

## Oral corticosteroids in asthma: A review of benefits and risks

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Oral corticosteroids (OCS) play an integral role in the pharmacological management of asthma, as well as a number of other inflammatory and autoimmune disorders. However, although their broad spectrum of effect is beneficial in controlling inflammation, it can also lead to undesirable effects on other cells, resulting in adverse effects. The purpose of the present review is to discuss the particular benefits of OCS and to outline the optimal role of these agents in the management of asthma, drawing on evidence-based medicine and current clinical practice guidelines. The mandate for the present review also covers an analysis of the risk:benefit ratio as it pertains to OCS use in asthma. The more common adverse effects will be discussed and weighed against the possible benefits.

**Key Words:** *Asthma; Oral corticosteroids*

Oral corticosteroids (OCS) play an integral role in the pharmacological management of asthma, as well as a number of other inflammatory and autoimmune disorders including other respiratory disorders (eg, acute exacerbations of chronic obstructive pulmonary disease), endocrine disorders (eg, adrenocortical insufficiency), rheumatic disorders and collagen diseases (eg, rheumatoid arthritis, lupus erythematosus), dermatological diseases (eg, pemphigus vulgaris, acute severe contact dermatitis), ophthalmic diseases (eg, iritis, keratoconjunctivitis), other allergic conditions (eg, drug hypersensitivity reactions), hematological disorders (eg, thrombocytopenia), neoplastic diseases (eg, leukemia, lymphoma), gastrointestinal diseases (eg, ulcerative colitis, Crohn's disease), central nervous system disorders (eg, multiple sclerosis), transplantation and many other conditions.

Their powerful systemic anti-inflammatory properties make OCS indispensable for controlling acute exacerbations of inflammatory diseases and as an adjunct in chronic diseases that are inadequately controlled with optimal standard medication.

Their utility does not, however, come without a price. OCS have effects on many cell types besides inflammatory cells. While their broad spectrum of effect is beneficial in

## Les corticostéroïdes dans le traitement de l'asthme : Aperçu général des bienfaits et des risques

Les corticostéroïdes oraux (CSO) jouent un rôle central dans la prise en charge pharmacologique de l'asthme, ainsi que de plusieurs autres maladies inflammatoires et auto-immunes. Cependant, bien qu'ils aient d'importants effets bénéfiques dans la maîtrise de l'inflammation, ces agents peuvent également avoir des effets nuisibles sur d'autres cellules et occasionner des effets indésirables. L'objectif du présent article de synthèse est de discuter des bienfaits particuliers des CSO et de souligner le rôle central de ces agents dans la prise en charge de l'asthme, et ce, à partir de données probantes et des lignes directrices actuelles quant à la pratique clinique. Le mandat du présent article de synthèse est également d'analyser le rapport risque/avantage de l'utilisation des CSO dans le traitement de l'asthme. Les effets indésirables les plus fréquents seront présentés et pondérés par rapport à leurs bienfaits possibles.

controlling inflammation, it can also lead to undesirable effects on other cells that result in adverse effects.

The purpose of the present review is to discuss the particular benefits of OCS and to outline the optimal role of these agents in the management of asthma, drawing on evidence-based medicine and current clinical practice guidelines. The mandate for the present review also covers an analysis of the risk:benefit ratio as it pertains to OCS use in asthma. The more common adverse effects will be discussed and weighed against the possible benefits. First, however, brief reviews of the mechanism of action of these agents, and their efficacy in asthma, are presented.

### MECHANISM OF ACTION OF OCS

The efficacy of OCS in alleviating symptoms in a broad range of disorders with inflammatory and/or autoimmune components results from the pleiotropic effects of the glucocorticoid receptor on multiple signalling pathways within the body (1).

In allergic diseases such as asthma and allergic rhinitis, for example, approximately 100 known inflammatory mediators are produced. These include lipid mediators, inflammatory peptides, chemokines, cytokines and growth factors. In asthma, evidence indicates that structural cells of the airways (ie, epithelial cells,

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**TABLE 1**  
Possible adverse effects of oral corticosteroid (OCS) therapy

System/tissue affected	Potential adverse effects
Adrenal gland	Adrenal atrophy, Cushing's syndrome
Cardiovascular system	Dyslipidemia, hypertension, thrombosis, atherosclerosis
Central nervous system	Changes in behaviour, cognition, memory, and mood (ie, glucocorticoid-induced psychoses), cerebral atrophy
Gastrointestinal tract	Gastrointestinal bleeding*, pancreatitis, peptic ulcer*
Immune system	Broad immunosuppression, activation of latent bacteria† and viruses
Integument	Atrophy, delayed wound healing, erythema, hypertrichosis, perioral dermatitis, petechiae, glucocorticoid-induced acne, striae rubrae distensae, telangiectasia
Musculoskeletal system	Bone necrosis, muscle atrophy, osteoporosis, retardation of longitudinal bone growth
Eyes	Cataracts, glaucoma
Kidney	Increased sodium retention and potassium excretion
Reproductive system	Delayed puberty, fetal growth retardation, hypogonadism

