Review Article

The Glucocorticoid Taper: A Primer for the Clinicians

Gagan Priya, Bashir A. Laway[1], Mythili Ayyagari[2], Milinda Gupta[3], Ganesh H. K. Bhat[4], Deep Dutta[5]

Departments of Endocrinology and [3]Medicine, Fortis Hospital, Mohali, Punjab, [1]Department of Endocrinology, Sher-i-Kashmir Institute of Medical Sciences, Srinagar, Kashmir, [2]Department of Endocrinology, MEDICOVER Hospital, Vishakhapatnam, Andhra Pradesh, [4]Department of Endocrinology, AJ Institute of Medical Sciences, Mangalore, Karnataka, [5]Department of Endocrinology, Cedar Super Specialty Clinic, Delhi, India

Abstract

Glucocorticoid (GC) therapy can ameliorate debilitating and life-threatening symptoms in several inflammatory/immunological disorders. However, it can also cause significant side effects, especially with higher doses and longer duration of use. Therefore, GCs should be used at the lowest effective dose for the shortest possible time to minimise adverse effects. GC therapy may cause suppression of the endogenous hypothalamic-pituitary-adrenal (HPA) axis and abrupt discontinuation predisposes patients to features of GC-induced adrenal insufficiency. The practice of tapering GC therapy allows for recovery of the HPA axis while minimising the risk of a disease flare-up or symptoms of AI. Moderate-to-high dose GC therapy may be tapered rapidly to near-physiological doses while watching for features of disease reactivation. Once close to the physiological dose, tapering is slower and at longer intervals to allow for recovery of the HPA axis. It is important to use short- or intermediate-acting GC preparations such as hydrocortisone or prednisolone in physiological doses, administered in the morning to mimic the endogenous cortisol rhythm. A general principle to follow is that HPA axis recovery takes longer if the period of suppression has been long. In such cases, tapering should be slower over a few months to even a year. In select cases at high risk of AI or if symptoms appear during tapering, the decision to further taper and discontinue steroids may be based on testing of HPA axis function using basal and/or stimulated serum cortisol. All patients on exogenous steroids should be advised about the need for an appropriate increase in GC doses during acute medical or surgical illness and should carry a steroid alert card to avoid adrenal crisis.

Keywords: Steroid taper, glucocorticoid taper, glucocorticoid withdrawal syndrome, steroid-induced adrenal insufficiency, glucocorticoid-induced adrenal insufficiency, adrenal suppression, recovery of HPA axis

Introduction

Glucocorticoids (GCs) are potent anti-inflammatory and immunomodulatory drugs when used in supraphysiological doses.[1,2] Cortisol, the predominant endogenous GC, is secreted from the adrenal cortex under the regulation of the hypothalamic-pituitary-adrenal (HPA) axis. GCs bind to GC receptors and have both genomic and non-genomic actions.[2,3] Synthetic analogues of GCs are one of the most widely prescribed medications, for a range of inflammatory, immunological, allergic, and malignant diseases,[1-5] as listed in Table 1. They can ameliorate life-threatening and debilitating symptoms and lead to significant and rapid clinical improvement. 1-3% of the adult population is reported to receive GC prescriptions[6-10] with high rates of inappropriate use[11,12] and long-term use.[9,7,13]

However, the use of GCs is limited by several adverse effects,[3,14] depicted in Figure 1, which can be as dangerous as the underlying disease for which they are prescribed.[3] Adverse effects may depend on the type, potency, and dose of GC, the route, duration, and time of administration, and patient susceptibility.[14] Hyperglycaemia and hypokalaemia may appear immediately after initiation of systemic GC therapy and depend highly upon individual susceptibility.[4,14] Emotional lability, increased appetite, sleep disturbance, and venous thromboembolism may be seen as early as one month with even moderate doses.[4,5,14] Weight gain, Cushingoid features, myopathy, hypertension, diabetes, decreased bone mineral

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Address for correspondence: Dr. Gagan Priya, Department of Endocrinology, Fortis Hospital, Mohali, Punjab – 160 059, India.
E-mail: gpriya77@gmail.com

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Table 1: Indications for the use of glucocorticoids

Organ-specific disorders	Indications for glucocorticoid therapy
Endocrine (physiological replacement doses)	Adrenal insufficiency (primary, secondary, or tertiary)
	Congenital adrenal hyperplasia
	Glucocorticoid remediable aldosteronism
Endocrine (supraphysiological doses)	Lymphocytic hypophysitis
	Subacute thyroiditis
	Diagnostic protocols for Cushing's syndrome
Respiratory disease	Bronchial asthma
	Acute exacerbation of chronic obstructive pulmonary disease
	Coronavirus disease 2019
	Acute lung injury/acute respiratory distress syndrome
	Cytokine storm
	Pulmonary or systemic sarcoidosis
	Allergic bronchopulmonary aspergillosis
	Hypersensitivity pneumonitis
	Interstitial lung disease
	Sarcoidosis
	Cystic fibrosis
	Allergic rhinitis
	Nasal polyposis
Cardiovascular conditions	Acute hypovolemic shock not responding to vasopressors
	Septic shock not responding to vasopressors
	Anaphylaxis
Rheumatological disorders	Rheumatoid arthritis
	Systemic lupus erythematosus
	Ankylosing spondylitis
	Polymyositis/dermatomyositis
	Polymyalgia rheumatica
	Systemic vasculitis
	Polyarteritis nodosa
Haematological	Lymphoma/ leukaemia
	Idiopathic thrombocytopenic purpura
	Hemolytic anaemia
Dermatological	Acute severe dermatitis
	Pemphigus vularis
	Severe urticaria/ angioedema
	Vitiligo
Gastrointestinal	Ulcerative colitis
	Crohn's disease
	Autoimmune hepatitis
Renal	Nephrotic syndrome
	Lupus nephritis
	Systemic vasculitis
Neurological	Acute or chronic demyelinating polyneuropathy
	Multiple sclerosis
	Guillain-Barre syndrome
	Cerebral edema
	Bell's palsy
	Myasthenia gravis
	Acute traumatic spinal cord injury
Ophthalmological	Uveitis
	Keratoconjunctivitis
	Optic neuritis
Malignancy	Malignancy associated hypercalcemia
	Before chemotherapeutic agents
Post-transplant	To suppress graft versus host reaction (heart, kidney, liver and cornea transplant)

density, and fracture risk usually appear over 3-6 months or longer.[5,15,16] An increased cardiovascular risk and higher mortality have been reported even with replacement doses of GCs in patients with adrenal insufficiency (AI), as current

