Adrenal Insufficiency Coalition
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United States of America

www.adrenalinsufficiency.org

Glucocorticoid tapering and adrenal suppression testing guide

This tapering guide is a compilation of medical information available and patient experience. References for the medical information are provided at the end of the document. This guide is not a substitute for advice and direction from your own physician. You may find this a useful discussion point if you are encountering difficulties in your attempts at tapering.

Research is lacking on the topic of glucocorticoid tapering and our guide hopes to provide parameters for patients and medical providers in an easy to use format that will keep patients safe during the process. Discuss any tapering program with your doctor before you begin. This is meant to be an aid in discussing tapering with your physician. Tapering must be done carefully to avoid both a reoccurrence of the underlying disease activity, and possible cortisol deficiency resulting from Hypothalamus-pituitary-adrenal, (HPA) axis suppression from glucocorticoid use.

Don't begin reducing steroids if you have an infection or are recovering from an illness. Primary and Secondary Adrenal Insufficiency patients may require a tapering program to return to physiologic levels after a prolonged illness, or in the presence of serious side effects such as hypertension or Cushing symptoms. Corticosteroid induced Secondary Adrenal Insufficiency patients may be put on a tapering program with the objective of restarting adrenal cortisol production and discontinuing steroid therapy.

Patients taking a physiological dose of 5 mg prednisone or 20 mg hydrocortisone per day or higher, for a period of three weeks or more should be considered at risk of HPA axis suppression. (1)

HPA axis suppression by exogenous glucocorticoid treatment is not trivial and has been associated with adrenal crisis in patients treated with systemic, inhaled or topical steroids. The route of administration of corticosteroids associated with adrenal suppression includes intra-articular, topical, ocular, rectal, inhaled and systemic. (2)

Physicians should be aware that patients successfully weaned from glucocorticoid therapy might need supplemental steroids during illness, trauma or surgery. It is recommended that patients continue to wear medic alert jewelry for up to one year.

When deciding on a tapering program, patient's general health status, stability of the disease being treated, and the drug regimen that has been used should be considered. Some patients may require more time adjusting due to coexisting conditions, medications, emotional stress and other factors. Programs should to be tailored to fit individual patient profiles. (1)

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Note for medical specialists who treat patients that require high-dose glucocorticoid therapy for a primary disease

The clinical experience of the physician is paramount. Specialists treating the primary diseases must monitor the clinical and physiologic responses to the taper for recurrence of the disease. Until the glucocorticoids are successfully tapered to physiologic equivalence of normal production, the dosage started and the rate of taper are entirely dependent on the disease response.

The following schedules for tapering may be too slow for a disease that only requires a short course of therapy, and therefore may contribute to the complication of secondary adrenal insufficiency. A general guideline is that recovery takes one month for every month of suppression, with up to 9 to 12 months when steroids are used for more than one year. There is a greater likelihood of permanent secondary adrenal insufficiency due to adrenal atrophy with the length of time suppressive doses are needed.

Physicians must also manage glucocorticoid-induced complications concurrently. For example, steroid induced type 2 diabetes will often require drug therapy which will need its own tapering while the steroids are tapered. Management of blood pressure, electrolytes, infections, skin breakdown, muscle atrophy, as well as emotional and psychiatric manifestations need to be addressed. Patients must be educated about specific features of the primary disease that are affected by the steroids.

The role of ACTH testing is to assess restoration of the normal physiologic response of the adrenal glands after a steroid taper. ACTH testing should be performed only on those patients who are more likely to have permanent secondary adrenal insufficiency, where the test results will confirm or deny the need for permanent replacement therapy, or to monitor recovery during the final phases of the tapering program. Understanding that a gradual further tapering is necessary to overcome the slow recovery of the hypothalamus-pituitary-adrenal axis should be emphasized. During this phase, mild to moderate adrenal insufficiency symptoms must be tolerated by the patient if clinically possible.

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Corticosteroid induced Secondary Adrenal Insufficiency patients tapering with the objective of restarting adrenals require special consideration.

The goal is to use a rate of change that will prevent both recurrent activity of the underlying disease and manage symptoms of cortisol deficiency due to persistent HPA suppression. (1) This regimen will generally prevent symptoms of cortisol deficiency. At some point, however, many patients with rheumatic diseases complain of recurrent symptoms of the underlying disease. In this setting it may be difficult to distinguish between mild symptoms of glucocorticoid withdrawal or recrudescence of the underlying rheumatic disease. (1)