\*More common with the concomitant use of OCS and nonsteroidal anti-inflammatory drugs; †Concern about reactivation of mycobacterium infection. Adapted from reference 1

airway smooth muscle cells, endothelial cells, fibroblasts) are a major source of inflammatory mediators. Epithelial cells may play a particularly important role, because they may be activated by environmental signals and may release multiple inflammatory proteins, including cytokines, chemokines, lipid mediators and growth factors (1-3).

Most inflammatory proteins are regulated by increased gene transcription, which, in turn, is controlled by proinflammatory transcription factors (eg, nuclear factor-kappa B), which are activated in asthmatic airways (1-3).

OCS (and corticosteroids in general) potently suppress inflammation in asthmatic airways, which leads to improvement of clinical symptoms and reduces the risk of exacerbations. There are a multitude of different pathways through which this is accomplished. Greatly simplified, some of the major mechanisms are through inhibition of proinflammatory transcription factors causing reduced recruitment, decreased function and enhanced apoptosis of inflammatory cells (eg, eosinophils, T lymphocytes, mast cells and dendritic cells) in the airways (1-3).

#### Molecular mechanisms of corticosteroid adverse effects

It is the broad spectrum of activity of OCS that makes them so potent in reducing inflammation and reducing symptoms. However, the broad spectrum of activity is also implicated in a number of potential adverse cellular effects in a number of organ systems. (Table 1). The various mechanisms by which OCS induce some of these effects will be discussed in detail later in the present paper.

#### EFFICACY OF OCS IN ASTHMA

For patients who are responsive to OCS, therapy can significantly improve pulmonary function; improvement in forced expiratory volume in 1 s typically exceeds 30% (4). There are,

however, many patients who are resistant to OCS; these patients may experience a rise in forced expiratory volume in 1 s of less than 15%, despite high doses of OCS (5,6).

Early use of OCS in the setting of an acute asthma exacerbation has been shown to be effective in reducing hospital admissions. A meta-analysis (7) published in 2001 evaluated 12 studies involving 863 adult and pediatric patients with acute exacerbations. Patients in these studies received intravenous, intramuscular or oral corticosteroids within 1 h of arrival at the emergency department. Overall, the use of systemic corticosteroids in this setting reduced hospital admission rates by 60% (Figure 1).

The benefit of systemic corticosteroids has also been shown in the postdischarge setting. A separate meta-analysis (8), published by the same group in the same year, included seven studies in which a short course of OCS or intramuscular corticosteroids after treatment of an acute exacerbation reduced the risk of relapse during the subsequent week by 65% (8).

Compared with placebo, administering a short course of systemic corticosteroids at emergency department discharge has also been shown to decrease the need for repeat emergency care (5.9% for corticosteroids versus 21% for placebo), as well as to reduce symptoms (15.6% versus 36.4%) (9).

As an adjunct to controller medication to achieve symptom control, OCS were evaluated in the Gaining Optimal Asthma Control (GOAL) study (10). In this study, patients were administered increasing doses of inhaled corticosteroids, with or without long-acting bronchodilators, in an effort to provide complete control of asthma symptoms. Those who still had not achieved totally controlled asthma were entered into a four-week, open-label phase during which they were administered oral prednisolone (0.5 mg/kg up to 60 mg/day for 10 days) and (if they were not already receiving it) salmeterol/fluticasone 50/500 µg twice a day for four weeks.

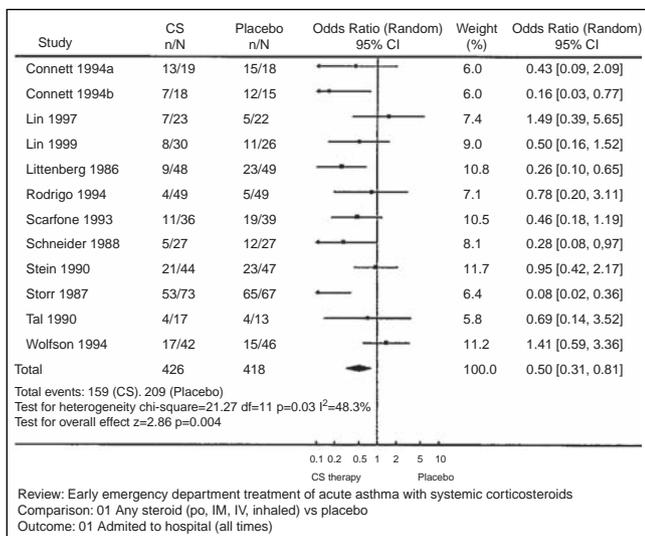
Of those patients previously on salmeterol/fluticasone, an additional 5% to 6% achieved totally controlled asthma with the addition of OCS, while an additional 4% to 7% achieved well-controlled asthma. This finding shows that there is a subgroup of patients with asthma for whom high-dose systemic steroids have no effect.