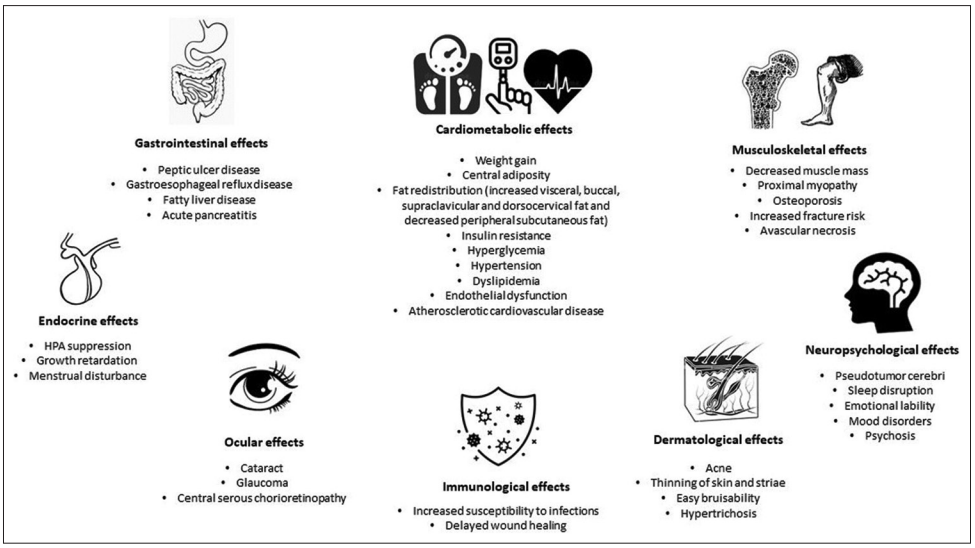


Figure 1: Adverse effects of glucocorticoid therapy

replacement regimens are unable to mimic the normal circadian cortisol rhythm.[1,14,17,18]

Therefore, there is an urgent need for steroid stewardship to minimise risk and optimise the benefit-to-risk ratio. GC therapy should be centred on treating the underlying disease with the lowest effective dose for the shortest possible time with close monitoring for adverse effects.[1] Exposure to supraphysiological doses leads to suppression of the endogenous HPA axis and abrupt discontinuation predisposes a patient to development of cortisol insufficiency and even adrenal crisis.[1,14] There is also a risk of reactivation of the underlying disease for which GCs were prescribed. The practice of tapering GC therapy allows for recovery of the HPA axis while minimising the risk of a disease flare-up or symptoms of AI. However, there is a lack of evidence-based guidelines on how to taper systemic GC therapy effectively and safely.

The current review summarises the interplay between primary disease, GC use, and HPA suppression and proposes a pragmatic approach to steroid tapering from an endocrinologist's perspective.

Methods

We searched for published literature between January 01, 1960, and July 31, 2023, using the search words: "steroid taper", "glucocorticoid taper", "glucocorticoid withdrawal syndrome", "steroid-induced adrenal insufficiency", "glucocorticoid-induced adrenal insufficiency", "adrenal suppression", and "recovery of hypothalamic-pituitary-adrenal axis" in PubMed and Medline database. The writing group includes five endocrinologists and one physician. GP and BL carefully read through the abstracts and selected relevant articles that were then extensively reviewed. The first draft was prepared by GP and edited by BL and MA. The other authors reviewed the manuscript and appropriate suggestions were incorporated. The final draft was approved by all authors.

Glucocorticoid Therapy and the Risk of HPA Suppression

Cortisol exerts a negative feedback effect on the secretion of corticotropin-releasing hormone (CRH) and adrenocorticotrophic hormone (ACTH).[3] Supraphysiological doses of GCs, therefore, cause suppression of the HPA axis, as depicted in Figure 2. With a short course of GC therapy, the HPA axis recovers rapidly after discontinuation.[19] However, long-term use can cause hypoplasia and atrophy of pituitary corticotrophs as well as adrenal cortical cells, leading to prolonged HPA suppression and tertiary AI.[5,20,21] An abrupt discontinuation or rapid reduction in GC doses may, therefore, cause symptoms of AI. Due to the widespread long-term use of GCs, tertiary AI is the most common form of AI in clinical practice.[5,22,23]

Factors increasing the risk of HPA suppression

Several factors are associated with an increased risk of HPA suppression. These include the potency and dose of GCs, route, and timing of administration, and duration of treatment. Orally administered GCs have a greater risk of adrenal suppression than inhalational or topical GCs.[1,5] Commonly used oral GC preparations vary in their pharmacokinetic profile, potency of effect on GC receptors, and selectivity for mineralocorticoid (MC) receptors,[3] as listed in Table 2. Prednisolone is the most prescribed GC for anti-inflammatory and immunosuppressive effects, due to high GC activity compared to MC activity.[1] Therefore, for quantification, GC doses are mentioned as prednisolone equivalent (PE).[2]

The equivalent doses of GCs in terms of their efficacy at the GC receptor are the following:

Prednisone 5 mg = prednisolone 5 mg = methylprednisolone 4 mg = cortisone acetate 25 mg = hydrocortisone 20 mg = dexamethasone 0.75 mg.

