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Drugs in the medical treatment of Cushing's syndrome

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Cushing's syndrome is a complex endocrine condition with potential serious complications if untreated or inadequately treated. Transsphenoidal surgery with resection of a pituitary adenoma is successful in 75 – 80% of patients, but approximately 20 – 25% show persistence of Cushing's, and a similar proportion may experience recurrence within 2 – 4 years post-op. When surgery fails, medical treatment can temporarily suppress excessive cortisol production and ameliorate its clinical manifestations while more definitive therapy becomes effective. We describe pharmacological approaches to the treatment of Cushing's syndrome. Drugs used to suppress cortisol secretion are mostly inhibitors of steroidogenesis. Ketoconazole, fluconazole aminoglutethimide, metyrapone, mitotane and etomidate are in that category. Ketoconazole is in current use while other drugs, although mostly available in the past, continue to have a potential role either alone or in combination. Drugs that suppress adrenocorticotropic hormone (ACTH) secretion are less popular as standard treatment and include cyproheptadine, valproic acid, cabergoline, somatostatin analogs, PPAR-γ agonists, vasopressin antagonists. Some of these drugs have been tested in limited clinical trials but there is potential therapeutic benefit in analogs with better specificity for the class of receptors present in ACTH-secreting tumors. A third category of drugs is glucocorticoid receptor antagonists. Mifepristone is currently being tested in clinical trials in patients with persistent or recurrent Cushing's disease and in patients with metastatic adrenal cortical carcinoma or ectopic ACTH syndrome not amenable to surgery. We also review replacement therapy after surgery and non-specific drugs to treat complications in patients with severe hypercortisol. The review provides a complete survey of the drugs used in the medical treatment of Cushing's, and new advances in the development of pituitary-active drugs as well as receptor blockers of glucocorticoid action. It also provides avenues for exploration of new drugs active on somatostatin, dopamine and vasopressin receptors. There are effective pharmacological agents capable of chronically reversing biochemical and clinical manifestations of hypercortisolemia in Cushing's syndrome but new drugs are needed with action at the pituitary level.

Keywords: ACTH, glucocorticoids, hypercortisolemia, pituitary tumors

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1. Background

Cushing's syndrome is the clinical manifestation of glucocorticoid steroid hormone excess. It consists of weight gain with trunkal adiposity, impaired glucose tolerance or diabetes, hypertension, irritability, insomnia, cognitive impairment, mood changes ranging from anxiety and depression to psychosis and foremost,

Article highlights.

- If inadequately treated, Cushing's syndrome is associated with serious complications.
- When surgical treatment fails, medical treatment offers temporary relief.
- Drugs suppress Cortisol secretion by inhibiting steroidogenesis.
- Glucocorticoid receptor antagonists are useful when inhibition of steroidogenesis is inadequate.
- New drugs are needed with primary action at the pituitary level.

This box summarises key points contained in the article.

Table 1. Etiologic types of Cushing's syndrome.

ACTH dependent
Pituitary
Microadenomas
Macroadenomas
Hyperplasia
Ectopic
CRH and ACTH
ACTH independent
Adrenal cortical tumors
Adenomas
Carcinomas
Adrenocortical
Hyperplasia
Macronodular
Primary pigmented micronodular – Carney complex
Secondary to expression of illicit receptors

manifestations of protein catabolism, with skin and muscle atrophy, loss of bone mineral density and osteoporosis. Cushing's syndrome can result from the administration of glucocorticoids or spontaneous cortisol hypersecretion. There are several etiologies of endogenous hypercortisolism, including excessive adrenocorticotropic hormone (ACTH) secretion or a primary increase in cortisol production [1]. Rarely, overexpression of glucocorticoid receptors can lead to Cushing's syndrome. These various sub-types are listed in **Table 1**.

Pituitary ACTH-dependent hypercortisolism, also known as Cushing's disease (CD), account for 70% of all cases, the majority of them being caused by a microadenoma measuring less than 10 mm. These adenomas can be detected by MRI or in case of questionable MRI imaging, by inferior petrosal sinus (IPS) sampling. Macroadenomas may extend into the supra or parasellar areas and invade the cavernous sinus. Syndromes of ectopic ACTH and/or corticotropin releasing hormone (CRH) secretion can be characterized by high ACTH and cortisol levels and associated hypokalemia but frequently resemble the clinical picture of pituitary ACTH-dependent disease. Neoplasms secreting ACTH may be located in the head (paranasal sinus neuroendocrine tumors), neck (medullary thyroid cancer), chest (oat-cell lung cancer, malignant thymomas, bronchial carcinoids) or abdomen (islet cell tumors, paragangliomas) [1]. They are distinguished from pituitary tumors by lack of central to peripheral gradients of ACTH during IPS sampling.

