

Exogenous Cushing's Syndrome and Glucocorticoid Withdrawal

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The first therapeutic use of glucocorticoids in 1948 resulted in dramatic clinical improvement in a patient's severe rheumatoid arthritis. Almost immediately, however, the potential adverse effects of exogenous steroid administration became evident [1]. Cushing's syndrome resulting from exogenous glucocorticoids now is well-recognized and documented. It also has been clear for some time that the discontinuation of chronic steroid use is fraught with difficulties.

Clinical presentation and diagnosis

For the most part, exogenous Cushing's syndrome presents with the same signs and symptoms as spontaneous Cushing's syndrome. There are nevertheless a few important differences in presentation [2]. Many patients who develop iatrogenic Cushing's syndrome do so after receiving high doses of steroid over long periods of time. Therefore, the clinical manifestations can be more striking than those of spontaneous Cushing's syndrome, which tend to occur more gradually. The traditional stigmata include weight gain, usually presenting as central obesity with redistribution of body fat to truncal areas and the appearance of dorsocervical and supraclavicular fat pads and the classic moon face. Plethora, easy bruising, thin skin, striae, myopathy, and muscle weakness (particularly proximal muscles) can be seen. Patients are susceptible to poor wound healing and increased incidence of infection [3] and atherosclerotic disease. The psychologic adverse effects of steroid treatment can be quite severe and include depression and psychosis.

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Although the incidence of hypertension in chronic steroid treatment is increased, these patients may have relatively less hypertension and hypokalemia compared with patients who have spontaneous Cushing's syndrome depending on the mineralocorticoid activity of the steroid they are taking. Along the same lines, patients who have iatrogenic Cushing's syndrome are unlikely to have significant increases in androgens, and therefore they have less hirsutism and other virilizing features than those who have spontaneous disease. Patients who have iatrogenic Cushing's syndrome may have an increased incidence of glaucoma and other ocular disease such as posterior subcapsular cataracts [4]. In addition, avascular necrosis is more common in iatrogenic than in spontaneous Cushing's syndrome [5]. Although rare, spinal epidural lipomatosis occurs primarily in the setting of exogenous glucocorticoid use [6].

Osteoporosis is a common and severe adverse effect of glucocorticoid excess and one of the major limitations to long-term glucocorticoid therapy. A significant number of patients on long-term steroid therapy will have at least some loss of bone density [7,8], and oral and inhaled corticosteroid use are associated with increased bone fractures [9,10]. The bone loss caused by glucocorticoids tends to be in trabecular bone as opposed to cortical bone. Therefore, most loss is in the vertebrae and ribs of the axial skeleton.

In many cases, the diagnosis of exogenous Cushing's should be fairly obvious in the setting of treatment with high-dose glucocorticoids. The diagnosis requires, first and foremost, clinical suspicion. This can be more difficult in cases caused by local delivery of steroid (eg, intra-articular and inhaled therapy) when clinicians might be less aware of Cushing's syndrome as a possible adverse result of treatment. Once the possibility of exogenous Cushing's syndrome is recognized, biochemical confirmation of the diagnosis is usually straightforward. The most striking biochemical finding is a suppressed endogenous cortisol level. Administration of hydrocortisone (cortisol) interferes with measurement of endogenous cortisol; in fact many synthetic glucocorticoids, with dexamethasone being a rare exception, can cross-react to some extent with standard cortisol assays [11]. In the authors' clinical experience, this has been especially problematic with prednisone. Nonetheless, in most cases of exogenous Cushing's syndrome, the morning serum cortisol is found to be remarkably low, especially given the setting of Cushingoid symptoms. Corticotropin (ACTH) levels also should be relatively low, as pituitary production will be suppressed by exogenous steroids. The suppression of ACTH leads to atrophy of the adrenal cortex, and thus stimulation with cosyntropin should result in a decreased or absent plasma cortisol response. In some cases, diagnosis of exogenous Cushing's syndrome has been aided or confirmed by measurement of the glucocorticoid in question, although this may require specialized laboratory analysis [12,13].