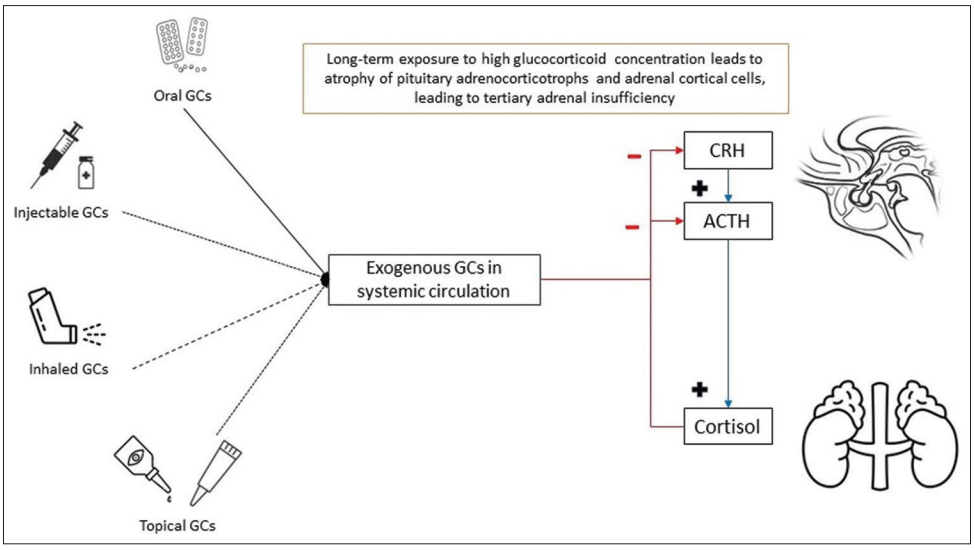


Figure 2: The negative feedback loop of the hypothalamic-pituitary-adrenal axis and HPA suppression with exogenous glucocorticoids. Corticotropin-releasing hormone (CRH) from the paraventricular neurons of the hypothalamus stimulates the secretion of adrenocorticotropic hormone (ACTH) from the anterior pituitary corticotrophs. ACTH, in turn, stimulates the secretion of cortisol from the adrenal cortex. Cortisol exerts a negative feedback effect on the HPA axis and supraphysiological cortisol concentrations suppress the secretion of CRH and ACTH. Exogenous glucocorticoids that enter systemic circulation act to suppress the HPA axis by decreasing the synthesis and secretion of CRH as well as ACTH. The net result is decreased endogenous cortisol production. Long-term exposure to exogenous glucocorticoids can lead to atrophy of pituitary corticotrophs and adrenal cortical cells, leading to tertiary adrenal insufficiency

Table 2: Common oral glucocorticoid preparations and their equivalent potency

	Type of GC	Duration of action (hours)	Relative GC activity*	Relative MC activity*	Equivalent dose*	HPA suppression*	Primary indications
Short acting	Hydrocortisone	8–12	1	1	20 mg	1	GC replacement therapy in adrenal insufficiency
	Cortisone acetate	8–12	0.8	0.8	25 mg	1	
Intermediate acting	Prednisone	12–36	4	0.8	5 mg	4	Anti-inflammatory and immunosuppressive
	Prednisolone	12–36	4	0.8	5 mg	4	
	Methylprednisolone	12–36	5	Minimal	4 mg	4	
Long acting	Dexamethasone	36–72	30	Minimal	0.75 mg	17	
	Betamethasone	36–72	30	Negligible	0,6 mg	-	
	Fludrocortisone	12–36	10–15	125–150		12	MC replacement in primary adrenal insufficiency Not used for GC activity due to very high MC activity

*Relative to hydrocortisone which is the pharmaceutical equivalent of endogenous cortisol. GC – glucocorticoid, MC – mineralocorticoid. Data from Liu *et al*., 2013,[1] Nicolaides *et al*., 2018,[5] and Pelewicz *et al*., 2021[23]

Some conventional terms for GC doses used in the management of inflammatory or immunological disorders are given in Table 3.

GCs with higher potency and longer duration of action, such as dexamethasone or betamethasone, have a greater risk of causing HPA suppression than intermediate-acting GCs, such as prednisolone or methylprednisolone, which in turn have a greater risk than hydrocortisone.[1,5,24,25]

The risk is also proportional to the dose and duration of therapy.[1,24,25] Patients receiving high-dose GC therapy for longer than a few weeks (≥20 mg/day PE for more than 3 weeks) are likely to have adrenal suppression. In a systematic review of 73 studies measuring HPA function after systemic GC therapy, a median of 37% (13-63%) patients had AI.[20]

Suppression is unlikely in patients who have been exposed to systemic GCs for less than 3 weeks.[26,27] However, recent studies have reported HPA suppression even with short-term high-dose (<4 weeks) or long-term low-dose (<5 mg/day PE) GC use.[20,28,29] The risk further increases with multiple short courses.[1,30-32]

The timing of the GC dose may also influence the nocturnal ACTH surge. Suppression is more with multiple daily doses administered during the day[33,34] or evening/bedtime dose[5,35] compared to a single daily morning dose. Alternate-day dosing carries less risk.[1,36] Concomitant use of CYP3A4 inhibitors

Table 3: Conventional terms used for quantification of glucocorticoid dose

Dose	Definition
Low	≤7.5 mg prednisolone equivalent/day
Medium	>7.5 but ≤ 30 mg prednisolone equivalent/day
High	>30 mg but ≤ 100 mg prednisolone equivalent/day
Very high	>100 mg prednisolone equivalent/day
Pulse therapy	≥250 mg prednisolone equivalent/day for one day or a few days

Data from Buttgereit *et al*.[2]

reduces GC clearance and, therefore, increases cortisol exposure and risk of HPA suppression.[1,5,21]

HPA suppression may be under-appreciated in patients with asthma on inhaled steroids.[12] Inhaled GCs that are more potent, for example, fluticasone propionate, especially in medium to high doses, have been associated with GC-induced AI.[25,37-39] A large meta-analysis reported cortisol suppression in 18% of patients on low-dose, 27% on medium-dose, and 36% on high-dose inhaled corticosteroids.[40] On the other hand, intravenous methylprednisolone pulse therapy in patients with Graves' ophthalmopathy was not associated with HPA suppression.[41]

While local GC application (topical, intra-articular, or nasal) has been associated with less risk of HPA suppression, factors that increase absorption of topical steroids such as inflammation or injury may increase the risk.[1,21] Topical fluorinated corticosteroids, such as dexamethasone, betamethasone, triamcinolone, and beclomethasone, have greater skin penetration and more systemic absorption and have been associated with adrenal suppression in infants.[5,42] AI secondary to nasal or intra-articular GC administration is less commonly reported.[43,44]