A primary adrenal etiology is identified by the finding of elevated cortisol with suppressed ACTH levels, and the discovery on adrenal imaging of a unilateral adrenal mass or bilateral micro or macronodular hyperplasia. The benign or malignant nature of unilateral adrenal masses can be suspected on the basis of size and lipid content. Masses larger than 5 cm have a greater probability of being malignant, and lipid-rich masses have higher probability of being benign [2]. Bilateral primary pigmented micronodular adrenal disease (PPNAD) can be associated with extra-adrenal neoplasmas and lentiginosis syndrome (Carney complex). Carney is due to mutations in the *PRKAR1A* gene which may act as a tumor suppressor gene by regulating PKA activity. This in turn can suppress or stimulate cell growth and differentiation. Bilateral macronodular hyperplasia may be associated with adrenal cortical expression of aberrant receptors [1].

Treatment of Cushing's syndrome depends on its etiologic sub-type. The primary treatment for pituitary ACTH-dependent disease is transsphenoidal resection of a pituitary adenoma and occasionally hypophysectomy [1]. Resection of the primary tumor is the treatment for ectopic ACTH syndrome, and resection of the adrenal tumor or unilateral or bilateral adrenalectomy, the treatment for ACTH-independent disease.

2. Medical need

Transsphenoidal surgery with resection of a pituitary adenoma is successful in 75 – 80% of patients, depending on the skill and experience of the surgeon performing the surgery. Approximately 20 – 25% have persistence of Cushing's, and a similar proportion may experience recurrence within 2 – 4 years post-op. Invasive ectopic ACTH-secreting tumors can present with local invasion or distant metastases and be unresectable, and patients with Stage IV, metastatic adrenal cortical carcinoma may not be amenable to surgical control or suppression with chemotherapy. Patients with adrenal cortical hyperplasia may not wish to have a bilateral adrenalectomy that will render them adrenal insufficient for life.

When surgery fails to reverse the hypercortisolemia, medical treatment is available to temporarily suppress excessive cortisol production and ameliorate its clinical manifestations while more definitive therapy becomes effective. Untreated or inadequately treated Cushing's syndrome can lead to cardiovascular mortality, skeletal fractures, limiting proximal muscle weakness, insulin resistant hyperglycemia and persistent cognitive deficits.

Table 2. Drugs used for treatment of Cushing's syndrome.

Category	Drugs
Adrenal inhibitors	Ketoconazole, fluconazole aminoglutethimide, metyrapone, mitotane, etomidate, trilostane
Suppressors of ACTH	Cyproheptadine, valproic acid, cabergoline, somatostatin analogs, PPAR-γï agonists, VP antagonists
Antagonists of aberrant adrenal receptors	β-blockers, V1a receptor antagonists, GnRH antagonist, somatostatin analogs
Reverse cortisol effect	Glucocorticoid receptor antagonists, mifepristone
Substitution therapy	Hydrocortisone, prednisone, fludrocortisone, DHEA
Drugs to treat symptoms	CNS active: antidepressants, anxiolytic, antipsychotic, hypnotics
	Antihypertensive, diuretics
	Glucose lowering
	Lipid lowering
	Antiresorptive

ACTH: Adrenocorticotropic hormone; DHEA: Dehydroepiandrosterone; GnRH: Gonadotropin-releasing hormone; VP: Vasopressin.

3. Existing treatment

Various pharmacological agents are available to suppress cortisol production and ameliorate the clinical manifestations of Cushing's syndrome. The majority of the available drugs are old but still in use. The efficacy of newer drugs still needs to be validated by well-designed and powered clinical trials. Given the infrequent occurrence of Cushing's syndrome and the heterogeneity of its etiology, this is not likely to be accomplished any time soon.

Drugs used in the treatment of Cushing's syndrome fall into several categories:

1) Adrenal inhibitors/adrenalytic drugs
2) Suppressors of ACTH secretion
3) Drugs to block aberrant adrenal receptors
4) Drugs to reverse the effect of excessive cortisol; secretion.
5) Substitution therapy following pituitary or adrenal surgery
6) Drugs to treat symptoms associated with Cushing's syndrome

Table 2 summarizes the major drugs involved and **Table 3** their mechanism of action.