If the symptoms are not major, it is recommended to treat the symptoms with a nonsteroidal anti-inflammatory drug (NSAID) or other analgesic for seven to ten days. (**Caution,** NSAID's are not appropriate for some primary diseases, for example asthma or Crohn's disease) Resolution of symptoms during this period of time suggests pseudorheumatism. If the symptoms do not subside within this time frame, increase the prednisone dose by 10 to 15 percent (or the next convenient mg tablet increment) and maintain that dose for two to four weeks. If the symptoms resolve, the tapering regimen can be resumed, using two to four weeks between decrements rather than one to two weeks. (1)

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If this modest increase in dose is not sufficient to alleviate symptoms it is recommended to double the prednisone dose. The disease flare is allowed to subside and the taper can be reinstituted at a slower rate (eg, once monthly) or at smaller decrements, (eg, one half of the original decrement). (1)

Incremental change is inappropriate if life-threatening flares occur (as in acute recurrence of lupus nephritis, severe hemolysis, acute polymyositis, or vasculitis) In this setting, a return to the original, highest dose of steroids should be instituted. (1)

Methods for tapering

Symptoms are milder at high cortisol amounts and intensify when milligrams are reduced below a certain point. A longer adjustment period is recommended at lower doses.

Percentage method:

This method lowers dosage by a relatively stable decrement of 10 to 20 percent, while accommodating convenience and individual patient response.

- 5 to 10 mg every one to two weeks from an initial dose above 40 mg of prednisone per day.

For example, a patient taking 55 mg's of prednisone per day would lower dosage to 45 mg or 50 mg depending on the individual patients' profile. The patient would then stay on that dose for one to two weeks based on their response to the lower amount.

- 5 mg every one to two weeks at prednisone doses between 40 and 20 mg per day.
- 2.5 mg every two to three weeks at prednisone doses between 20 and 10 mg per day.
- 1 mg every two to four weeks at prednisone doses between 10 and 5 mg per day.
- 0.5 mg every two to four weeks at prednisone doses from 5 mg per day and lower.

This can be achieved by alternating daily dose, e.g., 5 mg day one, 4 mg day two. (1)

A patient taking hydrocortisone using the percentage method would decrease by the following dosages.

- 10 to 20 mg every one to two weeks from an initial dose of 100 mg hydrocortisone or above per day.

For example, a patient taking 100 mg hydrocortisone would lower dosage to 80 or 90 mg depending on the individual patients' profile. The patient would then stay on that dose for one to two weeks depending on their response to the lower amount.

- 10 to 7.5 mg every one to two weeks at hydrocortisone doses between 100 and 75 mg per day.
- 7.5 to 5 mg every two to three weeks at hydrocortisone doses between 75 and 45 mg per day.
- 5 to 2.5 mg every two to four weeks at doses 45 mg and below per day.

We are not aware of any evidence-based data related to glucocorticoid tapering on an alternate-day regimen. However, we are providing this method based on patient experience. Patients who encounter difficulties adjusting on the percentage method may have better results using this version of alternate day dosing.

Although the alternate day method is effective in most rheumatic diseases, patients with rheumatoid arthritis often do not tolerate it well. (1)

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Alternate day method:

- **Week 1.** Alternate total daily dosage by 2.5 mg hydrocortisone. For example; Day 1-65 mg, Day2-62.5, Day 3-65, Day 4-62.5 Day 5-65, Day 6-62.5 Day 7-65.
- **Week 2.** Stay on the lower dose. Using the hydrocortisone example above, the patient would stay on 62.5 mg's for one week to give the body time to adjust.
- **Week 3.** Return to alternating daily by 2.5 mg as in week one. Using the example above, the patient would start week three by taking 62.5 mg, and alternate with a 60 mg dose.
- **Week 4.** Stay on the lower dose to give patients' body time to adjust. In the example above patient would stay on 60 mg's for the entire week.

A patient taking prednisone would use decrements of 1 or 2 mg on the alternate day method. For example, a patient taking 25 mg prednisone per day would lower dosage to 24 or 23 mg on alternate days during week one. The patient would remain on the lower amount during week two.

This program can be tailored to individual needs by shortening or lengthening the amount of time spent in each stage depending on the patients' response. During week one the patient may experience alternating good and bad days. In week two the patient should feel a gradual lessening of symptoms. Don't begin lowering again until the patient has a minimum of two good days in a row.

Glucocorticoid equivalents

Prednisone		Cortisone Acetate		Dexamethasone		Hydrocortisone
5 mg	=	25 mg	=	0.75 mg	=	20 mg

Testing guide for SAI patients attempting to restart cortisol production

The progression of any tapering program relies on the clinician's evaluation of the patients' response. The appropriate endpoints are the patients' signs and symptoms. (1)

> The role of ACTH testing is to assess restoration of the normal physiologic response of the adrenal glands after a steroid taper. ACTH testing should be performed only on those patients who are more likely to have permanent secondary adrenal insufficiency, where the test results will confirm or deny the need for permanent replacement therapy, or to monitor recovery during the final phases of the tapering program.