In a systematic review of 74 studies including 3753 participants, Broersen *et al*.[24] reported GC-induced AI in 48.7% of patients on oral, 7.8% on inhalational, 4.7% on topical, and 4.2% on nasal GCs. The risk was dependent on the dose and duration of treatment. Overall, only 2% of patients had symptoms of AI while 19% failed to achieve a normal cortisol response on dynamic testing.[24] While most studies have reported biochemical AI with few patients having clinical symptoms, symptoms of AI are non-specific and may often be attributed to other causes.[21] A recent Danish population-based study assessed the clinical indicators of AI in 286,680 patients after discontinuing long-term (≥3 months) oral GCs. There was a high incidence of typical symptoms such as hypotension, gastrointestinal disturbance, hypoglycaemia, and hyponatremia.[45] Symptoms peaked up to 3 months after stopping GCs. There are also several reports of adrenal crises resulting from GC-induced AI.[12,15,46-51]

There is no certain way to predict which patient will develop significant HPA suppression. Therefore, clinicians need to be vigilant of the possibility of HPA suppression at all degrees of GC exposure, especially in those receiving systemic GCs for periods longer than 3 weeks, multiple short courses, or prolonged medium-to-high dose inhaled GCs, as listed in Table 4. Any patient on GC therapy presenting with Cushingoid features or clinical features of adrenal insufficiency should be assumed to have adrenal suppression.[1,29,52]

GC exposure can also be surreptitious in the form of over-the-counter or adulterated indigenous medications, requiring HPA axis evaluation in patients presenting with features of cortisol excess or deficiency.[53-57]

Basic Principles of Tapering Glucocorticoids

Systemic GCs are often administered in moderate-high doses to control underlying inflammatory/immunological disease and then withdrawn or reduced to the minimal possible dose.[14] The aim is to minimise the risk of adverse effects related to long-term exposure to supraphysiological doses.

Abrupt discontinuation is advisable if GC use has been for a short duration (<3 weeks) and if the indication for their use has resolved.[5] For example, several asthma management guidelines recommend short-term use of oral GCs (40-50 mg/day PE) for 5-10 days for acute exacerbation of asthma followed by abrupt discontinuation.[12,32,58,59] In other conditions, stopping GCs abruptly is not advisable as it can cause a flare-up of the underlying disease or unmask GC-induced AI. Therefore, GCs are usually tapered gradually to prevent both disease reactivation and symptoms of cortisol deficiency.

Most disease-specific recommendations on GC dose and duration emphasise that GCs should be tapered once clinical improvement occurs but often do not propose a tapering plan.[12,58-71] The optimal rate of tapering is also debated.[21] While rapid tapering is generally safe and effective,[60,67] some suggest that this may be less effective in maintaining long-term disease remission compared to slow tapering.[65] Most guidelines recommend that GCs should be discontinued after tapering,[2] but recent studies in rheumatoid arthritis (RA) suggest that long-term use of low-dose GCs (<5 mg/day PE) may prevent disease reactivation and be safe.[61,68]

Alternate routes of GC administration should be considered instead of long-term oral use, due to lower systemic absorption, for example, inhalational steroids for bronchial asthma[12,32] or oral budesonide MMX (with high first-pass metabolism) in ulcerative colitis.[69] The use of steroid-sparing medications should be prioritised in case of persistent need for GCs, for example, in RA, post-organ transplant, systemic vasculitis, etc., to minimise GC exposure.[2]

Some recommendations related to GC use in the management of various disorders are summarised in Table 5.

Endocrinologist's perspective of glucocorticoid tapering

From an endocrinologist's perspective, GC tapering is an art in the background of science. The main aim of tapering is to allow HPA axis recovery without affecting the primary disease.

Table 4: Factors associated with the risk of hypothalamic-pituitary-adrenal suppression

Factors	Higher risk of HPA suppression	Lower risk of HPA suppression
Type of glucocorticoid	Longer-acting and more potent GCs, especially dexamethasone, betamethasone, and beclomethasone	Short- or intermediate-acting and less potent GCs such as hydrocortisone, cortisone acetate, prednisolone, methylprednisolone
Dose of glucocorticoid	Higher daily dose (>20 mg/day)*	Lower daily dose
	Higher cumulative dose (>1 g)*	Lower cumulative dose
Regimen and duration of glucocorticoid therapy	Prolonged use (>3−4 weeks)	Short course (<2−3 weeks)
	Multiple short courses	Pulse systemic therapy
	Multiple daily doses	Alternate day dose
	Evening or bedtime dose	Early morning dose
Route of administration	Systemic oral therapy	Intravenous pulse therapy
	Inhaled: moderate to high dose (>500 µg/d)**, daily for >6 months, potent GCs such as fluticasone propionate and concomitant use of oral GCs	Inhaled: low dose, short-term use, use of GCs such as ciclesonide with a higher clearance rate
	Topical: long-term use of high potency GCs, presence of skin inflammation, use of occlusive dressings, use on mucus membranes, use in infants (larger body surface area for systemic absorption)	Topical: short term use, no dressing
	Intra-articular: repeated injections, higher doses, presence of inflammatory arthropathy	Intra-articular: single injection
Individual susceptibility	Certain glucocorticoid receptor polymorphisms	
Concomitant drugs	Concomitant use of CYP3A4 inhibitors (decrease clearance and increase systemic exposure to GCs) – clarithromycin, erythromycin, itraconazole, ritonavir, lopinavir, mifepristone, amiodarone	
	Drugs suppressing HPA axis – opioids	
Clinical features	Clinical features of adrenal insufficiency or acute adrenal crisis	
	Clinical features of Cushing's syndrome	

*Dose is mentioned as prednisolone equivalent. **Dose is mentioned as an equivalent of fluticasone propionate. CYP3A4 – cytochrome p450 3A4, HPA – hypothalamic-pituitary-adrenal, GC – glucocorticoid. References: Blakey *et al*.,[12] Prete A *et al*.,[21] Pelewicz *et al*.,[23] Borresen *et al*.[52]

This is achieved by gradually decreasing the dose and finally stopping the GCs. It is a teamwork and involves a close liaison between the primary physician, the endocrinologist, and the patient. There seem to be no hard-and-fast rules on how to taper GCs and the plan should be individualised. The factors that need to be considered during GC taper are listed in Table 6.

