REVIEW

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Glucocorticoid-induced adrenal insufficiency and glucocorticoid withdrawal syndrome: Two sides of the same coin

ABSTRACT

Diseases of the adrenal glands can lead to primary adrenal insufficiency, and suppression of the hypothalamic-pituitary-adrenal axis can cause secondary adrenal insufficiency (adrenal suppression). The most common cause of adrenal suppression is exogenous steroids, a condition recently termed *glucocorticoid-induced adrenal insufficiency* (GIAI). Similarly, weaning from high doses of glucocorticoids or giving insufficient glucocorticoid replacement after curative surgery for endogenous hypercortisolism (Cushing syndrome) can lead to glucocorticoid withdrawal syndrome, which overlaps with GIAI.

KEY POINTS

- GIAI is common in patients treated with glucocorticoids.
- GIAI may go unrecognized when caused by non-oral formulations of glucocorticoids: intra-articular, epidural, inhaled, and even topical.
- When tapering high doses of glucocorticoids, patients can develop symptoms of glucocorticoid withdrawal similar to those of GIAI.
- Patients with GIAI are a vulnerable population with a poor baseline quality of life. Lack of awareness of GIAI among patients and physicians often leads to worse clinical outcomes and quality of life.

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Glucocorticoid-induced adrenal insufficiency (GIAI) is a well-known side effect of glucocorticoid therapy, and clinicians usually expect it in patients who receive systemic (oral, intravenous, and intramuscular) glucocorticoids in doses equivalent to more than 5 mg of prednisone for at least 3 weeks.[1] However, glucocorticoids given through other routes can also suppress the adrenal glands.

Unfamiliarity with GIAI, especially when caused by nonsystemic formulations of glucocorticoids, can lead to delay in diagnosis or misdiagnosis and lack of proper patient education. This lack of awareness often leads to failure to implement an adrenal action plan and underuse of injectable glucocorticoids at home or, in cases of adrenal crisis, in the emergency room.[2] Ultimately, gaps in care in managing adrenal suppression often worsen clinical outcomes and quality of life in this vulnerable patient population, who tend to have a poor quality of life at baseline.[3]

This review highlights the differences between primary adrenal insufficiency, secondary adrenal insufficiency (including GIAI), and glucocorticoid withdrawal syndrome.

DEFINITION AND TYPES OF ADRENAL INSUFFICIENCY

The adrenal cortex produces 3 main types of hormones[4]:

TABLE 1
Common causes of primary adrenal insufficiency

Autoimmune
Isolated
Autoimmune polyglandular syndrome type 1
Autoimmune polyglandular syndrome type 2
Adrenal infection
Tuberculosis
Human immunodeficiency virus
Cytomegalovirus
Fungal infections: candidiasis, histoplasmosis, paracoccidioidomycosis
Syphilis
African trypanosomiasis
Adrenal metastases
Breast, lung, colon, stomach cancers or lymphoma
Adrenal hemorrhage
Trauma
Anticoagulation
Antiphospholipid syndrome
Congenital adrenal hyperplasia
21-hydroxylase deficiency
11-hydroxylase deficiency
3B-hydroxysteroid dehydrogenase II deficiency
Drug-induced primary adrenal insufficiency
Adrenal enzyme inhibitors: mitotane, ketoconazole, metyrapone, etomidate
Drugs that accelerate cortisol metabolism: fluconazole, phenytoin, rifampin, barbiturates
Immune checkpoint inhibitors
Anti-PD-1 (programmed cell death protein 1) monoclonal antibodies: pembrolizumab, nivolumab
CTLA-4 (cytotoxic T-lymphocyte antigen 4) inhibitor: ipilimumab
Others
Adrenoleukodystrophy and adrenomyeloneuropathy
Familial glucocorticoid deficiency
Familial glucocorticoid resistance

- Glucocorticoids (primarily cortisol) from the zona fasciculata
- Mineralocorticoids (aldosterone, deoxycorticosterone) from the zona glomerulosa
- Androgens and their precursors (androstenedione, dihydroepiandrostenedione, dihydroepiandrostenedione sulfate, testosterone, and 11-oxygenated 19-carbon androgens) from the zona reticularis.

