Interpretation of the International Pituitary Society' s "Consensus for the Diagnosis and Management of Cushing's Disease (Updated Version)" (II) —Pharmacotherapy Section Postprint

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Abstract

Cushing' s disease represents the most common etiology of endogenous Cushing' s syndrome, a clinical syndrome characterized by hypercortisolism due to pituitary adrenocorticotropic hormone-secreting adenoma. Sustained hypercortisolism may lead to clinical manifestations including moon facies, buffalo hump, central obesity, and metabolic disturbances in patients with Cushing' s disease. Accurate diagnosis, appropriate treatment, and subsequent follow-up are of paramount importance for Cushing' s disease. Based on recent research evidence, the International Pituitary Society published the "Consensus on the Diagnosis and Management of Cushing' s Disease (Updated Edition)" in December 2021, which provides updates on screening and diagnostic algorithms, postoperative monitoring, pharmacological and radiation therapy, and complication management for Cushing' s disease. This article focuses on interpreting the medical therapy section of the guideline, aiming to facilitate standardized diagnosis and treatment of Cushing' s disease by both general practitioners and specialists.

Full Text

Interpretation of the Pituitary Society Consensus on Diagnosis and Management of Cushing' s Disease (Updated Version) (II) -Medication Section

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Abstract

Cushing' s disease (CD) is the most common cause of endogenous Cushing' s syndrome, representing a clinical syndrome of hypercortisolemia caused by pituitary adrenocorticotropic hormone (ACTH)-secreting adenomas. Persistent hypercortisolemia leads to characteristic clinical manifestations including moon facies, buffalo hump, central obesity, and metabolic disturbances. Accurate diagnosis, appropriate treatment, and subsequent follow-up are critically important for patients with Cushing' s disease. Based on recent evidence, the International Pituitary Society published the *Consensus on Diagnosis and Management of Cushing' s Disease: A Guideline Update* in December 2021, which provides updated recommendations on screening and diagnostic procedures, postoperative monitoring, medical and radiation therapy, and complication management. This article focuses on interpreting the medication section of these guidelines to assist both general practitioners and specialists in standardizing the diagnosis and treatment of Cushing' s disease.

Keywords: Cushing' s disease; Pituitary Society; guideline update; drug therapy

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Cushing' s disease is a clinical syndrome characterized by hypercortisolemia resulting from excessive ACTH secretion by pituitary adenomas and represents the most common form of endogenous Cushing' s syndrome. In December 2021, the International Pituitary Society published the *Consensus on Diagnosis and Management of Cushing' s Disease: A Guideline Update* (hereinafter referred to as the 2021 CD Guideline) [1], building upon the 2008 and 2015 Endocrine Society clinical practice guidelines for Cushing' s syndrome [2-4]. The 2021 CD Guideline reviews recent clinical evidence and grades both the quality of evidence and strength of consensus recommendations. The guideline recommends pharmacological therapy for patients with persistent or recurrent Cushing' s disease, those unsuitable for or refusing surgery, or those requiring control of hypercortisolemia after radiotherapy, emphasizing individualized treatment based on clinical symptoms and severity of hypercortisolemia [5, 6]. Drug options include three main categories [7]: (1) agents that directly inhibit adrenal corticosteroid synthesis (e.g., ketoconazole, osilodrostat, metyrapone, mitotane, etomidate); (2) drugs acting on pituitary somatostatin receptors to inhibit ACTH synthesis (e.g., pasireotide) and dopamine receptors (e.g., cabergoline); and (3) glucocorticoid receptor blockers (e.g., mifepristone). Additionally, the 2021 CD Guideline classifies evidence quality into four levels (high, moderate, low, very low) and categorizes recommendations as strong, conditional, or not recommended.

1. Adrenal Corticosteroid Synthesis Inhibitors

Adrenal corticosteroid synthesis inhibitors reduce cortisol production and secretion by blocking one or more enzymes involved in steroidogenesis [8]. These agents suppress cortisol secretion but do not directly target the ACTH-secreting pituitary adenoma nor restore the normal circadian rhythm of the hypothalamic-pituitary-adrenal (HPA) axis. This class includes long-established drugs such as ketoconazole, metyrapone, mitotane, and etomidate, as well as the 11β-hydroxylase inhibitor osilodrostat, which was approved by the FDA in March 2020 and by the European Medicines Agency (EMA) in January 2020.