3.1 Description of drugs

3.1.1 Adrenal inhibitors

3.1.1.1 Ketoconazole

An imidazole derivative, it inhibits the synthesis of ergosterol in fungi and cholesterol in mammalian cells by blocking demethylation of lanosterol. In addition to the effect on cholesterol synthesis, ketoconazole inhibits mitochondrial cytochrome P-450-dependent enzymes such as 17α-hydroxylase, 11β-hydroxylase and cholesterol side chain cleavage enzyme in rat and mouse adrenal preparations. Used in clinical practice as an antifungal medication, ketoconazole has become an important inhibitor of gonadal and adrenal steroidogenesis in doses as low as 200 – 600 mg/day. Several reports have been published on long-term treatment with ketoconazole in patients with Cushing's syndrome which resulted in sustained decrease of urinary free cortisol and reversal of the clinical manifestations of hypercortisolism [3,4]. The drug can be used as initial treatment in cases of severe hypercortisolism and in preparation for more definitive therapy such as transsphenoidal surgery. Early reports suggested that not all types of Cushing's respond to a similar degree and that patients with ACTH-independent disease have a more sustained suppression [5]. Overall, the response to ketoconazole has been quite consistent, regardless of the etiology of hypercortisolism. Patients with very high cortisol levels such as seen in metastatic adrenal cancer or ectopic ACTH syndrome may require doses as high as 1200 mg/day. When patients are treated with ketoconazole, adrenal insufficiency is avoided by adjusting the dose to allow normal cortisol levels. Toxic side-effects are rare with the lower doses but significant with the higher doses. The most frequent adverse effects of ketoconazole are nausea, vomiting, abdominal pain and pruritus. Hepatotoxicity, primarily of the hepatocellular type, can occur. Early markers for these side-effects are serum alkaline phosphatase, ALT, AST, and bilirubin. These should be monitored at frequent intervals during treatment and ketoconazole should be discontinued if there is elevation of enzymes > 3 times above the ULN.

3.1.1.2 Fluconazole

Like ketoconazole, fluconazole is an antifungal azole derivative which has been shown to suppress cortisol secretion in isolated case reports of patients with adrenal cortical carcinoma at a dose of 200 mg/day [6]. However, fluconazole may not be as effective as ketoconazole in suppressing steroid production [7].

3.1.1.3 Aminoglutethimide

We were the first to report that aminoglutethimide can inhibit cortisol secretion and reverse the clinical manifestations of cortisol excess in a patient with functioning adrenal cancer, an effect that could be sustained for 6 months [8]. Aminoglutethimide blocks steroid production by inhibiting cholesterol side chain cleavage and blocking the conversion of cholesterol to pregnenolone. As a consequence, the synthesis of cortisol, aldosterone and androgens is suppressed. The drug had been used in adults and children in doses of 500 – 2000 mg/day. Cortisol levels would fall gradually but eventually patients might have needed glucocorticoid replacement. In patients with ACTH-dependent Cushing's, aminoglutethimide had

Table 3. Drug treatment of Cushing's syndrome: mechanism of drug action.

Drug	Main mechanism of action
Ketoconazole	↓ 17-hydroxylase, 11β-hydroxylase, cholesterol scc
Aminoglutethimide	↓ Cholesterol scc
Metyrapone	↓ 11β-hydroxylase
Mitotane	Formation of ccyl chloride, binding to bionucleophiles
Etomidate	↓ 11β-hydroxylase
Trilostane	↓ 3β-hydroxysteroid dehydrogenase
Cyproheptadine	Serotonin receptor antagonist
Cabergoline	Dopamine agonist
Somatostatin analogs	Somatostatin receptor agonists
Valproic acid	↓ GABA reuptake; ↑ GABA
Glitazones	PPAR-γ agonists
Mifepristone	Type II glucocorticoid receptor antagonist

temporary suppressive effects on cortisol secretion but this effect could be reversed under the stimulating effect of ACTH [9]. The effect of aminoglutethimide was promptly reversed if therapy was interrupted. A subsequent report [10] showed palliation of the clinical manifestations of hypercortisolism in a much larger series of patients with Cushing's syndrome. Aminoglutethimide could cause gastrointestinal (anorexia, nausea, vomiting) and neurologic (lethargy, sedation, blurred vision) side-effects and hypothyroidism in 5% of patients. Skin rash was frequent in the first 10 days of treatment but it subsided with continued administration. Headaches could occur with larger doses. Because of its ability to block early steps in steroidogenesis, aminoglutethimide was a useful drug for treating patients with adrenal cancer whose tumors produced combination of cortisol, aldosterone and androgens. Unfortunately, the manufacturer stopped producing the drug in 2007 and it is no longer available.