Adrenal insufficiency is the inability of the adrenal cortex to synthesize and produce glucocorticoids, mineralocorticoids, or both.

Primary adrenal insufficiency

Diseases of the adrenal cortex can lead to primary adrenal insufficiency, with insufficient production of glucocorticoids, mineralocorticoids, or both. The prevalence of primary adrenal insufficiency in the United States is not well documented. However, it is rising in Europe, where it has been reported to be as high as 22.1 per 100,000 population.[5,6]

Autoimmune adrenalitis (also known as Addison disease, for Thomas Addison,[7] who first described it in 1855) is the most common cause of primary adrenal insufficiency in developed countries.[8] Other causes include tuberculosis, human immunodeficiency virus infection, trauma, and use of immune checkpoint inhibitors (**Table 1**).

Secondary adrenal insufficiency

Secondary adrenal insufficiency occurs when the hypothalamus does not produce enough corticotropin-releasing hormone or the anterior pituitary gland does not produce enough adrenocorticotropic hormone, so that the adrenal cortex is not stimulated and does not produce enough glucocorticoids. Mineralocorticoid secretion, however, is usually preserved, as the renin-angiotensin-aldosterone system, involving the cardiovascular and renal systems, is not affected.[9] Therefore, patients with secondary adrenal insufficiency are less likely to have hypotension than those with primary adrenal insufficiency.

Adrenal insufficiency caused by suppressed corticotropin-releasing hormone is sometimes called *tertiary adrenal insufficiency*. However, this term remains controversial. Here, we will use *secondary adrenal insufficiency* for both pituitary and hypothalamic causes of adrenal insufficiency.

Secondary adrenal insufficiency is more common than primary, with an estimated prevalence of up to 28 per 100,000 people.[10] Common causes include pituitary tumors, other tumors metastasizing to the pituitary gland, and head trauma (**Table 2**).

Other important causes are the many drugs that can affect the hypothalamic-pituitary-adrenal axis (HPAA) at different levels (**Figure 1**). The drugs that primary care clinicians most often encounter are immune checkpoint inhibitors, opioids, and glucocorticoids. Secondary adrenal insufficiency caused by emerging immunotherapies such as monoclonal antibody targeting programmed cell death protein 1 (PD-1; nivolumab and pembrolizumab) and monoclonal antibody targeting cytotoxic T-lymphocyte antigen 4 (CTLA-4; ipilimumab) is also common, more so when these agents are used in combination or sequence.[11] Of note, these

medicines can also cause primary adrenal insufficiency, though infrequently.[12]

Opioids are believed to suppress the adrenal glands by binding to receptors in the hypothalamus and pituitary, exerting tonic inhibition on the HPAA.[13] Opioid-induced adrenal insufficiency is estimated to affect approximately 15% of patients treated with opioids for at least 3 to 6 months.[14] Li et al[15] reported that 9 (9%) of 102 patients who were receiving more than 20 morphine milligram equivalents per day developed adrenal insufficiency. All were treated with glucocorticoid replacement while weaning off opioids until their HPAA recovered, which occurred within 1 to 14 months of stopping the opioid. Glucocorticoid replacement improved pain, quality of life, and physical function.[15]

THE DEEP SLEEP OF ADRENAL GLANDS: ADRENAL SUPPRESSION AND GIAI

Glucocorticoids are powerful anti-inflammatory agents used to treat autoimmune and other conditions. However, long-term use in supraphysiologic doses can suppress the HPAA and consequently cause GIAI.

GIAI is a fairly new term and has been used by some authors interchangeably with *adrenal suppression*.[16] Other authors use the term more specifically to describe symptoms in patients with HPAA suppression who receive inadequate treatment with glucocorticoids during stressful situations.[17] The rest of the discussion will focus on GIAI, given that exogenous glucocorticoid use is the most common cause of adrenal suppression.