Two treatment strategies may be considered when using adrenal corticosteroid synthesis inhibitors for Cushing' s disease. The first involves titrating the drug dose to achieve cortisol normalization, though overtreatment carries the risk of adrenal insufficiency. The second employs high-dose inhibitors combined with exogenous glucocorticoid replacement to prevent adrenal insufficiency (the "block-and-replace" approach), which however risks glucocorticoid excess. The 2015 Endocrine Society and European Society of Endocrinology guidelines for Cushing' s syndrome treatment recommended the block-and-replace approach when there is evidence suggesting significant cyclical hypercortisolemia.

The 2021 CD Guideline emphasizes that rapid cortisol normalization is urgent and necessary for patients with severe Cushing' s disease, typically initiating treatment with adrenal corticosteroid synthesis inhibitors (high-quality evidence, strong recommendation). Ketoconazole offers relatively easy dose titration but requires close monitoring of liver function due to hepatotoxicity that may lead to underdosing (moderate-quality evidence, strong recommendation). Additionally, male patients may develop pituitary-gonadal axis dysfunction. Metyrapone and osilodrostat have the fastest onset of action, are both orally administered, are not limited by gonadal dysfunction in men, and osilodrostat offers a more convenient dosing regimen. Detailed dosing and characteristics are summarized in .

1.1 Ketoconazole

Ketoconazole, an antifungal agent, inhibits multiple enzymes in steroid biosynthesis pathways including side-chain cleavage enzyme, 17α-hydroxylase, 17,20-lyase, 11β-hydroxylase, and 18-hydroxylase, thereby suppressing synthesis of various adrenal steroids including pregnenolone, 17α-hydroxypregnenolone, 17α-hydroxyprogesterone, dehydroepiandrosterone, androstenedione, corticosterone, cortisol, and aldosterone [9]. It was approved for Cushing' s syndrome treatment in Europe in November 2014. Previous studies indicate that ketoconazole at a mean daily dose of 600 mg normalizes urinary free cortisol (UFC) in over 50% of patients with Cushing' s disease, improving weight, blood pressure, glucose metabolism, and muscle weakness [6, 10]. However, 15-25% of patients gradually develop treatment escape (loss of efficacy) over time. The mechanism underlying this escape phenomenon remains unclear, though studies suggest it

occurs primarily in patients receiving ketoconazole as first-line therapy rather than in those previously treated with surgery or radiotherapy [11].

Gastrointestinal side effects and adrenal insufficiency occur in 5-20% of patients with Cushing' s disease receiving ketoconazole. Hepatic function requires careful monitoring during treatment, as liver injury typically occurs during the dose-titration phase, manifesting as mild-to-moderate transaminase elevation, particularly during initial treatment of Cushing' s syndrome [12]. Interestingly, some reports describe high-dose ketoconazole combined with metyrapone and mitotane improving rather than worsening liver function in patients with ectopic severe Cushing' s syndrome and pre-existing hepatic dysfunction [13]. As both a substrate and inhibitor of CYP3A4, ketoconazole has potential interactions with numerous medications, necessitating careful review of patients' complete medication lists [6].

Data from the FDA Adverse Event Reporting System indicate that ketoconazole' s hepatic effects are not dose-dependent, with both short-term high-dose and long-term low-dose therapy potentially causing severe liver injury even in patients without apparent risk factors. Some cases resolve after drug discontinuation, while others do not. The FDA has issued a black box warning for serious hepatotoxicity and adrenal problems, recommending weekly liver function monitoring. Due to severe hepatotoxicity risks outweighing benefits, China halted production, sales, and use of oral ketoconazole formulations in June 2015. In the United States, ketoconazole use for Cushing' s syndrome remains off-label.