Most cases of exogenous Cushing's syndrome are iatrogenic. Glucocorticoids are used in many different forms for several neoplastic, inflammatory, and autoimmune disorders. Many of these conditions lead to high-dose or

chronic steroid use that can result in Cushingoid effects. Not all cases of exogenous Cushing's syndrome come from prescribed or therapeutic use of glucocorticoids, however. It is important to be aware that numerous cases of factitious Cushing's syndrome resulting from surreptitious use of steroids have been reported. Villaneuva et al described four cases of Cushing's syndrome seen within a 2-year period in their practice caused by surreptitious glucocorticoid use [12]. As with many such patients, only one of those confronted was willing to admit to his or her surreptitious glucocorticoid use. Another situation, which might be termed occult Cushing's syndrome, is that in which a patient unknowingly receives glucocorticoid therapy. This can occur in the form of alternative remedies which, upon inspection, contain glucocorticoids. A case of Cushing's syndrome caused by an herbal remedy containing betamethasone was described recently [13]. In some communities, over-the-counter and traditional curatives contain significant amounts of potent glucocorticoids, or glucocorticoids may be prescribed by practitioners for questionable diagnoses. In a recently described case, a 32-year-old Vietnamese woman presented with an unexpected opportunistic infection [14]. Only after extensive investigation did the patient remember that she had received twice-daily subcutaneous injections of an unknown substance over 8 weeks during a visit to Vietnam. In another case, a neonate became Cushingoid after continuation for 2 months of betamethasone drops that were prescribed for an upper respiratory infection [15].

Megestrol acetate, a progestational agent used in the management of AIDS cachexia and in the treatment of breast, uterine, and prostate cancers, has been identified as having glucocorticoid activity. Megestrol acetate has been implicated in causing several cases of Cushing's syndrome, adrenal insufficiency, and hyperglycemia [16,17]. Because it is not commonly considered to have glucocorticoid activity, physicians prescribing this agent may not be aware of the associated risks. To the authors' knowledge, megestrol acetate and a related agent, medroxyprogesterone, are the only two medications not intended for therapeutic use as glucocorticoids that have glucocorticoid activity significant enough to cause Cushing's syndrome.

Factors in the development of Cushing's syndrome

Steroids with glucocorticoid activity are available in many different preparations with different modes of delivery. Glucocorticoids generally are absorbed well from various sites of application. Although the use of topical, intra-articular, or aerosol therapy has the advantage of allowing more targeted therapy and therefore theoretically fewer systemic adverse effects, every mode of exogenous glucocorticoid delivery has been implicated in the development of Cushing's syndrome.

All available forms of steroids with glucocorticoid activity are capable of producing Cushing's syndrome. Attempts at separating anti-inflammatory

from metabolic effects with synthetic steroids have not been successful. The naturally occurring glucocorticoids cortisone and cortisol, and synthetic derivatives, including prednisone, prednisolone, methylprednisolone, dexamethasone, betamethasone, triamcinolone, and others are used clinically and have the potential for adverse effects. It is difficult to say which of these agents is most likely to cause Cushing's syndrome, because so many factors are involved in the generation of this disorder. Relevant properties of the steroids themselves include the formulation used, pharmacokinetics, affinity for the glucocorticoid receptor, biologic potency, and duration of action [18]. Pharmacokinetic factors include binding affinities to cortisol-binding globulin (CBG) and other plasma proteins, metabolic inactivation, and plasma half-life. Most synthetic glucocorticoids do not have significant binding to CBG and bind instead to albumin or circulate as free steroid. In contrast, synthetic glucocorticoids have a much higher affinity for the glucocorticoid receptor than cortisol itself. Potency and duration of action also are affected by rates of absorption and metabolism. Traditional assessments of potency generally have not accounted for these factors, and so published estimates of glucocorticoid activity can be taken as estimates only [18].

Whatever specific agent is involved, the development of Cushingoid signs and symptoms generally is related to dose and duration of treatment, so that even lower-potency agents with short half-lives (hydrocortisone and cortisone) can cause Cushingoid effects if given in adequate amounts with frequent delivery. Predicting doses and time courses at which Cushing's syndrome will develop is complicated by some of the issues just discussed (including the different potencies of the various glucocorticoids available), the different formulations and modes of delivery, and the fact that individual patients have different levels of sensitivity to glucocorticoids.

Some manifestations of glucocorticoid excess occur relatively quickly. Psychiatric effects, insomnia, and increased appetite can occur within hours. Generally, a Cushingoid appearance takes weeks or even months to develop, as does development of osteoporosis. With regard to dose, again there is tremendous variability between individuals. Although supraphysiologic doses usually are required before patients manifest significant Cushingoid effects, the authors' clinical experience reveals that some patients, in particular those on glucocorticoids following renal transplant, can develop Cushingoid appearance with chronic administration of as little as 5 mg/d of prednisone.