In a systematic review and meta-analysis of 73 studies, the median prevalence of GIAI was 37% in patients receiving any form of glucocorticoids.[18] In another meta-analysis, the median prevalence was 48.7% in those receiving oral glucocorticoids and 52.2% in those receiving intra-articular injections.[19]

Excessive glucocorticoids, whether endogenous due to adrenal lesions secreting excessive cortisol or from an exogenous source, bind to receptors in the hypothalamus and pituitary, triggering negative feedback on adrenocorticotropic hormone release. Chronic suppression of adrenocorticotropic hormone eventually leads to atrophy of the zona fasciculata but not the zona glomerulosa, resulting in impaired cortisol secretion but intact mineralocorticoid secretion.[20]

Risk factors for GIAI

Although high-quality evidence is lacking, available data suggest that many factors affect the risk of GIAI, including glucocorticoid dose, duration, formulation, frequency and timing of administration, pharmacokinetics, interaction with other medications, and cushingoid features.[16]

Glucocorticoid dose and duration. In studies in patients with asthma,[19] GIAI occurred in 2.4% of those treated with low doses of systemic glucocorticoids, 8.5% of those receiving medium doses, and 21.5% of those receiving high doses. Short-term use (< 1 month) resulted in GIAI in 1.4%, medium-term use (1 month to 1 year) resulted in GIAI in 11.9%, and long-term use (> 1 year) resulted in GIAI in 27.4%. The patterns were similar in patients treated only with inhaled glucocorticoids. However, other studies have found no correlations between glucocorticoid dose or duration and risk of GIAI.[18]

TABLE 2
Common causes of secondary adrenal insufficiency

Pituitary tumors
Pituitary tumors replacing normal corticotropic cells
Adrenocorticotropic hormone deficiency after tumor resection or radiation treatment
Nonpituitary tumors
Meningioma
Craniopharyngioma
Sellar or suprasellar metastases (lung, colon, and breast cancer)
Pituitary infiltration
Granulomatosis with polyangiitis
Sarcoidosis
Amyloidosis
Hemochromatosis
Lymphoma
Autoimmune
Lymphocytic hypophysitis
Isolated (usually with pregnancy)
Associated with other autoimmune disease (thyroid, vitiligo, type 1 diabetes, pernicious anemia)
Sheehan syndrome
Infarction in the pituitary gland due to excessive postpartum hemorrhage
Pituitary apoplexy
Acute hemorrhage in the pituitary adenoma
Head trauma
Severe head trauma leading to fracture of the skull base and injury in the pituitary gland
Drug-induced central adrenal insufficiency
See **Figure 1**
Rare congenital causes
Mutations of *TBX19* (T-box transcription factor 19) and *PCSK1* kexin (proprotein convertase subtilisin) genes
Mutations of *POMC* (proopiomelanocortin) gene