The 2021 CD Guideline notes that ketoconazole is often limited by hepatotoxicity, though mild liver dysfunction does not necessarily require discontinuation. Because ketoconazole acts on early steroidogenic enzymes, it prevents excessive accumulation of androgen and mineralocorticoid precursors. However, reduced sex steroid synthesis may cause hypogonadism and gynecomastia in men [14].

1.2 Metyrapone

Metyrapone inhibits 11β-hydroxylase in the steroid synthesis pathway, reducing production of corticosterone, cortisol, and aldosterone. A multicenter retrospective study of 164 patients with Cushing' s syndrome (including 115 with Cushing' s disease, 37 with ectopic Cushing' s syndrome, and 43 with adrenal-dependent ACTH-independent Cushing' s syndrome) treated with metyrapone monotherapy reported a 43% efficacy rate for UFC control in Cushing' s disease patients, with a median treatment duration of 8 months and median dose of 1375 mg/day [15]. A meta-analysis of four studies including 66 patients with Cushing' s disease demonstrated a 66% control rate for morning cortisol (95% CI: 46%-87%) [16]. In a prospective study of 50 patients with Cushing' s syndrome, 47% (23/49) achieved normal UFC levels after 12 weeks of dose-titrated metyrapone therapy, with 66% showing clinical improvement in hypertension, glucose metabolism abnormalities, psychiatric symptoms, and muscle weakness [17]. The most common adverse events included hirsutism, dizziness, arthral-

gia, fatigue, and hypokalemia, while abdominal pain, dermatitis, and adrenal insufficiency were less frequent [6].

Both the 2021 CD Guideline and 2015 Cushing's syndrome treatment guidelines note that long-term 11β-hydroxylase blockade leads to accumulation of androgen precursors, potentially worsening hyperandrogenism manifestations such as hirsutism and acne, while accumulation of the mineralocorticoid precursor 11-deoxycortisol may exacerbate hypokalemia, edema, and hypertension [1-3]. The 2015 guidelines also emphasize that cortisol assays used for monitoring blood or urinary free cortisol must not cross-react with 11-deoxycortisol to avoid erroneous dose adjustments due to apparent cortisol elevation [3].

1.3 Osilodrostat

Osilodrostat is an inhibitor of both 11β-hydroxylase and aldosterone synthase, suppressing cortisol, corticosterone, and aldosterone production with good efficacy and tolerability [18]. A multicenter, randomized Phase III study of 137 patients with Cushing' s disease demonstrated that after 12 weeks of open-label dose titration and 12 weeks of dose optimization, 72 patients achieved normal UFC and were randomized to osilodrostat (n=36) or placebo (n=35). At week 34, 31 of 36 patients in the osilodrostat group maintained normal UFC compared to 10 of 35 in the placebo group (OR 13.7, 95% CI: 3.7-53.4; p<0.0001) [19]. Another multicenter Phase III study conducted from 2016-2020 across multiple countries including China, the United States, Brazil, Canada, and Spain enrolled 73 patients with Cushing' s disease in a double-blind phase, randomized 2:1 to osilodrostat (n=48) or placebo (n=25). After 12 weeks, all participants entered open-label osilodrostat treatment through week 48. At 12 weeks, the UFC normalization rate was 77% in the osilodrostat group versus 8% in the placebo group (OR 43.4, 95% CI: 7.1-343.2; P<0.0001), and by week 36, 81% of all participants achieved normal UFC [20].

Osilodrostat improves weight, blood pressure, cholesterol, and HbA1c, while enhancing quality of life and reducing depression scores. Adverse effects include fatigue, dizziness, arthralgia, and decreased appetite. Nausea, anemia, and headache occurred in 8-11% of patients. Approximately half (70/137) reported cortisol reduction-related adverse events, with 25 requiring glucocorticoid replacement. Additionally, 42% (58/137) developed hypokalemia and hypertension due to elevated adrenal steroid precursor corticosterone levels, and female patients experienced hirsutism and acne from increased testosterone or estrogen [18-20]. Osilodrostat was approved in the United States in 2020 for Cushing' s disease and subsequently in the EU and Japan for Cushing' s syndrome, with registration pending in China.