Specific modes of delivery

Oral corticosteroid therapy remains a mainstay of treatment of many inflammatory and autoimmune disorders. In the United States, prednisone is probably the most commonly used oral corticosteroid, at least for long-term use. The potential for development of Cushing's from oral steroid

treatment is so well documented that most physicians are aware of the dangers. Nonetheless, there are many instances of patients who have developed unfortunate sequelae from prolonged use, most commonly in the setting of chronic disorders. In this setting, a balance must be struck between treatment of the underlying disorder and avoidance of adverse effects. In the authors' experience, many patients who present with iatrogenic Cushing's syndrome either have been lost to follow-up or treated with steroids for unclear diagnoses in the first place. Therefore, ongoing monitoring of patients and careful attention to the actual therapeutic efficacy of the steroid treatment is essential.

Although low doses of over-the-counter topical glucocorticoids are used commonly and safely, it is known that systemic absorption of steroids from topical preparations does occur and that at higher doses or with more potent preparations both adrenal axis suppression and Cushing's syndrome can occur. Breakdown of skin integrity may be an important factor. A recent report in the dermatologic literature described the case of an 11-year-old boy who has psoriasis and presented with stigmata of Cushing's syndrome after 6 months of treatment with topical halobetasol propionate and betamethasone dipropionate [19]. Signs and symptoms resolved after cessation of steroid treatment. In another case, a 72-year-old woman developed manifestations of Cushing's syndrome after long-term topical therapy with clobetasol propionate ointment. She also suffered signs of adrenal insufficiency after tapering the steroid dose and developing a urinary tract infection [20]. A 4-month-old baby developed Cushing's syndrome after his mother supplemented prescribed hydrocortisone cream with clobetasol cream [21]. Important factors in this case included use of a high-potency steroid in ointment form (as opposed to cream or lotion) and use of occlusive dressings, both of which increase the potency of topical steroids. Another case of Cushing's syndrome caused by topical steroid application was exacerbated by additional injection of periocular corticosteroids [22]. There also has been concern that over-the-counter combination preparations of steroids and antifungals may lead to unsupervised and inappropriate use of topical steroids [23]. A severe case of Cushing's syndrome was attributable to a 4-year period of Lotrisone (betamethasone dipropionate and clotrimazole) use for self-diagnosed vaginal candidiasis [24].

It once was thought that treatment with inhaled glucocorticoid therapy was relatively risk-free, because it was believed that little, if any, of the medication was absorbed systemically. It is now clear that significant systemic effects of inhaled corticosteroids can be seen, although fewer than with equivalent oral doses. These effects are dose-related and come in the form of adrenal suppression and Cushingoid stigmata, particularly bone, ocular, and skin manifestations [25]. Recent literature provides specific examples of asthmatic patients who developed both Cushing's syndrome and adrenal suppression [26,27]. In both of these cases, patients had been

treated with fluticasone propionate, the most potent of the inhaled steroids currently available. This same agent has been implicated in causing adrenal insufficiency in several children treated for asthma [28,29].

Many reported cases of Cushing's syndrome resulting from inhaled glucocorticoids involved interactions with other medications. Several cases have been reported involving patients who had been on inhaled budesonide and developed Cushing's syndrome after the addition of itraconazole [30]. This has been a problem for young patients who have cystic fibrosis, for whom both inhaled corticosteroids and itraconazole have become a mainstay of therapy for management of allergic bronchopulmonary aspergillosis. At least two cases of such patients developing Cushing's syndrome have been described [31,32]. Itraconazole is a strong inhibitor of hepatic CYP3A, the same cytochrome P450 enzyme system involved in metabolism of most (and perhaps all) steroids. Therefore, it is believed that interference with P450 metabolism prolonged the systemic half-life of the glucocorticoid in these patients. The same mechanism is implicated in recently reported cases of patients who have HIV found to develop Cushing's syndrome while taking fluticasone propionate and ritonavir, another potent P450 inhibitor. One of the patients initially was diagnosed with HIV lipodystrophy [33,34]. Thus far, itraconazole and ritonavir have been the only P450 inhibiting agents implicated in Cushing's syndrome in the literature. It is plausible, however, that any agent that interferes with the cytochrome P450 system would have the potential to interfere with glucocorticoid metabolism and lead to the development of Cushing's syndrome.