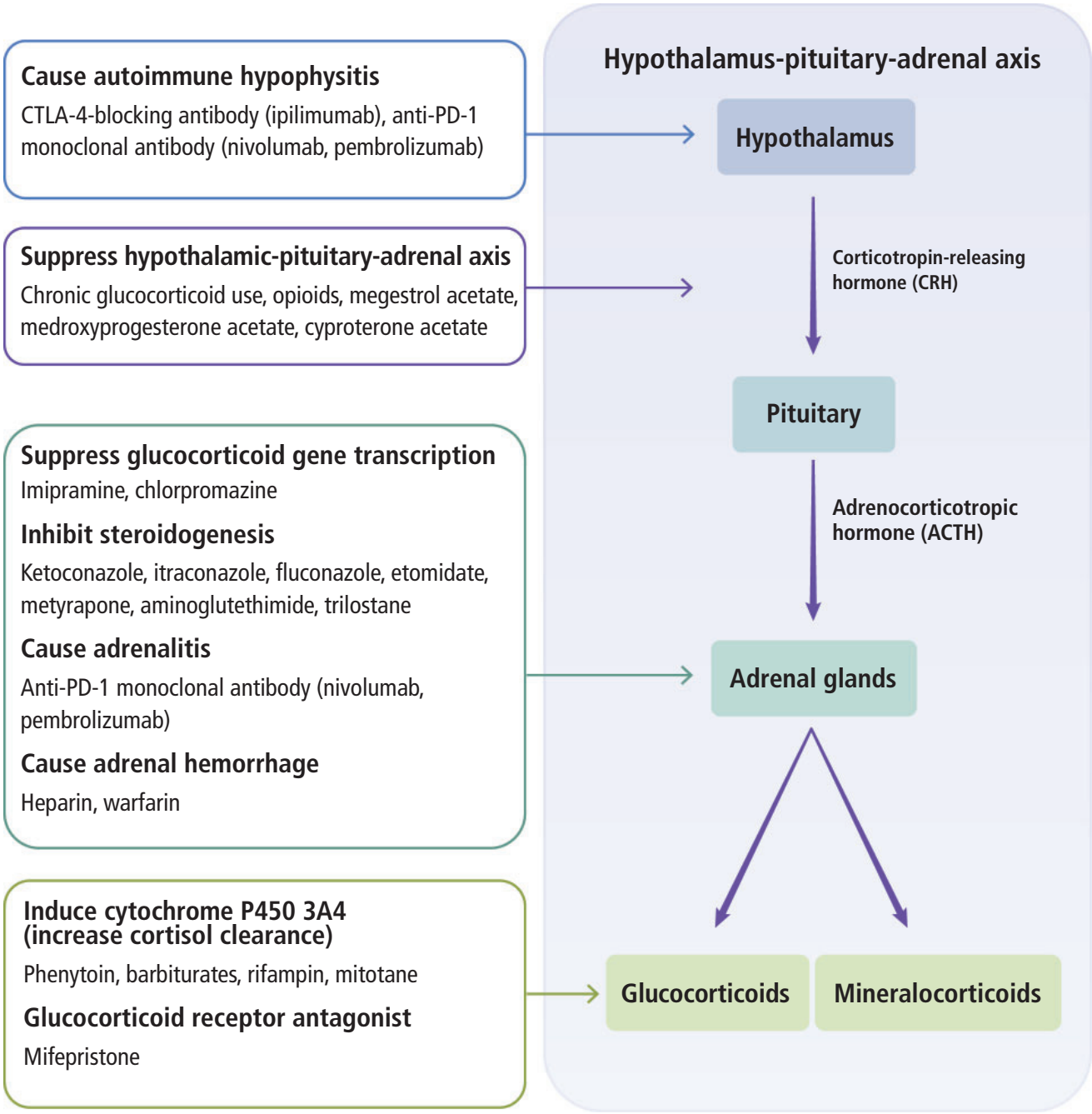

Figure 1. How various drugs can cause secondary adrenal insufficiency.

CTLA-4 = cytotoxic T-lymphocyte antigen 4; PD-1 = programmed cell death protein 1

TABLE 3
Risk factors for glucocorticoid-induced adrenal insufficiency

Route of administration	Reported risk	Factors that increase the risk	Factors that decrease the risk
Inhaled	Dose- and duration-dependent[41] 20.3% in patients treated for > 1 year[19]	High doses (any glucocorticoid > 0.8 mg/day or fluticasone propionate > 0.75 mg/day)[42] Concurrent use of intranasal or oral glucocorticoids[43,44] Use of spacer device to deliver more medication to the lower airways[45] Higher lung volumes[45]	Beclomethasone dipropionate, budesonide, and triamcinolone acetonide are less likely to suppress the HPAA compared with fluticasone propionate[42] Ciclesonide has the lowest risk of HPAA suppression[46] Lower lung volumes[45]
Intranasal	Low (≤ 4.2%)[19,46,47]	Long-term use (> 12 months)[46]	Short-term use[46]
Intra-articular injections	52.2%[19] GIAI usually occurs 1 to 8 weeks after injection[48] After single and repeated injections[49]	Higher doses[49] Patients with inflammatory disease[49] Administration in bilateral joints simultaneously[48]	Patients with degenerative disease[49]
Epidural injections	52.2%[19]	Higher doses[50] Longer-acting glucocorticoids (eg, methylprednisolone, triamcinolone)[51]	Lower doses[50] Shorter-acting glucocorticoids[51]
Topical	4.7%[19,52] Shampoo formulations are not linked to GIAI[53]	Disruption of skin barrier[52,54] Long-term use (> 12 months)[52,55] Higher-potency topical glucocorticoids (eg, betamethasone dipropionate, clobetasol propionate)[52,55,56] Higher doses Application to larger body surface[52,54] Use of occlusive bandage[52,54] Application on the eyelids, scrotum, and mucosal surfaces[52,54]	Lower-potency topical glucocorticoids (eg, dexamethasone cream 0.1%, hydrocortisone 0.5%, hydrocortisone 1%, hydrocortisone 2.5%, methylprednisolone 1%)[55]

GIAI = glucocorticoid-induced adrenal insufficiency; HPAA = hypothalamic-pituitary-adrenal axis

Based on information in references 19 and 41–56.