The initial tapering is governed by the underlying disease for which GCs are being used. Once disease control has been achieved, usually within a few days or weeks, rapid tapering can begin while watching for disease reactivation. Once near-physiological doses are reached, tapering is done gradually to allow for recovery of the HPA axis while watching for features of GC withdrawal or AI.

There can be three stages of tapering steroids, viz., an initial rapid taper followed by gradual tapering and then slow tapering,[5,21,52,67,72] as depicted in Flowchart 1.

1. **Initial rapid tapering:** In patients on high dose GC (>20-40 mg/day PE), the dose can be reduced by 5-10 mg at weekly intervals or by 30-50% every 2-4 weeks, till a dose of 20 mg/day PE is reached. The rate of tapering is reduced once the patient is on ≤20 mg/day PE, with decrements of 5 mg every 2 weeks or 2.5 mg every week till a dose of 10 mg/day PE is reached. For patients who are on long-acting GCs such as dexamethasone, it is preferable to switch to prednisolone. The initial rapid tapering can be accomplished by the primary physician while maintaining vigilance for disease flare-ups, in which case, the dose may be temporarily increased.
2. **Gradual tapering:** When a patient is on the dose of ≤10 mg/day PE, tapering should be done gradually, in decrements of 2.5 mg every 2 weeks till a dose of 5 mg/day PE is reached. During gradual tapering, clinicians should be vigilant for the symptoms of GC withdrawal syndrome (GWS), which requires a temporary increase in dose and slow tapering.
3. **Slow tapering:** Once patients are on a near-physiological dose (5 mg/day PE), tapering is done more slowly to allow for recovery of HPA suppression and prevent features of cortisol insufficiency. A patient may be continued on once-daily oral prednisolone 5 mg/day administered in the morning, which is further tapered to 2.5 mg/day over 2-4 weeks. Alternatively, the patient may be switched to an equivalent dose of hydrocortisone, that is, 15-20 mg/day in 2-3 divided doses. Hydrocortisone may be reduced by 2.5 mg every 1-2 weeks till a dose of 10 mg/day is reached. Hydrocortisone 10 mg/day is administered in two divided doses and then reduced to 5 mg/day or 2.5 mg twice daily and stopped after 2-4 weeks. At any time during slow taper, if the patient develops symptoms of AI, the GC dose before taper should be maintained longer. Slow tapering often requires close supervision by an endocrinologist for features of AI, especially in patients on long-term GC therapy or having Cushingoid features. There is a need to educate patients about stress doses of GCs to avoid adrenal crises during any acute illness.