The response to administration of synthetic adrenocorticotropic hormone (ACTH) [cosyntropin] is the preferred method to assess adrenocortical function. Testing for HPA axis function is appropriate when patients are using <5 mg per day of prednisone or equivalent and there is difficulty reducing the dose further because of non-disease related symptoms. In most patients who require testing, we recommend the low dose (1 mcg) ACTH stimulation test for evaluation. (3)

Some studies indicate that the low dose test can detect partial adrenal insufficiency (as can occur with the chronic use of inhaled glucocorticoids or early adrenal destruction by infectious or autoimmune disease) that may be missed by the standard high-dose test, which provides a supraphysiologic stimulus that can stimulate a diseased adrenal gland that still has some residual function. (5)

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Hydrocortisone should be discontinued the evening before testing. Testing can be performed 24 hours after the last dose of Prednisone. (1) Dexamethasone does not affect cortisol tests.

Full recovery of the adrenals may take four to twelve months. Some may never recover due to adrenal atrophy. (1) A definitive diagnosis of adrenal suppression due to steroid use is important. If the hypothalamus or pituitary is damaged restarting normal function will be unsuccessful. (1)

A baseline plasma ACTH concentration may be used to rule out adrenal insufficiency due to low ACTH production if the physician deems it necessary.

All glucocorticoids must be discontinued before testing ACTH levels. Hydrocortisone should be discontinued the evening before testing. Testing can be performed 24 hours after the last dose of Prednisone or Dexamethasone. (1)

ACTH basal plasma

- Reference range, 6 to 48 pg/mL (4) {Blood test results should always be interpreted using the reference range provided by the lab performing the test.}

8:00 am Cortisol basal test parameters

- Cortisol serum or plasma, adults 8.0 to 19 ug/dL. (4) {Blood test results should always be interpreted using the reference range provided by the lab performing the test.}

Several protocols have been used to assess the response to exogenous corticotropin (ACTH). The agent used is synthetic ACTH (1-24) (cosyntropin), which has the full biologic potency of native ACTH (1-39). Short (one hour or less) tests involve administration of a single dose in a "low" or "high" concentration and can be performed on an outpatient basis. Both tests result in supra-physiological plasma ACTH concentrations: about 60,000 pg/mL (1320 pmol/L) after the standard high-dose ACTH test and about 1900 pg/mL (41.8 pmol/L) after the low-dose test. There are no untoward side effects. Allergic reactions are almost unheard of with cosyntropin. Prolonged ACTH stimulation tests are seldom performed because measurements of plasma ACTH in conjunction with the low-dose ACTH test provide the necessary information. (3)

There is controversy regarding whether the low-dose test is superior to the high-dose ACTH stimulation test. A meta-analysis including 1021 patients studied with the high-dose test and 402 patients with the low-dose test found similar sensitivities, 57 percent and 61 percent, respectively, for the diagnosis of secondary adrenal insufficiency. The positive and negative likelihood ratios had overlapping confidence intervals, further suggesting that the two tests perform similarly. This information conflicts with earlier smaller studies suggesting that the low-dose test is more sensitive. The low-dose test can detect partial adrenal insufficiency (as can occur with the chronic use of inhaled glucocorticoids or early adrenal destruction by infectious or autoimmune disease) that may be missed by the standard high-dose test, which provides a supraphysiologic stimulus that can stimulate a partially diseased adrenal. It is possible that differences in the study populations or cortisol assays and criteria for interpretation may account for these differences. Further studies are needed to determine whether the low-dose test is preferable in specific clinical circumstances. (3)

The advantage of the high-dose test is that the cosyntropin can be injected IM as well as IV, because pharmacologic plasma ACTH concentrations are still achieved. The low-dose test has not been evaluated after IM injection and may not provide valid results by this route. (3)

Data indicates that the low-dose test (like the 250 mcg test) is not valid if there has been recent pituitary injury, and supports the conclusion that a 30-minute serum cortisol concentration less than 18 mcg/dL (500 nmol/L) indicates impaired adrenocortical reserve. This is the most conservative current criterion and its use is recommended until more data on the 1 mcg ACTH test becomes available. (3)

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Plasma ACTH can also be measured in the basal sample, as in all ACTH stimulation tests. In healthy individuals, cortisol responses are greatest in the morning, but in patients with adrenal insufficiency, the response to cosyntropin is the same in the morning and afternoon. Thus, it is recommended that the test be done in the morning to minimize the risk of misdiagnosis in a normal individual. This dose stimulates maximal adrenocortical secretion up to 30 minutes post-injection and in normal subjects results in a peak plasma ACTH concentration about twice that of insulin-induced hypoglycemia. (3)