Formulation. Dexamethasone is 25 times more potent than hydrocortisone, and prednisone is 4 times more potent. Duration of effect is more than 36 hours for dexamethasone, 18 to 36 hours for prednisone, and 8 to 12 hours for hydrocortisone.[21,22] At equivalent doses (0.75 mg of dexamethasone is equivalent to 5 mg of prednisone or 20 mg of hydrocortisone),[21,22] dexamethasone has stronger suppressive effects on the HPAA compared with hydrocortisone. However, studies have not shown any difference in HPAA suppression in patients treated with equivalent doses of prednisone compared with dexamethasone.[23,24]

Frequency and timing of administration. Pulse therapy with high-dose glucocorticoids (eg, intravenous methylprednisolone 250–500 mg weekly for 6–12 weeks)[25,26] and alternate single-day dosing are less likely to cause GIAI[27,28] compared with bedtime dosing and frequent dosing (more than once daily).[29–31] GIAI after short bursts of glucocorticoids (7–14 days) has been infrequently reported,[28,32,33] particularly in patients with chronic obstructive pulmonary disease who receive frequent short bursts of glucocorticoids[34] and patients with malignancies who receive bursts of dexamethasone to mitigate chemotherapy-related nausea.[35]

Interactions with other medications. Concomitant use of glucocorticoids and hepatic cytochrome P450 3A4 inhibitors (eg, protease inhibitors, azoles, clarithromycin, erythromycin) increases the levels of active metabolites of glucocorticoids, and consequently, the risk of GIAI.[36,37] This happens with all glucocorticoid formulations metabolized by cytochrome P450 3A4 regardless of route of administration: oral, injectable, intra-articular, and even inhaled and intranasal formulations.[38–40] Primary care clinicians should be aware of these interactions when

they suspect GIAI, especially in patients with chronic obstructive pulmonary disease or human immunodeficiency virus infection.

Cushingoid features. A cushingoid appearance usually indicates that the glucocorticoid dose is excessive. Some authors have indicated that patients with cushingoid features while on glucocorticoids are at a very high risk for GIAI.[16]

Unrecognized sources of exogenous glucocorticoids

Inhaled glucocorticoids bind to receptors in the lungs, mouth, and oropharynx, leading to systemic exposure and possibly HPAA suppression.[21] **Table 3** summarizes the reported risk of GIAI after exposure to the different formulations and factors that can increase or decrease the risk.[19,41–56]

Intra-articular and epidural injections. Systemic absorption of intra-articular glucocorticoids has been widely described.[57,58] Similarly, HPAA suppression after epidural corticosteroid injections has been reported with multiple formulations, doses, and frequencies (after both single and recurrent doses).[59]

Some patients do not know that these injections contain steroids and therefore may not report this exposure if they present with GIAI symptoms.[60] Serum and urine testing for synthetic steroids are important tools when GIAI is suspected.[61] Urine screening for synthetic glucocorticoids (liquid chromatography-tandem mass spectrometry with stable isotope dilution analysis) is reported to detect prednisone and prednisolone for up to 40 days after epidural injections and for up to 62 days after triamcinolone epidural injections.[60]

Topical formulations. Several studies reported GIAI induced by topical cutaneous glucocorticoids.[19,52]

Eye drops. GIAI due to ophthalmic glucocorticoids has been reported in adult, pediatric, and animal studies.[62,63]

Locally active enteral formulations. Rectal glucocorticoids and oral budesonide are used to treat inflammatory bowel disease. The risk of GIAI is dose- and duration-dependent in patients taking oral budesonide, being higher when patients take more than 6 mg daily for at least 8 weeks.[64] GIAI has been reported in patients using prednisolone enemas,[65] whereas beclomethasone dipropionate enemas seem to be safer.[66]