#### OCS IN ASTHMA GUIDELINES

OCS are used for two distinct purposes in asthma management: as a controller medication for patients unable to achieve control on other medications (ie, chronic use); and as short-course therapy (or 'burst') to control acute exacerbations. Guidelines are relatively clear in addressing the place of OCS in the former scenario, but provide less guidance for the latter.

#### OCS for control of refractory asthma

The Canadian guidelines for the management of asthma, published in 1999 (11) and updated in 2003 (12), recognize the importance of OCS, but also emphasize that they should be reserved for use only in refractory patients. To achieve control of asthma symptoms, the guideline authors recommended a step-wise approach to therapy starting with environmental control and fast-acting bronchodilators on demand. If the patient remains symptomatic, inhaled corticosteroids in increasing doses, with or without adjunctive controller medication (eg, long-acting beta<sub>2</sub>-agonists), leukotriene receptor antagonists) are added. OCS use is recommended only after these therapies have proven inadequate (Figure 2).



**Figure 1)** Meta-analysis of oral, intravenous and intramuscular corticosteroids (CS) in the emergency department for the reduction of hospital admissions. Reproduced with permission from Rowe BH, Spooner C, Ducharme FM, et al. Early emergency department treatment of acute asthma with systemic corticosteroids. *Cochrane Database Syst Rev* 2001;CD002178. Copyright Cochrane Collaboration

These recommendations are similar to those of other national and international guidelines for asthma. The Global Initiative for Asthma (GINA) guidelines, last updated in 2006 (13), state that long-term inhaled glucocorticosteroid use is always more favourable than long-term systemic glucocorticosteroids in asthma. While the authors acknowledge that long-term (ie, longer than two weeks) OCS therapy may be required for severely uncontrolled asthma, its use is limited by the risk of significant adverse effects.

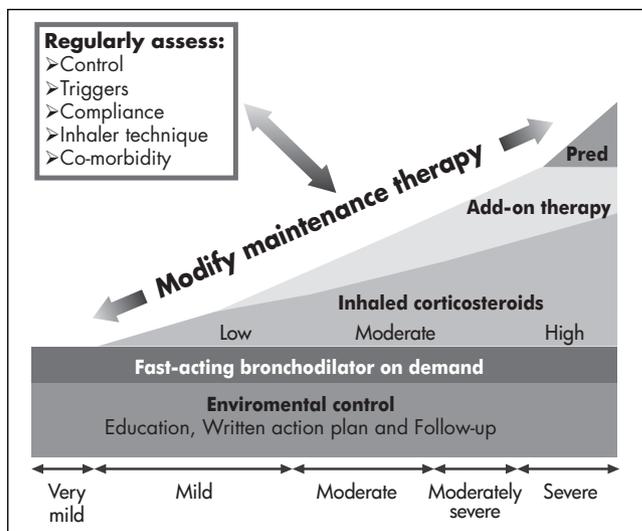
In the United States, the guidelines endorsed by the National Asthma Education and Prevention Program (NAEPP) recommend adding an OCS when inhaled corticosteroids and a second controller medication, such as a long-acting beta<sub>2</sub>-agonist, an antileukotriene agent or theophylline, are insufficient to control severe, persistent asthma (14). In an update published in 2003 (15), the authors state that rather than adding an OCS to the combination of inhaled corticosteroids and long-acting bronchodilators, clinicians should consider adding another controller agent instead.

In terms of dosing, there is no published Canadian consensus. The exact wording in the Canadian guidelines (1) is: "Given the side-effects associated with both short- and long-term use of these agents, doses should be kept to the minimum necessary to achieve the desired level of asthma control". No mention is made about the optimal duration of treatment.

The authors of the GINA and NAEPP guidelines are somewhat more specific regarding OCS dosing over the long term. The GINA paper states that for long-term use, alternate day use, dosed in the morning, produces less toxicity. The NAEPP authors echo this recommendation, but also cite a study that showed that 15:00 administration was associated with improved efficacy with no increase in adrenal suppression (14,16).

**OCS for control of acute exacerbations**

The Canadian, GINA and NAEPP guidelines provide guidance about the use of OCS to achieve rapid control of an asthma exacerbation (11,13,14). The Canadian recommendation (11) is that:



**Figure 2)** Stepwise management approach for asthma. Pred Prednisone. "Summary of recommendations from the Canadian Asthma Consensus Guidelines, 2003" Reprinted from CMAJ 13-Sept-05;173(6):S3-S11 by permission of the publisher. © 2005 Canadian Medical Association.