Table 5: Recommendations for glucocorticoid therapy in different disorders

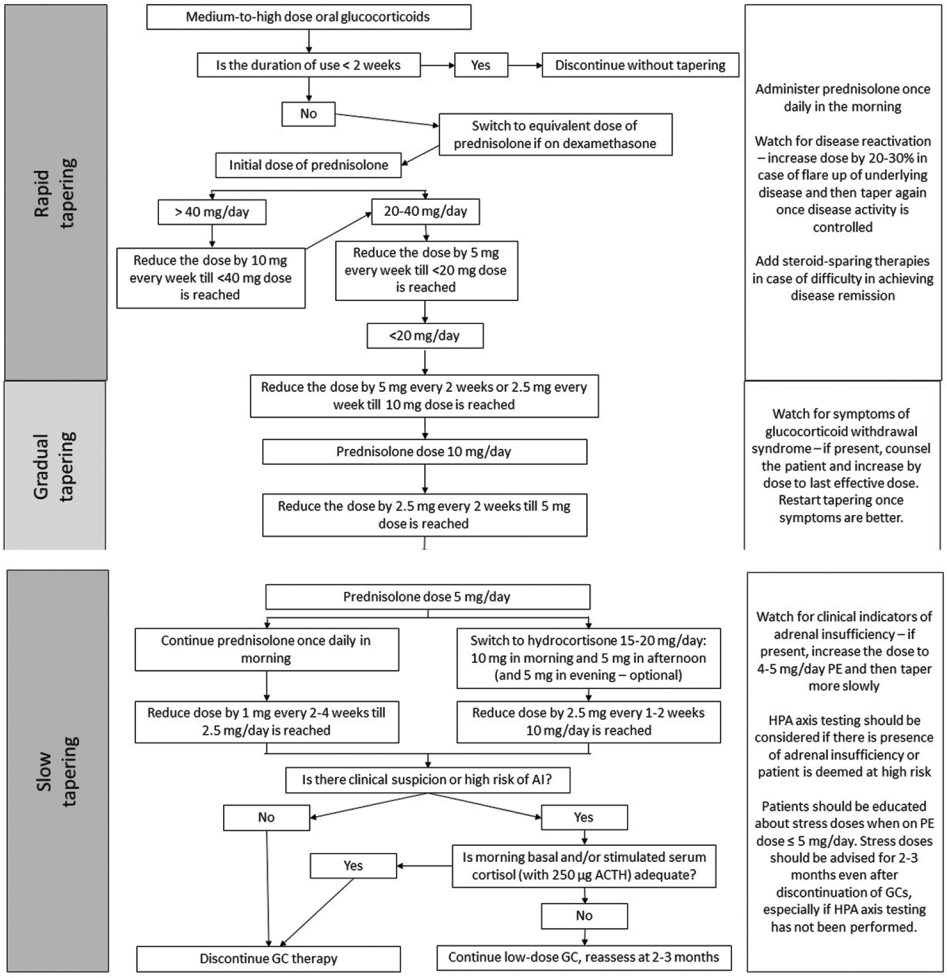
Disease	Recommending body	Recommendation
Bronchial asthma	Global Initiative for Asthma[59]	Use long-term oral GCs sparingly and taper as soon as possible to the lowest possible dose
	Thoracic Society of Australia and New Zealand[12]	Use maintenance oral steroids for severe asthma and complex asthma variants (allergic bronchopulmonary aspergillosis or eosinophilic granulomatosis with polyangiitis)
		Once a maintenance dose of 10 mg/day PE is reached, evaluate for adrenal insufficiency clinically and with testing for HPA axis activity. If the patient has HPA suppression, tapering should be done slowly.
	Delphi consensus of 137 experts[58]	Long-term oral GC should be considered only for severe asthma and tapered to the lowest effective dose, preferably <5 mg/day PE. The rate of tapering should be individualised.
Rheumatoid arthritis	European League Against Rheumatism (EULAR)[61,62]	Advocate the use of GCs as an adjunct to conventional disease-modifying agents at the lowest possible dose for the shortest possible time
		GCs should be tapered as rapidly as possible and discontinued, usually within 3 months (or exceptionally 6 months) once there is clinical improvement.
		Low-dose GC therapy is considered as < 7.5 mg/d PE
	American College of Rheumatology (ACR)[63]	Recommend adding GCs for disease flares at the lowest dose for the shortest possible time (<3 months, maximum 6 months)
		Continued long-term use may be required in patients who do not respond to disease-modifying drugs
		<10 mg/day PE is considered as low-dose therapy
Polymyalgia rheumatica	British Society of Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR)[64]	Recommend initiation of moderate-dose GCs – 15 mg/day PE for 3 weeks, then 12.5 mg/day for 3 weeks, 10 mg/day for 4−6 weeks, and further reduction by 1 mg every 4−8 weeks.
		For mild cases – recommend intramuscular methylprednisolone 120 mg every 3−4 weeks and reduce by 20 mg every 2−4 months
		Average duration of treatment 1−2 years
Large vessel vasculitis	EULAR[65]	Recommend high-dose GCs (40−60 mg/day PE), taper once the disease is controlled to target dose of 15−20 mg/day within 2−3 months and over 1 year to ≤5 mg/day for giant cell arteritis and ≤10 mg/day for Takayasu's arteritis
		Treatment may be needed for approximately 2 years
ANCA-associated vasculitis	EULAR[66]	Recommend oral prednisolone at 1 mg/kg/day (maximum 60 mg/day) and tapered to 15 mg/day at 12 weeks, 10 mg/day by month 4, 7.5 mg/day by month 5, 5 mg/day by month 6 and then 2.5 mg/day over 18−24 months
Inflammatory bowel disease	American College of Gastroenterology[69]	Recommend oral systemic steroids (60 mg/day PE) to induce remission in moderate-severe ulcerative colitis but discourage long-term use to maintain remission. The duration of systemic steroids should be as short as possible. Speed of taper to be guided by clinical symptoms, cumulative steroid exposure, and onset of effect of alternative therapies
		Acute severe ulcerative colitis – recommend IV methylprednisolone 60 mg/day or hydrocortisone 100 mg 3−4 times daily to induce remission
Thyroid associated ophthalmopathy	European Thyroid Association[70]	Recommend oral prednisolone prophylaxis in patients undergoing radioactive iodine ablation if they have or are at risk of progression of Graves' ophthalmopathy – 0.3−0.5 mg/kg/day as starting dose, tapered and withdrawn after 3 months if high risk; 0.1−0.2 mg/kg/day as starting dose, tapered and withdrawn after 6 weeks if moderate risk.
		In moderate to severe and active GO, recommend intermediate dose regimen – 0.5 g IV methylprednisolone weekly for 6 weeks, then 0.25 g IV weekly for 6 weeks with a cumulative dose of up to 4.5 g.
		In severe and active GO, recommend a high-dose regimen – 0.75 g IV methylprednisolone weekly for 6 weeks, then 0.5 g IV weekly for 6 weeks with a cumulative dose of up to 7.5 g.
	American Thyroid Association[71]	Recommend intravenous glucocorticoids for active moderate-to-severe thyroid eye disease – standard dosing of IV methylprednisolone 0.5 g weekly for 6 weeks and then 0.25 g weekly for 6 weeks to cumulative dose of 4.5 g. Avoid cumulative dose of >8.0 g.

GC – glucocorticoids, PE – prednisolone equivalent

Discontinuation of GCs may be considered if patients remain asymptomatic at the end of slow tapering. HPA axis testing with a morning serum cortisol and, if required, ACTH stimulation test, may facilitate the decision to stop GCs safely, especially in patients at risk of AI. If the cortisol response to ACTH stimulation is normal, GCs can be discontinued but if it is inadequate, GCs should be continued in physiological replacement dose, and reassessment done after 3-6 months.

Testing for Recovery of HPA Axis

Testing for HPA axis function may not be feasible in all patients being tapered from GC therapy but a low threshold for screening is desired.[52] The recovery of normal endogenous cortisol secretion may vary depending on the cumulative dose and duration of GC therapy. With medium-term use (<3 months), recovery usually occurs within a few weeks and GCs can be safely tapered and discontinued without testing.[24] However, with long-term use, HPA suppression is more prolonged and



Flowchart 1: Algorithm for tapering oral glucocorticoids. Note: Since the lowest strength of prednisolone available in many countries is 5 mg, alternate day dosing may be considered during slow tapering, for example, one tablet and half tablet of prednisolone 5 mg on alternate days

Table 6: Factors to be considered during glucocorticoid taper

Category	Factor
Underlying disease	Clinical disease activity – is the disease in remission?
	What is the risk relapse or reactivation?
	Is the patient on steroid-sparing medications that reduce the risk of relapse?
GC therapy	What is the average dose and cumulative dose of GC received?
	What is the duration of GC exposure?
	Does the patient have Cushingoid features due to supraphysiological GC exposure?
	Does the patient have documented HPA suppression or is at risk of HPA suppression?
Other factors	What is the overall health status?
	Has tapering been attempted in the past? Was it successful?
	Is the patient on glucose-lowering medications?*

*Antidiabetic medications may need to be down-titrated when dose of GC is reduced. Adjustment of antidiabetic medications should be based on blood glucose monitoring values and trends

HPA axis testing should be considered before discontinuation of GCs or if the patient develops clinical features suggestive of AI.[24,67] HPA axis testing should be performed once the GC dose has been tapered to <5 mg/day PE for 2-4 weeks.[21,22]