Other medications with glucocorticoid activity

Megestrol acetate is a synthetic progestin with glucocorticoid-like activity commonly used as an appetite stimulant in patients with malignancy and anorexia. Several reports have highlighted the incidence of adrenal insufficiency, Cushing syndrome, or both in patients treated with megestrol acetate,[67,68] specifically, when megestrol acetate is combined with dexamethasone.[35]

Medroxyprogesterone acetate, another progestin that binds glucocorticoid receptors,[69,70] is used to treat endometrial cancer, endometriosis, and abnormal uterine bleeding, and as a contraceptive, and is reported to cause HPAA suppression.[71]

GLUCOCORTICOID WITHDRAWAL SYNDROME

Excessive endogenous hormone secretion or exogenous administration often leads to tolerance (decreased response to the elevated hormones and the need for even higher levels to achieve the same effect) followed by physiologic and psychologic dependence.[1] In this situation, gradually tapering or abruptly stopping the glucocorticoids can induce glucocorticoid withdrawal syndrome,[1] even while patients are still receiving supraphysiologic doses of glucocorticoids.

Glucocorticoid withdrawal syndrome manifests as a spectrum of nonspecific symptoms and is mediated by multiple mechanisms. Chronic suppression of corticotropin-releasing hormone after stopping or tapering from glucocorticoids leads to adrenal insufficiency, adrenal crisis, depressive mood changes,[72] hypersomnia, and lethargy.[73,74] Prolonged suppression of proopiomelanocortin-related peptides causes myalgia, arthralgia, fever, and headache.[1] Depressed central noradrenergic and dopaminergic systems cause nonspecific withdrawal symptoms along with anorexia, nausea, vomiting, and weight loss.[1] Loss of glucocorticoid's suppressive effect on calcium absorption results in hypercalcemia and hyperphosphatemia.[1]

These symptoms can develop at any time—during glucocorticoid taper (while the patient is still on supraphysiologic doses), after completely stopping glucocorticoids, and even after there is biochemical evidence of HPAA recovery.[1]

Long-term treatment with supraphysiologic doses of glucocorticoids often leads to HPAA suppression and adrenal insufficiency. At the same time, tolerance to and dependence on high doses of glucocorticoids causes glucocorticoid withdrawal syndrome when attempting to taper or discontinue these drugs. Therefore, adrenal insufficiency and glucocorticoid withdrawal syndrome share similar clinical features (**Table 4**); however, they are completely different clinical entities that often overlap until the HPAA recovers. Results of biochemical testing including early morning cortisol levels and the corticotropin stimulation test can be normal or suboptimal, and hence, not helpful in making this diagnosis.[75]

TABLE 4
Adrenal insufficiency, glucocorticoid-induced adrenal insufficiency, and glucocorticoid withdrawal syndrome

	Adrenal insufficiency	Glucocorticoid-induced adrenal insufficiency	Glucocorticoid withdrawal syndrome
Diagnosis	Clinical symptoms and biochemical testing: Low 8 AM cortisol (< 4.8 µg/dL)[a] Abnormal response to corticotropin stimulation test (cortisol peak < 12.6 µg/dL at 30 minutes and 60 minutes)[a] Variable adrenocorticotropic hormone (for primary adrenal insufficiency > 63.3 pg/mL, for secondary adrenal insufficiency < 7.2 pg/mL)[b]	After abrupt discontinuation or quick taper of exogenous glucocorticoid or Cushing syndrome: Low 8 AM cortisol (< 4.8 µg/dL)[a] Low adrenocorticotropic hormone (< 7.2 pg/mL)[b] Low dehydroepiandrosterone sulfate[c] Abnormal response to corticotropin stimulation test (cortisol peak < 12.6 µg/dL at 30 and 60 minutes)[a]	Clinical symptoms of adrenal insufficiency with or without cushingoid features while gradually tapering or after abrupt discontinuation of glucocorticoid No laboratory test to diagnose
Mechanism	Lack of glucocorticoid secretion from adrenal cortex due to either adrenal etiology (primary adrenal insufficiency) or pituitary or hypothalamic etiology (secondary adrenal insufficiency)	HPAA suppression due to excessive endogenous or exogenous glucocorticoid, leading to atrophy of adrenal cortex	Tolerance of and dependence on supraphysiologic doses of glucocorticoid
Prevention	Replace with physiologic doses of glucocorticoid	Gradually taper glucocorticoid until completely stopped	Use the lowest effective supraphysiologic glucocorticoid dose when indicated
Treatment	Replace with physiologic doses of glucocorticoid	Gradually taper glucocorticoid until completely stopped Consider stress-dose glucocorticoid under stressors	No effective treatment: empirically increase glucocorticoid to prolong HPAA suppression