Both osilodrostat and metyrapone enable rapid control of most Cushing' s disease symptoms without requiring intensive liver function monitoring or causing male hypogonadism, though monitoring for androgen and mineralocorticoid accumulation side effects is necessary. For rapid cortisol normalization, the 2021

CD Guideline recommends adrenal steroid synthesis inhibitors, with osilodrostat and metyrapone having the fastest onset among oral agents (high-quality evidence, strong recommendation). When using high-dose therapy with glucocorticoid replacement, vigilance for potential overtreatment and over-replacement is essential [21].

1.4 Mitotane

Mitotane inhibits multiple steroidogenic enzymes including side-chain cleavage enzyme, 3β-hydroxysteroid dehydrogenase, 11β-hydroxylase, and 18-hydroxylase, suppressing production of pregnenolone, progesterone, corticosterone, aldosterone, 17-hydroxyprogesterone, cortisol, and androstenedione. It exerts direct and persistent cytotoxic effects on adrenal cortical cells [3]. Due to slow onset, long half-life, and induction of CYP3A4-mediated rapid cortisol inactivation, mitotane readily causes adrenal insufficiency requiring increased glucocorticoid replacement [22]. Currently rarely used for Cushing' s disease, most experts restrict its use to adrenal carcinoma. The 2021 CD Guideline states that mitotane is seldom used as monotherapy for Cushing' s disease in most centers (low-quality evidence, conditional recommendation).

1.5 Etomidate

Originally developed as an anesthetic agent, etomidate rapidly normalizes cortisol concentrations and is used in intensive care settings for patients with severe hypercortisolemia unsuitable for immediate surgery, serving as a bridge to other therapies or surgery [23]. Continuous monitoring of its sedative effects is required during use. Studies since 1990 have demonstrated low-dose etomidate ($ $0.1 mg/kg/h) effectively treats severe hypercortisolemia in Cushing' s syndrome [24]. Intravenous hydrocortisone can prevent etomidate-induced adrenal insufficiency. Propylene glycol formulations should be administered via central venous access to avoid thrombophlebitis, pain, hemolysis, and renal tubular injury [25]. The 2021 CD Guideline recommends etomidate for intravenous administration in severe cases (high-quality evidence, strong recommendation).

2. Drugs Acting on Pituitary Somatostatin and Dopamine Receptors

Somatostatin receptor ligand pasireotide and dopamine agonist cabergoline are therapeutic options for Cushing' s disease patients [3, 5, 6].

2.1 Pasireotide

Since 1978, various somatostatin receptor ligands have been developed to regulate hormone secretion from multiple organs including the pituitary, pancreas, and gastrointestinal tract [26]. Pasireotide (SOM-230) is a next-generation multi-receptor somatostatin analog with high affinity for somatostatin receptor subtypes 5 and 1 (SSTR5 and SSTR1). Since SSTR5 is highly expressed

in ACTH-secreting pituitary adenomas, pasireotide has been investigated for Cushing' s disease treatment [3].

A global multicenter Phase III randomized controlled study initiated in 2006 enrolled 162 patients with Cushing' s disease, randomized to subcutaneous pasireotide 600 g twice daily (n=82) or 900 g twice daily (n=80) for 6 months, achieving cortisol control rates of 15% and 26%, respectively, with significant clinical symptom improvement [27]. Another Phase III randomized controlled study beginning in 2011 across 57 sites in 19 countries enrolled 150 patients with Cushing' s disease receiving long-acting pasireotide 10 mg or 30 mg intramuscularly every 4 weeks, with dose escalation to 30 mg or 40 mg if UFC exceeded 1.5 times the upper limit of normal (ULN) at month 4. UFC normalization rates at month 7 were 41.9% (31/74) and 40.8% (31/76), respectively, with best responses in patients with baseline UFC 1.5-2 times ULN versus >2-5 times ULN. Regardless of complete UFC control, patients showed significant improvements in BMI, weight, waist circumference, and quality of life [28]. Long-term follow-up of this long-acting pasireotide study (39 patients completed) demonstrated sustained biochemical and clinical remission for up to 5 years.