Another therapeutic issue that has arisen most commonly in children is development of Cushing's syndrome and adrenal insufficiency related to the use of nasal steroid preparations. Typically, intranasal betamethasone has been the medication involved, but at least one case has been described involving dexamethasone [35,36]. Cases of Cushing's syndrome and adrenal suppression involving children have been used as warnings of the importance of carefully tailoring doses to children. Nasally induced Cushing's syndrome has been seen in adults also, with a recent case of a 28-year-old woman who developed Cushing's syndrome while using betamethasone nasal drops over a 2-year period. It was found that the patient had been taking doses far beyond those prescribed by her physician [37].

Several forms of injectable steroid therapy have been associated with signs and symptoms of Cushing's syndrome. Intravenous therapy is used almost exclusively for short-term treatment in emergency room or hospital settings. Therefore, this form of therapy is unlikely to result in Cushing's syndrome, although some patients do experience temporary adverse psychiatric effects, and certainly diabetic patients can experience blood glucose derangements even from very short courses of high-dose intravenous steroids.

Cushing's syndrome has been reported in patients taking relatively high doses of intra-articular glucocorticoids or with accidental overdose of these

injections [38,39]. Pediatric cases of intra-articular and intradermal steroid injections causing Cushing's syndrome have been reported [40]. In addition, several cases of children who had received intralesional injections into keloid scars or other wounds (such as burns) have been described in the literature [41]. One of the remarkable features of these cases is the duration of Cushingoid symptoms (up to 9 months). It is proposed that the relatively avascular nature of keloids and other scars can lead to very slow absorption and thus prolonged systemic effects of steroids injected into these sites. Absorption of steroids injected into intra-articular sites can be delayed. In one case, extreme overdose likely made absorption the rate-limiting step in systemic drug disposition.

Cases of Cushing's syndrome from paraspinal depot injections also have been reported [42], and in two cases, local epidural steroid injection has led to development of spinal epidural lipomatosis [43].

Additional unusual cases that have been reported in the literature include Cushing's syndrome induced by serial occipital nerve blocks containing triamcinolone [44] and acute adrenal crisis in a patient after withdrawal of rectal steroids [45].

Issues affecting withdrawal from steroid therapy

The discontinuation of steroid therapy can present a significant clinical challenge. Three issues exist with regard to withdrawal from steroid therapy: (1) the possibility of suppression of the hypothalamic–pituitary–adrenal (HPA) axis and resulting secondary adrenal insufficiency, (2) the possibility of worsening of the underlying disease for which steroid therapy was initiated, and (3) a phenomenon, sometimes called the steroid withdrawal syndrome, in which some patients encounter difficulty, and even significant symptoms, discontinuing or decreasing steroid doses despite having demonstrably normal HPA axes.

Treatment with supraphysiologic doses of corticosteroids at levels commonly used for treatment of inflammatory and autoimmune disorders will suppress the HPA axis. In fact, some level of suppression occurs even at physiologic doses, as ACTH secretion is decreased by the addition of exogenous steroids. At this level, however, the suppression does not appear to be clinically significant. As with exogenous Cushing's syndrome, the exact doses and duration of treatment required for significant HPA axis suppression vary between individuals. After studying the effects of various doses and different durations of treatment in glucocorticoid-treated patients, Schlaghecke et al concluded that neither dose, duration, nor basal plasma cortisol concentrations could be used reliably to predict pituitary-adrenal function in these patients [46]. Some patients who had been taking less than the equivalent of 5 mg/d of prednisone were found to have a suppressed or absent response to corticotropin-releasing hormone (CRH) stimulation. Conversely, some patients who had been on very high doses, equivalent to

more than 25 mg/d of prednisone, had a normal response to CRH testing. It was not clear what the time course of treatment was that corresponded with these doses. In another study, patients who had been treated with the equivalent of 25 mg/d of prednisone for 5 to 30 days were given a low-dose (1 μ g) corticotropin stimulation test [47]. Forty-five percent of the subjects were found to have a suppressed response immediately after discontinuation of steroids. All but two of these patients had recovered a normal response within 14 days. The remaining two patients continued to have a suppressed response even after 6 months. Overall, this study found no correlation between HPA axis suppression and the duration or dose of glucocorticoid treatment.

Some authors feel that glucocorticoid courses of less than 3 weeks duration will not lead to HPA axis suppression, no matter what the steroid dose, and therefore patients can be discontinued from steroid therapy immediately and safely up to that point [18]. Others believe that at relatively high doses, significant HPA suppression can occur after as little as 5 days, but that at physiologic doses, suppression is unlikely to occur in less than 1 month [48].