[a]Cortisol values per the Elecsys Cortisol II assay.
[b]Adrenocorticotropic hormone values per the Electro Chemiluminescence Immunoassay.
[c]Dehydroepiandrosterone sulfate normal values (µg/dL) per the Electro Chemiluminescence Immunoassay for females, by age:
15–19 years 65.1–368.0; 20–24 years 148–407; 25–34 years 98.8–340; 35–44 years 60.9–337; 45–54 years 35.4–256; 55–64 years 18.9–205; 65–74 years < 247; 75–99 years 12–154.

For males, by age:
15–19 years 70.2–492; 20–24 years 211–492; 25–34 years 160–449; 35–44 years 88.9–427; 45–54 years 44.3–331; 55–64 years 51.7–295; 65–74 years 33.6–249; 75–99 years 16.2–123.

HPAA = hypothalamic-pituitary-adrenal axis

Glucocorticoid withdrawal syndrome after successful treatment of Cushing syndrome

Evidence on glucocorticoid withdrawal syndrome in patients with GIAI caused by exogenous glucocorticoid use is lacking. However, several studies have looked into glucocorticoid withdrawal syndrome in patients with GIAI caused by adrenal lesions secreting excessive endogenous cortisol (adrenocorticotropic hormone-independent Cushing syndrome). Up to 99% of patients with Cushing syndrome have HPAA suppression.[76] Patients with Cushing syndrome can develop tolerance to and dependence on excessive endogenous cortisol, and hence, suffer from glucocorticoid withdrawal syndrome postoperatively.[76] After resection, glucocorticoid taper is indicated until the HPAA recovers.

Postoperative glucocorticoid withdrawal syndrome is usually characterized by biochemical evidence of HPAA suppression, with many signs and symptoms consistent with cortisol deficiency despite the use of supraphysiologic doses of glucocorticoids. Common symptoms include myalgias, arthralgias, fatigue, weakness, sleep disturbance, and mood changes. In a recent prospective observational study, myalgias, arthralgias, and weakness got progressively worse 5 to 12 weeks after surgery.[77] Glucocorticoid withdrawal syndrome can be difficult to differentiate from adrenal

TABLE 5
Approach to glucocorticoid taper in patients with glucocorticoid-induced adrenal insufficiency and after surgery for Cushing syndrome

Average daily prednisone dose
> 40 mg/day: decrease by 10 mg weekly until 40 mg daily
20–40 mg/day: decrease by 5 mg weekly until 20 mg daily
10–20 mg/day: decrease by 1–2.5 mg weekly until 10 mg daily
5–10 mg/day: decrease by 1 mg weekly until < 5 mg daily
< 5 mg/day: switch to equivalent dose of hydrocortisone (eg, 10 mg in the morning and 5 mg in the early afternoon); hold hydrocortisone for 24 hours and retest HPAA

Testing for HPAA recovery
If patient has been on prednisone 5 mg/day, switch to equivalent dose of hydrocortisone, wait for 2–4 weeks, and hold hydrocortisone for 24 hours before testing

Check 8 AM serum cortisol:
If < 10 µg/dL,[a] continue current dose of hydrocortisone and retest in 4–8 weeks
If ≥ 10 µg/dL, perform 250-µg corticotropin stimulation test:
- If suboptimal (cortisol peak < 12.6 µg/dL at 30 minutes and 60 minutes), consider stopping daily glucocorticoid replacement if patient has no withdrawal symptoms, but continue the sick-day rule (using stress-dose glucocorticoid) until repeating corticotropin stimulation test
- If optimal (peak cortisol ≥ 12.6 µg/dL), stop glucocorticoid if patient is comfortable

If 8 AM serum cortisol ≥ 12.6 µg/dL, consider stopping glucocorticoid if patient is ready in terms of withdrawal symptoms, or performing 250-µg corticotropin stimulation test or tapering glucocorticoid dose

Frequency of testing:
- If the results of tests are abnormal, recheck every 2–3 months
- If no recovery within 1 year, reassess every 3–6 months

Things to consider
- If glucocorticoid withdrawal syndrome develops at any point, increase the glucocorticoid dose to the most recent dose on which the patient did not have glucocorticoid withdrawal syndrome; consider decrements every other week rather than weekly
- If patient is on dexamethasone, consider switching to prednisone
- If patient is on twice-daily prednisone dosing, consider switching to equivalent dose of prednisone in the morning once daily

[a]Values per the Elecsys Cortisol II assay.