Diagnosis of HPA suppression is established by a low baseline and/or stimulated serum cortisol.[22,23] The initial screening may be done by measuring morning (8 am) serum cortisol as the endogenous cortisol secretion is highest in the morning. The 8 am serum cortisol value of <3 µg/dl (<100 nmol/L) is diagnostic of AI while levels >15 µg/dl (>450 nmol/L) rule out AI.[22,23,73] Serum cortisol values of 3-15 µg/dl (100-450 nmol/L) are inconclusive and would require further assessment with dynamic testing of the HPA axis.[22]

The most widely accepted test for evaluation of the HPA axis is the standard-dose ACTH stimulation test.[22,23] A dose of 250 µg synacthen (synthetic ACTH) is administered intramuscularly or intravenously with sampling for serum cortisol after 30 and 60 minutes. A peak serum cortisol value of <18 µg/dl (<550 nmol/L) is diagnostic of AI.[73] Some studies have suggested that the low-dose ACTH (1 µg) stimulation test may be better for the diagnosis of secondary

or tertiary AI than the standard-dose test.[73,74] However, a meta-analysis of 28 studies reported similar sensitivity for both tests in secondary AI.[75]

Acton prolongatum stimulation test with 25-30 U IM long-acting porcine sequence ACTH which is readily available, has demonstrated reliable accuracy as an alternative to the synacthen stimulation test.[76,77] Salivary cortisol has not been sufficiently validated for the diagnosis of AI.[78] Other stimulation tests, including insulin tolerance test (ITT), metyrapone stimulation test, CRH stimulation test, and glucagon stimulation test, are not routinely performed for diagnosis of GC-induced AI.[22,23,79] Measurement of morning plasma ACTH is not warranted if there is a known history of systemic GC exposure but should be measured if the cause of AI is unclear, such as surreptitious exposure to GCs.[73]

Exogenous GC preparations can interfere with cortisol assays. Therefore, hydrocortisone needs to be discontinued for 24 hours and prednisolone for 48-72 hours before the measurement of serum cortisol.[22,23,73]

If baseline and stimulated cortisol levels are inadequate, the patient should be continued on GC replacement therapy and reassessed after 3-6 months.[21]

Challenges during the Taper

Several challenges may arise during the GC taper such as flare-up of the underlying disease, AI or GWS.[14] There may be a significant overlap in their clinical presentation with symptoms being non-specific, for example, fatigue, malaise, loss of appetite, body aches, and weight loss. An empirical increase in GC dose may alleviate symptoms regardless of the cause. Therefore, a favourable response to increased GC dose does not help distinguish between them.[52] A low threshold should be maintained for further evaluation including assessment of underlying disease activity and HPA axis testing.

a. Disease flare-up

An assessment for underlying disease activity may be done using objective markers such as ESR or CRP in inflammatory arthritis; Asthma Control Questionnaire score, lung functions, and eosinophil count in asthma; or the presence of diarrhoea, bleeding, or abdominal pain in inflammatory bowel disease.[12,14] A disease flare-up requires an increase in GCs to supraphysiological doses, but a relatively modest increase in dose is usually enough.[14] In the meantime, other disease-modifying drugs can be intensified or steroid-sparing therapies added.[14,60] Topical GCs may be considered where indicated, for example, intra-articular steroids for arthritis or high-dose inhaled steroids for bronchial asthma.[14] Re-tapering should begin again after the disease has become quiescent.

b. Tertiary adrenal insufficiency

Adrenal insufficiency usually manifests when the GC dose has been tapered to below physiological replacement dose. Patients may have fatigue, loss of appetite, nausea, vomiting, weight loss, arthralgias, myalgias, postural dizziness, or fainting episodes.[23] In severe cases, there may be delirium, tachycardia, hypotension, and hypovolemic shock due to an acute adrenal crisis, which is usually triggered by an acute medical or surgical illness. Unlike primary AI, hyperkalemia and hypercalcemia are uncommon in central AI.[21,23]

However, GC-induced AI may present across a spectrum from adrenal crisis to moderate-severe symptoms, mild non-specific symptoms, or an asymptomatic biochemical finding.[21,52] The presentation is usually less dramatic than primary AI and requires a high index of suspicion as non-specific symptoms may be attributed to underlying disease. Diagnosis can be established by a low baseline or stimulated serum cortisol.

The Endocrine Society (ES) provides guidelines for the management of primary AI and hypopituitarism[22,80] but there are no guidelines for the management of GC-induced AI. Symptomatic patients should be treated with physiological replacement doses of GCs.[52] MC replacement is not required in tertiary AI.[22] In asymptomatic patients, GCs can be tapered to below physiological dose or even discontinued; however, they need to be monitored periodically and counselled about stress doses.[50,52] This approach was considered safe with no hospitalisations for adrenal crisis in two studies that included patients of chronic obstructive pulmonary disease and RA.[30,81]

Physiological replacement doses of GC: One of the major aims of tapering GCs is to allow recovery of the HPA axis without precipitating symptoms of AI.[23] This is achieved by maintaining the patient on a physiological replacement dose of GCs, which do not suppress the HPA axis, till endogenous cortisol production resumes. GC replacement therapy should mimic normal daily cortisol production and its circadian rhythm.

The ES guidelines recommend hydrocortisone 15-25 mg/day for the management of primary AI with a midpoint of 20 mg/day, in 2-3 divided doses.[80] However, endogenous cortisol production is estimated to be approximately 5.7-7.4 mg/m^2 body surface area/day, equivalent to a hydrocortisone dose of 5-22 mg/day with a midpoint of 15 mg/day or prednisolone dose of 2.5 mg/day in a non-stressed state.[14,82] Long-term use of hydrocortisone >15 mg/day is associated with a greater risk of cardiometabolic disease and mortality.[17-18,82] Hydrocortisone is preferred for GC replacement during pregnancy; dexamethasone is avoided as it is not inactivated by the placenta. The dose requirements may increase by 20-40% during the latter half of pregnancy to mimic the physiological rise in free cortisol.[80]

Endogenous cortisol secretion follows a distinct circadian rhythm with the highest concentrations of serum cortisol in the morning (6-8 am), decreasing by 50% during the afternoon and then reaching a nadir at midnight. ACTH secretion rises again in the early hours of the morning to cause an early morning surge of cortisol.[21] Administration of physiological replacement doses of short- or intermediate-acting GCs in the

morning allows the late nocturnal ACTH surge and recovery of the HPA axis. Therefore, hydrocortisone 10-15 mg/day in two or three divided doses, with the largest dose given in the early morning and smaller doses in the afternoon and evening, is considered the drug of choice for GC replacement therapy.[23] Alternatively, prednisolone administered in doses of 2.5-5 mg/day in the morning may be used. Switching to hydrocortisone may assist in faster recovery of the HPA axis, but there are no head-to-head comparisons.[21] More potent and longer-acting steroids such as dexamethasone or betamethasone should be avoided.