This long-acting pasireotide study also observed modest tumor volume reduction [28]. Research indicates that one-third to two-thirds of pituitary ACTH tumors harbor ubiquitin-specific protease-8 (USP8) mutations [29, 30], which are associated with higher SSTR5 expression compared to wild-type tumors [31]. Given pasireotide' s high SSTR5 affinity, the 2021 CD Guideline suggests USP8 mutation may be a potential biomarker for predicting pasireotide treatment response. Additionally, long-acting pasireotide has shown suppressive effects on ACTH levels in Nelson' s syndrome following bilateral adrenalectomy [32].

Notably, recent guidelines from both the Endocrine Society and Pituitary Society highlight the hyperglycemia risk associated with pasireotide, likely related to inhibition of insulin and incretin secretion [33]. The 2021 CD Guideline recommends using glucagon-like peptide-1 (GLP-1) receptor agonists or dipeptidyl peptidase-4 (DPP-4) inhibitors to manage pasireotide-induced hyperglycemia [34]. Based on favorable efficacy and safety, the FDA approved pasireotide in December 2012 for Cushing' s disease patients with unsuccessful surgery or incomplete remission.

2.2 Cabergoline

Cabergoline, a dopamine receptor agonist, inhibits ACTH secretion through binding to dopamine type 2 receptors. Current evidence for cabergoline in Cushing' s disease derives primarily from retrospective studies. A multicenter retrospective study from 2003-2015 reported 40% (21/53) UFC normalization at 12 months with cabergoline monotherapy (dose range 0.5-6 mg/week), with 5 patients developing adrenal insufficiency. Patients achieving biochemical remission showed improvement in hypercortisolism-related symptoms including weight and glycemic control and hypertension, though 28% (7/18) discontinued

due to treatment escape or intolerance during follow-up exceeding 1 year [35]. Another observational study demonstrated 75% (15/20) UFC normalization after 3 months of short-term cabergoline therapy, but long-term maintenance of normal UFC occurred in only 40% (8/20), with 5 patients experiencing treatment escape and 2 discontinuing due to intolerance. Tumor volume reduction was observed in 20% of patients [36].

Although not approved for Cushing' s disease, cabergoline has been used in pregnant women with Cushing' s disease who failed to achieve biochemical remission after transsphenoidal surgery, with dose adjustments enabling successful pregnancy outcomes [6, 37, 38]. The 2021 CD Guideline cautions about cabergoline' s risk of inducing impulse control disorders, manifesting as hypersexuality, pathological gambling, excessive alcohol consumption, binge eating, and compulsive shopping, which may emerge within months of initiation or later and improve/disappear after discontinuation [39]. Pre-treatment assessment for impulse control disorder history is recommended [3]. The clinical significance of cabergoline-associated cardiac valvulopathy risk remains controversial, with inconsistent findings across multiple studies regarding whether observed valve abnormalities are clinically meaningful [40-42].

Both somatostatin receptor ligand pasireotide and dopamine agonist cabergoline can reduce pituitary tumor volume in Cushing' s disease. The 2021 CD Guideline suggests considering pasireotide and cabergoline for mild-to-moderate Cushing' s disease with residual pituitary ACTH tumors (moderate-quality evidence, strong recommendation), while noting the need to manage pasireotide-induced hyperglycemia and screen for impulse control disorder history before cabergoline initiation.

3. Peripheral Glucocorticoid Receptor Antagonists

Mifepristone, a synthetic steroid initially developed for medical abortion, inhibits cortisol synthesis by blocking 11β-hydroxylase and effectively controls hypercortisolism manifestations. Clinical studies demonstrate mifepristone improves glycemia, blood pressure, insulin resistance, weight, waist circumference, and quality of life in Cushing' s syndrome patients [33]. However, due to its mineralocorticoid receptor activation, anti-progestogenic activity, and adrenal insufficiency induction, adverse effects may include blood pressure elevation, hypokalemia, and irregular menstrual bleeding [33]. Since mifepristone blocks glucocorticoid receptors, blood cortisol remains elevated during treatment, precluding cortisol monitoring for adrenal insufficiency assessment, which must rely on clinical features alone.