3.1.1.4 *Metyrapone*

An 11β-hydroxylase inhibitor, metyrapone was used initially in the differential diagnosis of Cushing's syndrome but was later applied to the management of hypercortisolism. Depending on the dose, cortisol suppression occurs within hours of a daily dose of 4.5 gm but the suppression can be maintained chronically with doses of 500 – 2000 mg/day. An early report [11] showed the possibility of prolonged amelioration of the clinical manifestations of CD with metyrapone.

Other case reports confirmed this result when the drug is administered alone [12] or combined with aminoglutethimide [13] but it was suggested the drug is useful only as adjunctive treatment of CD [14]. Metyrapone is no longer commercially available but it can be obtained for use on a compassionate basis in patients with severe hypercortisolism secondary to metastatic ACC or inoperable ectopic ACTH syndrome. Nausea, vomiting and dizziness are potential side-effects and they may be related to sudden cortisol withdrawal and adrenal insufficiency. Another side-effect, when given to patients with CD, is acne and hirsutism, because blocking steroidogenesis causes an increase in ACTH and stimulation of androgen synthesis by shunting steroidogenic precursors into the androgen pathway. The increase in androgens may be beneficial in patients with marked catabolic effects from the hypercortisolemia. Androgen increase is less likely to occur in ACTH-independent forms of Cushing's. As a consequence of inhibition of 11-β hydroxylase by metyrapone, desoxycorticosterone levels may increase and cause hypertension and hypokalemia in patients with pituitary ACTH-dependent disease. This effect is not likely in those with ACTH-independent types of Cushing's syndrome.

3.1.1.5 *Mitotane*

Of the various cytotoxic drugs used, mitotane is the oldest, with selective activity on the adrenal cortex. It has been used mainly in the treatment of patients with ACC but it is also effective in lower doses as an adrenalytic drug for the treatment of CD. Mitotane has well-proven adrenalytic effects in animals and humans. We reported that low doses of mitotane in combination with pituitary cobalt irradiation caused clinical and biochemical remission in 80% of patients with CD [15]. The adverse effects of mitotane are dose dependent and usually intolerable at doses above 6 g daily. Some patients with adrenal cancer may tolerate larger doses for limited time. The drug is best administered with fat-containing foods since its absorption and transport appears coupled to lipoproteins. The cortisol response to mitotane therapy should be followed by measuring urinary free cortisol. Serum cortisol levels can be elevated even when circulating free cortisol is not elevated, since mitotane increases binding of cortisol to corticosteroid binding globulin. In low doses (2 – 4 g daily), mitotane has less adrenalytic effects on the zona glomerulosa and is less likely to suppress aldosterone production. With larger doses, replacement with 9α-fluorocortisol may be necessary. Prominent early side effects of large doses of mitotane are anorexia, nausea, somnolence and incoordination. Side effects can be reversed by interrupting therapy for several days and restarting the drug at a lower dose. A maculopapular exanthem and exfoliative dermatitis can occur; but both are rare. Hepatotoxicity requiring interruption in therapy can occur. Because of potential teratogenicity, patients should be advised against pregnancy.

We have studied the mechanism of adrenalytic effect of mitotane. It involves transformation to and acyl chloride via P450-mediated hydroxylation and covalent binding to specific bionucleophiles [16]. It also involves oxidative damage with formation of free radicals such as superoxide that generates hydroxylated radicals and induces lipid peroxidation. We have postulated that the ability of mitotane to be metabolically

transformed and covalently bound to target proteins within the cell determines its pharmacological activity [17]. We have confirmed this by blocking the metabolic transformation by substituting the hydrogen on the beta carbon by a methyl group. Methylated mitotane does not have adrenalytic activity [18]. The metabolic activity of mitotane varies among species, the drug being most effective in dogs and modestly effective in humans.