ACTH stimulation tests

- A standard high-dose test consists of measuring serum cortisol before, 30 and 60 minutes after intravenous (IV) injection of 250 mcg of cosyntropin; at this high dose, it can also be injected intramuscularly (IM).
- The low-dose ACTH test is performed by measuring serum cortisol before and 30 minutes after IV injection of 1 mcg cosyntropin.
- The current criteria used to indicate normal adrenal function are a minimum serum cortisol concentration ≥18 (low-dose test) or 18 to 20 (high-dose test) mcg/dL (500 to 550 nmol/L) before or after cosyntropin injection.
- A lower cutoff is used (≥16 mcg/dL [440 nmol/L]) if high-dose cosyntropin is administered IM. (3)

Previous criteria that required a minimum increment in serum cortisol (eg, 3.3 mcg/dL [90 nmol/L]) are invalid, because individuals who have a high basal serum cortisol concentration, due either to normal circadian rhythmicity or acute stress, may be nearly maximally stimulated and unable to increase cortisol secretion further. In addition, approximately 20 percent of normal subjects with high-normal basal serum cortisol concentration have little or no rise after ACTH. It is therefore important to obtain both baseline and post-ACTH cortisol samples for accurate assessment of adrenal function. (3)

Furthermore, individuals may meet criteria for serum cortisol increment (eg, 3.3 mcg/dL [90 nmol/L]) with absolute values that clearly indicate adrenal insufficiency. As an example, an increase from 2 mcg/dL (55 nmol/L) to 5.3 mcg/dL (145 nmol/L) would not indicate that the patient had normal hypothalamic-pituitary-adrenal (HPA) function, nor would an increase from 20 mcg/dL (550 nmol/L) to 22 mcg/dL (607 nmol/L), an increment of only 2 mcg/dL (55 nmol/L), indicates that the patient had adrenal insufficiency. (3)

Some studies have used higher cutoff points (minimum serum cortisol 21.7 to 25.4 mcg/dL [600 to 700 nmol/L]) for the diagnosis of adrenal insufficiency, based upon results in patients known to have an abnormal response to insulin. However, these are not clinically useful criteria, as up to 43 percent of normal individuals would be diagnosed as having adrenal insufficiency when these criteria are used. (3)

Cortisol assays

Variability in cortisol assays creates an additional problem with setting criteria for a normal response to ACTH that apply to all centers. Two studies comparing cortisol results obtained with different assays showed a positive bias of radioimmunoassays and immunofluorometric enzyme assays of 10 to 50 percent compared with a reference value obtained using isotope dilution gas chromatography-mass spectrometry. As a result, in one study, depending on the combination of assay and criterion used, between 0 and 100 percent of healthy volunteers would be considered to have a normal response to ACTH. This illustrates the difficulty of interpreting cortisol responses that are close to the cut-off point. (3)

- High cortisol-binding globulin (CBG) levels in women using oral contraceptives (OCs) may falsify interpretation of ACTH test; they should be discontinued prior to testing to avoid underestimating hypocortisolism in these patients. (3)
- ACTH stimulation tests are not valid to evaluate hypothalamic-pituitary-adrenal (HPA) function if there has been a recent pituitary injury and insulin-induced hypoglycemia should be used in these circumstances. (3)

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Patient self-management tips

Be prepared and stay safe:

1. Create a crisis plan with your doctor. Visit our website emergency information page https://www.adrenalinsufficiency.org/emergency/
2. Print out crisis literature in case you need to go the emergency room.
3. Go slow and wait to see how your body reacts.
4. Wear your medic alert jewelry.
5. Keep your injection kit in plain sight with written instructions. Be sure you and someone close to you knows when and how to use it.
6. Stay hydrated
7. Monitor your blood pressure.
8. Know your individual electrolyte needs and supplement appropriately.
9. Blood sugar can fluctuate with cortisol levels. Eat frequent small meals.
10. Keep healthy snacks on hand for when cravings strike.
11. Don't be afraid to take more steroids temporarily if your symptoms become overwhelming. Taking more may keep you from having a crisis. You can begin lowering again when you are stable. Decreasing milligrams safely takes time.

Low cortisol symptoms:

- Headache
- Body ache
- Nausea
- Fatigue
- Sweats and or chills
- Racing heart
- High or low blood pressure
- Dizziness on standing
- Depression/weepiness
- Anxiety
- Confusion

You may experience some or all of these symptoms. Each person is different. Keeping a daily journal to track dosage amount and time, symptoms and blood pressure is helpful.

When to seek help:

Call your doctor and go to the emergency room if you experience these symptoms.

- Fever
- Persistent diarrhea
- Vomiting
- Severe abdominal pain

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