Despite efforts to understand the effects of long-term and high-dose steroid treatment on the HPA axis, clinicians remain unable to predict exactly which patients will have HPA suppression [49]. The actual risk of clinically significant adrenal insufficiency in patients who have been on long-term glucocorticoid therapy, however, may be somewhat overstated. A double-blind study of patients on long-term supraphysiologic glucocorticoid therapy with secondary adrenal suppression who underwent moderate to major surgical procedures found that those patients who underwent surgery on their usual dose of corticosteroids had no more complications than those given the traditional stress-dose steroids during the perioperative period [50]. Conversely, there certainly have been patients whose inability to mount an appropriate stress response after long-term glucocorticoid therapy had tragic results. Therefore caution on the side of short-term stress-dose therapy still seems prudent.

In past studies, tremendous individual variation has been found in rates of recovery from HPA axis suppression. Livanou et al [51] found that doses greater than 7.5 mg/d of prednisone (or equivalent) were more likely to result in prolonged suppression than were lower doses. There seemed to be no correlation between duration of therapy and time to recovery of the HPA axis. This study looked only at periods greater than and less than 18 months, however, and therefore, it might have missed some crucial threshold duration [51].

Controversy continues over which of the available tests of HPA function best correlates with a patient's actual ability to handle physiologic stress and which should be used in clinical practice. The gold standard is the insulin tolerance test. This is a cumbersome and somewhat risky test that needs to be performed in a monitored setting and is rarely done. The ACTH or

cosyntropin stimulation test using either 1 µg [52] or 250 µg doses is a simple test that can be done easily in the office setting. There is doubt, however, that either of these is sensitive or specific enough to screen for secondary adrenal insufficiency [53]. The CRH-stimulation test is advocated by many as a relatively simple, safe test that can be performed in the office setting, although it is very expensive. The overnight metyrapone test is a test of the entire HPA axis, and although less simple than the cosyntropin test, it usually can be done with the patient at home.

Patients who have underlying inflammatory or autoimmune disorders sometimes can experience worsening of their condition as the steroid dose is decreased. This should be dealt with by increasing the glucocorticoid dose back up to a level that allows control of the underlying disease, unless increase in the glucocorticoid dose is contraindicated for some other reason (such as severe Cushingoid symptoms or osteoporosis with fractures). Only when the underlying disease is quiescent should another attempt be made to begin withdrawing the glucocorticoid. Seeking auxiliary forms of treatment for the underlying disease can aid in the ability to begin withdrawing steroid therapy.

The previously mentioned steroid withdrawal syndrome is understood poorly. It is characterized by lethargy, malaise, anorexia, myalgias, headache, fever, and can even be accompanied by desquamation of the skin. Upon testing, patients who have this syndrome can be shown to have a normal HPA axis and therefore are not suffering from adrenal insufficiency [18]. This syndrome is rare, and the exact etiology is unknown. It is important to recognize that many of these patients have become psychologically dependent upon their steroids. Whatever the cause of their symptoms, these patients do not appear to be at risk for collapse of the cardiovascular system or other extreme effects of adrenal insufficiency. Therefore, the choice of whether to continue replacement doses of steroids must be decided between the physician and the patient.

Withdrawal schemes

Given how common the use of steroid therapy is, it is surprising that there are no controlled clinical trials of methods for withdrawal from glucocorticoids. A recent systematic review examined withdrawal of therapy in patients who have chronic medical disorders but found insufficient evidence to recommend any particular withdrawal regimens [54].

Withdrawal plans therefore are based on the dual goals of treating patients who have the lowest possible steroid dose (or complete discontinuation of therapy) in order to avoid adverse effects of prolonged steroid therapy while at the same time avoiding the potential consequences of adrenal insufficiency.

Traditionally, withdrawal schemes (Fig. 1) begin by reducing the glucocorticoid incrementally from supraphysiologic to physiologic doses.