The 2021 CD Guideline emphasizes the need for close monitoring of adrenal insufficiency signs and symptoms during mifepristone therapy, recommending its use only by experienced clinicians [43] (high-quality evidence, strong recommendation). Thyroid function requires close monitoring with thyroid hormone replacement adjustment as needed [44]. As mifepristone is metabolized

via CYP3A4, potential drug interactions through this hepatic pathway warrant careful review of all concomitant medications. The FDA approved mifepristone in February 2012 for controlling hyperglycemia secondary to type 2 diabetes or glucose intolerance in patients with endogenous Cushing' s syndrome who failed surgery or are not surgical candidates.

Combination Therapy

Evidence for combination drug therapy in Cushing' s disease remains limited. One study of 11 patients with severe complications used triple therapy with ketoconazole, metyrapone, and mitotane, achieving clinical improvement in 4 patients with Cushing' s disease within 5-22 months, enabling surgical intervention with immediate biochemical remission in 3 cases postoperatively and continued mitotane requirement in 1 case [45]. Another study of 14 patients initiated treatment with either cabergoline or ketoconazole, adding the alternative agent after 6 months if both late-night salivary cortisol (LNSC) and UFC remained abnormal. While 79% (11/14) achieved normal UFC, LNSC did not fully normalize, suggesting persistent subclinical hypercortisolemia [46]. A third study using sequential triple therapy with pasireotide, cabergoline, and ketoconazole in 17 patients achieved 90% UFC normalization [47]. However, these studies had small sample sizes, requiring larger trials for high-quality evidence. The 2021 CD Guideline states that clinical evidence rarely supports combination therapy (high-quality evidence, strong recommendation), and if used, requires close monitoring for drug toxicity and interactions.

Monitoring and Follow-up

The 2021 CD Guideline recommends enhanced follow-up for patients receiving adrenal corticosteroid synthesis inhibitors or glucocorticoid receptor blockers to assess clinical efficacy and adverse effects. Some patients may develop pituitary ACTH adenoma growth during medical therapy, though whether this results from loss of cortisol feedback inhibition or tumor progression remains unclear. Therefore, regular pituitary magnetic resonance imaging (MRI) is recommended for patients on long-term medical therapy, typically performed 6-12 months after treatment initiation, with subsequent intervals determined by clinical circumstances. Progressive tumor growth warrants treatment suspension and regimen reassessment (moderate-quality evidence, strong recommendation). Except for mifepristone-treated patients, regular therapeutic monitoring using UFC and LNSC is recommended for all patients [48, 49]. For monitoring adrenal insufficiency risk, morning serum cortisol concentration is the preferred indicator (high-quality evidence, strong recommendation). If cortisol levels remain elevated after 2-3 months of maximum tolerated dosing, treatment modification should be considered (moderate-quality evidence, strong recommendation).

Conclusion

The 2021 CD Guideline proposes four main drug classes for Cushing' s disease: (1) adrenal corticosteroid synthesis inhibitors acting on cortisol synthesis (ketoconazole, metyrapone, mitotane, osilodrostat); (2) pituitary ACTH secretion inhibitors including somatostatin receptor ligands (pasireotide) and dopamine agonists (cabergoline); and (3) peripheral glucocorticoid receptor antagonists (mifepristone) (see). Drug selection should consider onset speed, adverse effect tolerability, clinical and biochemical improvement, and drug accessibility (moderate-quality evidence, strong recommendation).

Given limited drug availability in China, pharmacotherapy is reserved for patients with life-threatening severe complications preoperatively, those with persistent or recurrent disease postoperatively, or as transitional therapy after radiosurgery to control cortisol levels and improve clinical symptoms. Individualized treatment remains paramount. Future directions include innovative basic and clinical drug research from leading Chinese pituitary centers to better guide and standardize diagnosis and treatment of pituitary diseases including Cushing' s disease.

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