**, 479–484 (1981)
114. C. Invitti, M. De Martin, L. Danesi et al., Effect of injectable bromocriptine in patients with Cushing's disease. Exp. Clin. Endocrinol. Diabetes **103**, 266–271 (1995)
115. C. de Bruin, R.A. Feelders, S.W. Lamberts et al., Somatostatin and dopamine receptors as targets for medical treatment of Cushing's Syndrome. Rev. Endocr. Metab. Disord. **10**, 91–102 (2009)

116. M. Rocheville, D.C. Lange, U. Kumar et al., Receptors for dopamine and somatostatin: formation of hetero-oligomers with enhanced functional activity. Science **288**, 154–157 (2000)
117. A.P. Heaney, M. Fernando, W.H. Yong et al., Functional PPAR-gamma receptor is a novel therapeutic target for ACTH-secreting pituitary adenomas. Nat. Med. **8**, 1281–1287 (2002)
118. X. Bertagna, R. Pivonello, M. Fleseriu, et al., Normal urinary cortisol with LCI699 in patients with Cushing's disease: preliminary results from a proof-of-concept study. 15th Congress of the European NeuroEndocrine Association (ENEA 2012), Vienna, Austria; Klinische Endokrinologie und Stoffwechsel, **5**, 22: abstract OC04 (2012)
119. A. Godbout, M. Manavela, K. Danilowicz et al., Cabergoline monotherapy in the long-term treatment of Cushing's disease. Eur. J. Endocrinol. **163**, 709–716 (2010)
120. M. Boschetti, F. Gatto, M. Arvigo et al., Role of dopamine receptors in normal and tumoral pituitary corticotropic cells and adrenal cells. Neuroendocrinology **92**, 17–22 (2010)
121. M.D. Culler, Somatostatin-dopamine chimeras: a novel approach to treatment of neuroendocrine tumors. Horm. Metab. Res. **43**, 854–857 (2011)
122. F. Pecori Giraldi, A.G. Ambrogio, M. Andrioli et al., Potential role for retinoic acid in patients with Cushing's disease. J. Clin. Endocrinol. Metab. **97**, 3577–3583 (2012)
123. M. Fleseriu, B.M. Biller, J.W. Findling et al., Mifepristone, a glucocorticoid receptor antagonist, produces clinical and metabolic benefits in patients with Cushing's syndrome. J. Clin. Endocrinol. Metab. **97**, 2039–2049 (2012)
124. F. Castinetti, B. Conte-Devolx, T. Brue, Medical treatment of Cushing's syndrome: glucocorticoid receptor antagonists and mifepristone. Neuroendocrinology **92**, 125–130 (2010)
125. F. Castinetti, T. Brue, B. Conte-Devolx, The use of the glucocorticoid receptor antagonist mifepristone in Cushing's syndrome. Curr. Opin. Endocrinol. Diabetes. Obesity. **19**, 295–299 (2012)
126. J.D. Carmichael, M. Fleseriu, Mifepristone: is there a place in the treatment of Cushing's disease? Endocrine **44**, 20–32 (2013)