3.1.1.6 Etomidate

Used as a hypnotic anesthetic agent, etomidate is associated with increased mortality in critically ill patients by causing acute adrenal insufficiency. Etomidate reduces serum cortisol and aldosterone but increases plasma ACTH, 11-deoxycortisol and deoxycorticosterone, suggesting inhibition of the P450c11β. In healthy men and women, etomidate causes a dose-dependent blunting of the cortisol response to exogenous corticotrophin [19]. Several studies report short-term, continuous infusions of etomidate reduce serum cortisol concentrations in 11 – 24 h. A case report of a patient with severe hypercortisolism secondary to ectopic ACTH syndrome showed intravenous infusion of etomidate was effective in suppressing cortisol levels for 8 weeks [20]. In a severe hypercortisolemic child, an etomidate infusion (3.0 mg/h i.v.) decreased serum cortisol from 1,250 to 250 nmol/l within 24 h and a combination of etomidate and hydrocortisone therapy maintained stable serum cortisol levels for 12 days [21]. In general, etomidate is only used in cases of severe and complicated hypercortisolemia as temporary treatment prior to more definitive therapy.

3.1.1.7 Trilostane

Trilostane is a competitive inhibitor of the steroidogenic enzyme 3-beta hydroxysteroid dehydrogenase. It blocks the conversion of pregnenolone to progesterone and eventually the synthesis of cortisol, aldosterone and androstenedione. It has been used in patients with CD with biochemical and clinical improvement in one series [22] but another series found no consistent fall in cortisol levels [23]. Currently, trilostane has been approved in veterinary practice for treatment of Cushing's syndrome in dogs and horses.

3.1.2 Corticotropin inhibitors

3.1.2.1 Cyproheptadine

A serotonin receptor antagonist, cyproheptadine, given in doses of 24 mg/day, was reported as being effective in suppressing ACTH and cortisol secretion in patients with CD [24]. This effect was sustained for several months and was reversed upon discontinuing the drug. Subsequent trials failed to show efficacy of cyproheptadine in the treatment of patients with CD.

3.1.2.2 Cabergoline

ACTH-secreting pituitary tumors associated with CD may express dopamine D_2 receptors and respond to dopamine agonists. Several cases have been described of suppression of ACTH levels and amelioration of symptoms of Cushing's syndrome with cabergoline, 7 mg/week, a much higher dose than the 1 – 2 mg/week used in patients with prolactinomas [25,26]. Cabergoline has also been used for the treatment of Nelson syndrome [27].

3.1.2.3 Somatostatin analogs

The majority of pituitary adenomas causing CD express somatostatin (ssr_5) and/or dopamine (D_2) receptors [28]. A somatostatin receptor agonist, pasireotide, binds to sst 1, 2, 3 and 5 and inhibits CRH-stimulated ACTH secretion *in vitro* acting mainly through the sts5 receptor [29]. This somatostatin analog has been tested in a Phase II, open label, single arm multicenter clinical trial in patients with persistent or recurrent CD but the results were insufficient and only a small percentage of patients normalized their cortisol level [30]. Somatostatin and somatostatin analogs can suppress ACTH secretion from ectopic ACTH-secreting neuroendocrine tumors. Tumors with positive octreoscan scintigraphy, indicating the presence of somatostatin receptors, are the most likely to respond to this therapy with suppression of ACTH and cortisol levels [31].

3.1.2.4 Valproic acid

This is a GABA reuptake inhibitor and by increasing GABA it can potentially suppress CRH. However, it has no proven efficacy in CD. Patients with Nelson syndrome and pituitary macroadenomas have been reported to have responded to valproic acid with decrease in ACTH secretion and reduction in tumor size but it is unlikely this would have occurred because of suppression of CRH, since CRH is usually low in patients with pituitary ACTH-dependent CD. It is possible that in those patients valproic acid may have had a direct effect on the tumor [33].

3.1.2.5 PPAR-γ agonists

The response of patients with Cushing's syndrome to PPAR-γ agonists is controversial. Some reports show suppression of ACTH and cortisol levels with rosiglitazone [34,35], while other studies failed to show a response to pioglitazone [36]. Another study failed to lower plasma ACTH levels in patients with Nelson's syndrome [37].

3.1.3 Antagonists of adrenal aberrant receptors

Several cases of Cushing's syndrome associated with ACTH-independent macronodular adrenal cortical hyperplasia (AIMAH) have been reported, in whom the hypersecretion of cortisol was regulated not by ACTH but by non-physiological mechanisms through aberrant receptors [38]. The aberrant adrenal expression and function of one or several G-protein-coupled receptors can lead to cell proliferation and abnormal regulation of steroidogenesis. In cases of

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