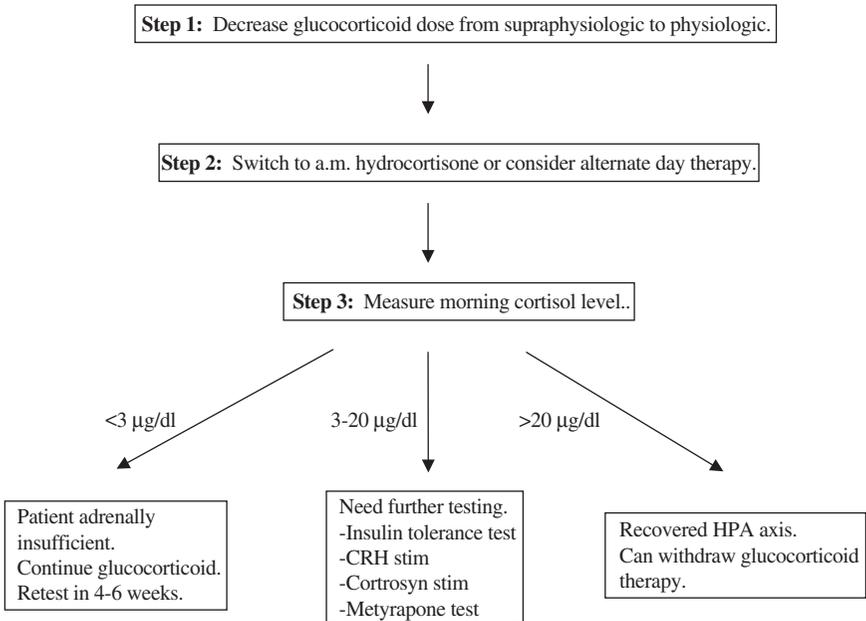


Fig. 1. A suggested algorithm for withdrawal from chronic steroid therapy. Physiologic doses of glucocorticoid are equivalent to prednisone 5 to 7.5 mg/d or hydrocortisone 15 to 20 mg/d.

The physiologic dose is approximately 5 to 7.5 mg a day of prednisone, 15 to 20 mg a day of hydrocortisone, or the equivalent. During this phase of withdrawal patients are not at risk for adrenal insufficiency, nor do most experience symptoms of withdrawal syndrome. Therefore, the greatest concern at this time will be exacerbation of underlying disease.

Once a patient is on a replacement dose of glucocorticoid, several approaches can be taken. Many practitioners like to switch to hydrocortisone if possible in order to take advantage of the short half-life of this medication. This switch may allow the HPA axis more opportunity to recover. For the same reason, some recommend switching to alternate-day therapy with an intermediate acting glucocorticoid such as prednisone being given as a single morning dose every 48 hours [48]. Although this type of regimen has been shown to work well as therapy for several diseases, it may not work as well for all patients being withdrawn from steroid therapy who have adrenal insufficiency. These patients may experience a lack of well-being during the off day of therapy.

During this stage of withdrawal it is appropriate to begin checking morning cortisol levels, which can be useful as a screening test for basal adrenal sufficiency. A cortisol level drawn at approximately 8 a.m. that measures less than 3 µg/dL indicates deficient basal cortisol secretion and the need for continued replacement therapy. If the morning cortisol is

greater than 20 µg/dL, the patient can be assumed to have a recovered HPA axis and can be withdrawn entirely from glucocorticoid therapy [11].

Patients who have cortisol levels that fall between 3 and 20 µg/dL may have sufficient basal cortisol production but still be lacking in sufficient capacity to respond to significant physiologic stress. In this case an insulin tolerance test, CRH stimulation, or an overnight metyrapone test would be reasonable for assessment of the HPA axis. The authors most commonly use the overnight metyrapone test, because it is reasonably safe, convenient, and provides a reasonable assessment of the entire HPA axis.

In lieu of further testing, an alternative approach would be to continue a very gradual taper from the level of physiologic replacement [11]. If this course is chosen, the patient must be warned that supplemental glucocorticoid therapy might be needed during illness or injury for approximately 1 year after discontinuation of therapy.

For patients who have been on long-term glucocorticoid therapy, the risk for adrenal insufficiency can continue for months. Suppression can be seen for up to 9 months or even a year. Therefore, the patient and physician must discuss the potentially prolonged nature of steroid therapy withdrawal and approach the problem with patience and, sometimes, determination.

Summary

Glucocorticoid therapy in various forms is extremely common for several inflammatory, autoimmune, and neoplastic disorders. It is therefore important for the physician to be aware of the possibility of iatrogenic and factitious Cushing's syndrome. Although most common with oral therapy, it is also important to be alert to the fact that all forms of glucocorticoid delivery have the potential to cause Cushing's syndrome. Withdrawal from chronic glucocorticoid therapy presents significant challenges. These include the possibility of adrenal insufficiency after discontinuation of steroid therapy, recurrence of underlying disease as the glucocorticoid is being withdrawn, and the possibility of steroid withdrawal symptoms. Nonetheless, with patience and persistence, a reasonable approach to withdrawal of glucocorticoid therapy can be achieved.

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