Stress doses: Once patients are on a dose of ≤5 mg/day PE, they must be counselled about stress doses during any acute medical or surgical illness[52] and provided steroid alert cards. The dose of GCs should be increased to 2-3 times for a few days to prevent adrenal crisis. Parenteral hydrocortisone is recommended in case of persistent vomiting, unconsciousness, severe illness, or major surgery. The risk of perioperative adrenal crisis has been greatly minimised by routine perioperative GC cover in patients with AI.[83-85] But there is debate on the optimal dose and regimen of perioperative steroid cover.[85] A short course of hydrocortisone 25 to 100 mg may be administered intravenously and then rapidly tapered to the baseline oral dose of GC, depending on the degree of surgical stress.[84,85]

Long-term HPA suppression: Patients on long-term systemic GC therapy may develop atrophy of adrenal cortical cells resulting in prolonged AI. Broersen *et al*.[24] reported that 15% of patients on long-term oral steroids had persistent AI 3 years after discontinuing GCs. GC tapering in such patients is more difficult and needs to be slower over a more protracted course. A general rule is that recovery of adrenal function takes approximately 1 month for every month of HPA suppression. So, if GC use has been for over 1 year, it may take 9-12 months or even longer for the recovery of endogenous cortisol secretion. Dynamic testing should be performed to demonstrate HPA axis recovery before discontinuing GCs in patients on long-term therapy.[86] If HPA axis suppression is demonstrated, testing should be repeated at 6-12 months intervals.[86]

c. Glucocorticoid withdrawal syndrome

GWS was first described in the 1960s as a symptom complex that resembled AI, but patients responded normally to HPA axis testing.[87] It has been reported in patients on exogenous steroids as well as following treatment of endogenous Cushing's syndrome.[72,88,89] Patients may have a loss of appetite and weight, nausea, vomiting, muscle and joint pains, weakness, headache, lethargy, fever, flu-like symptoms, skin desquamation, and emotional lability, delirium, or psychosis. Symptoms may appear even above the physiological replacement doses of GCs.[5,14,72,90]

The exact cause of GWS is not known but it has been attributed to a state of relative GC receptor resistance, resulting in physical dependence on supraphysiological cortisol levels.[5,14,72] This may occur due to steroid-induced downregulation of mediators such as CRH, pro-opiomelanocortin (POMC), and central noradrenergic and dopaminergic signalling, and upregulation of cytokines and prostaglandins.[21,72]

It is imperative to differentiate GWS from AI. Table 7 elaborates on the differences between tertiary AI and GCS. The management of GWS includes a temporary modest increase in GC dose to the lowest dose at which symptoms improve, followed by slow tapering over a few months.[14,72] The syndrome is self-limiting and usually resolves in 6-10 months.[90] Supportive and symptomatic care should be provided including adequate diet, physical activity, use of non-steroidal anti-inflammatory drugs, and mild antidepressants.[89] Patients should be counselled about the temporary nature of these symptoms and the need to taper and withdraw GCs due to the risk of side effects.[72]

Conclusion

GCs can ameliorate debilitating symptoms in several inflammatory/immunological disorders but also have

Table 7: Clinical features and management of adrenal insufficiency and glucocorticoid withdrawal syndrome

Feature	Adrenal insufficiency	Glucocorticoid withdrawal syndrome
Anorexia, nausea, vomiting, fatigue, arthralgia, myalgia, hypotension, fever	Yes	Yes
Emotional lability, delirium, psychotic states	No	Yes
Circulatory collapse	Yes	No
Steroid dose	Symptoms occur at below physiological dose	Symptoms may occur at a supraphysiological dose
Basal morning cortisol	<3 µg/dl	>15 µg/dl
Peak cortisol after ACTH	<18 µg/dl	>18 µg/dl
Risk of adrenal crisis	Yes	No
Treatment	Long term glucocorticoid replacement needed in physiological doses, followed by slow wean over one year.	Maintain glucocorticoids at a dose that controls symptoms, followed by very slow wean over months.
	Consider HPA testing prior to discontinuation	Patient education and reassurance
Need for stress doses of GC during intercurrent illness	Yes	No

significant side effects including suppression of the HPA axis. Therefore, GCs are used in the lowest effective dose for the shortest possible time. However, prompt discontinuation of GC therapy predisposes patients to the risk of AI.

Moderate-high dose GC therapy should be tapered to prevent features of disease reactivation, AI or GWS. Initial tapering is done rapidly to near-physiological doses while watching for features of disease reactivation. Once close to the physiological dose, tapering is slower and at longer intervals to allow for recovery of the HPA axis. It is important to use short- or intermediate-acting GC preparations such as hydrocortisone or prednisolone in physiological doses, administered in the morning to mimic endogenous cortisol secretion. In patients at high risk of AI or if symptoms appear during tapering, the decision to further taper and discontinue steroids may be based on testing of HPA axis function using basal and/or stimulated serum cortisol.

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Author contributions

Gagan Priya conceptualized the review. Gagan Priya and Bashir Ahmad Laway carefully read through the abstracts and selected relevant articles that were then extensively reviewed. The first draft was prepared by Gagan Priya and edited by Bashir Ahmad Laway and A Mythili. Ganesh HK, Melinda Gupta and Deep Dutta reviewed the manuscript extensively and suggested appropriate modifications which were incorporated. The final draft was approved by all authors.

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Conflicts of interest

There are no conflicts of interest.

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