HPAA = hypothalamic-pituitary-adrenal axis

Based in part on information in reference 81.

insufficiency, which complicates glucocorticoid dosing and tapering regimens.

In a retrospective study of the postoperative course of 81 patients with adrenocorticotropic hormone-independent Cushing syndrome,[78] glucocorticoid withdrawal syndrome was most common when the 8 AM serum cortisol level 24 hours after the last glucocorticoid dose was less than 5 µg/dL, whereas no withdrawal symptoms were reported when it was higher than 10 µg/dL.

ASSESSING AND EXPEDITING HPAA RECOVERY IN GIAI

Currently, there is no consensus on the best approach to assessing HPAA recovery in patients with GIAI and those who have undergone surgery for Cushing syndrome. However, several factors related to the patient's characteristics, glucocorticoid course of therapy, and biochemical testing could be used to estimate the recovery of the HPAA and help clinicians with their approach to patients with GIAI.

Studies have looked at recovery of the HPAA after successful surgery for endogenous adrenocorticotropic hormone-independent Cushing syndrome, and we could extrapolate some of their conclusions to GIAI.[78] Slower HPAA recovery is expected in patients treated with higher doses of glucocorticoids, women, patients with lower body mass index, and patients with cushingoid features. Faster recovery (in weeks to months) is reported in patients treated with high doses of oral glucocorticoids for less than 1 month.[19] HPAA recovery could take up to 6 to 12 months in patients treated with glucocorticoids for more than 12 months.[19,79] Future studies are needed to prove the hypothesis.

An observational study by Pofi et al[79] involving 776 patients suggested a cutoff of 3.6 µg/dL (using the Roche Modular System) between baseline cortisol and

30-minute cortisol levels after a 250-µg corticotropin stimulation test to predict recovery of the HPAA. If the change in cortisol level is less than 3.6 µg/dL and the random cortisol level is less than 7.2 µg/dL after 1 year, patients are less likely to recover HPAA function.[79]

Switching from a longer-acting glucocorticoid (eg, dexamethasone, prednisone) to a shorter-acting one (eg, hydrocortisone) has been hypothesized to expedite HPAA recovery, but evidence remains inadequate to recommend one glucocorticoid vs others for HPAA recovery.[16,80]

Corticosteroid taper in patients with GIAI and after surgery for Cushing syndrome

Clinicians should work in multidisciplinary teams and closely monitor conditions that could possibly worsen or relapse due to lowering glucocorticoid doses. Glucocorticoids should be tapered when appropriate to safely induce HPAA recovery while at the same time avoiding glucocorticoid withdrawal syndrome or adrenal crisis.

Based on available literature and expert opinion,[81] we suggest the approach to tapering glucocorticoids in patients with GIAI outlined in **Table 5**.

TAKE-HOME POINTS

Primary care clinicians should be aware of the high incidence of GIAI in patients who are treated with formulations of glucocorticoids other than oral forms. Glucocorticoid withdrawal syndrome develops due to dependance on supraphysiologic doses. Its symptoms closely resemble those of GIAI.

Primary care clinicians are encouraged to taper glucocorticoids when possible and test for HPAA recovery. If patients develop symptoms of glucocorticoid withdrawal syndrome while tapering, clinicians could consider increasing the glucocorticoid dose slightly and reattempting a slower taper.

DISCLOSURES

Dr. Li has disclosed conducting research for BridgeBio Pharma. Dr. Lansang has disclosed receiving research funding support from Abbott, serving as a research principal investigator for Abbott and Dexcom, and conducting research for Xeris. Dr. Nachawi reports no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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