"adults discharged from the emergency department who require glucocorticosteroid therapy should be given 30-60 mg/d of prednisone orally (or equivalent) for 7-14 days. No tapering is required over this period. Children should receive 1-2 mg/kg a day of prednisone or equivalent (up to a maximum of 50 mg) for 3-5 days (level I)".

The GINA guidelines suggest that for acute attacks, OCS should be administered at a dose of 40 mg to 60 mg daily in one or two divided doses for adults, or 1 mg/kg to 2 mg/kg daily in children (13). The NAEPP guidelines are similar (Table 2) (14). NAEPP and GINA also concur on the recommended duration of three to 10 days.

Furthermore, when prescribing OCS as a discharge medication to prevent a relapse, treatment should also be kept relatively short (three to 14 days). No tapering is required if patients are also receiving inhaled corticosteroids (17).

**RISKS ASSOCIATED WITH OCS**

It is widely recognized that OCS have deleterious adverse effects. The scope and spectrum of these side effects may not be as well understood. It is likely that OCS will cause adverse effects, depending largely on the duration and dose. The most common significant adverse effects associated with OCS use are osteoporosis, avascular osteonecrosis, subcutaneous fat redistribution, skin thinning, cutaneous striae, purpura, impairment of wound healing, increased cardiovascular risk, Cushing's syndrome, obesity, diabetes, hypothalamic-pituitary-adrenal (HPA) axis suppression, cataracts and glaucoma.

The following observations and recommendations apply primarily to the chronic use of OCS rather than for 'burst' therapy of three to 10 days' duration. However, repeated burst therapy clearly has cumulative effects in terms of risks and these should be considered in management decisions.

**TABLE 2**  
**Recommendations for oral corticosteroid use for acute asthma exacerbations: National Asthma Education and Prevention Program**

Systemic corticosteroids	Dosage forms	Adult dose*	Child dose*	Comments*
Methylprednisolone	4 mg, 16 mg tablets	Short-course 'burst'	Short-course 'burst'	Short courses or 'bursts' are effective for establishing control when initiating therapy or during a period of gradual deterioration.
Prednisolone	5 mg tablets; 5 mg/5 mL, 15 mg/5 mL	40 mg/day to 60 mg/day as single or two	1 mg/kg/day to 2 mg/kg/day;	
Prednisone	1 mg, 5 mg, 50 mg tablets; 5 mg/mL, 5 mg/5 mL	divided doses for 3 to 10 days	maximum 60 mg/day, for 3 to 10 days	The burst should be continued until patient achieves 80% PEF personal best or symptoms resolve. This usually requires 3 to 10 days, but may require longer. There is no evidence that tapering the dose following improvement prevents relapse

\*Applies to all three systemic corticosteroids. Adapted from reference 14. PEF Peak expiratory flow

## Bone

The use of OCS is a major risk factor for developing osteoporosis. Osteoporosis develops as the result of an imbalance between osteoclast and osteoblast activity. In a healthy body, these two types of cells work to renew bone tissue through a cycle of breakdown and rebuilding.

Glucocorticoids exacerbate osteoporosis by inducing apoptosis in osteoblasts (the cells responsible for bone matrix synthesis) and by increasing the activity of osteoclasts (cells that digest bone matrix). These changes are mediated both directly (by the action of glucocorticoid receptors in bone cells) and indirectly (through interactions with other endocrine signals) (1,18).

Investigators have documented strong correlations between cumulative OCS dose and risk of fracture (19). These increases in relative risk have been demonstrated for fractures overall, as well as site-specific fractures of the hip, vertebrae and forearm (Table 3) (19).

It should also be noted that the risk of fracture increases with increasing OCS dose. For example, excess fracture risk has been found to be approximately 20% higher than controls for patients taking maintenance prednisolone doses of 5 mg or more. A daily dose of 20 mg, for example, confers an approximate increased relative risk of 60% compared with no OCS (19).

The importance of OCS-related risk is reflected in the current osteoporosis literature. Osteoporosis Canada and the Canadian Association of Radiologists endorsed a set of recommendations for bone mineral density (BMD) reporting in Canada (20). The recommended method for estimating fracture risk begins with a measurement of BMD. Depending on the individual's T-score (a statistical expression of a patient's BMD relative to normal, young adults: negative scores show lower BMD than the reference), he or she is classified as being at low, moderate or high risk of fractures in the subsequent 10 years (20). Apart from BMD, there are other factors that independently increase the patient's 10-year risk of fractures. The most important of these are a history of fragility fractures after age 40 years (especially vertebral compression fractures) and OCS therapy of greater than three months' duration. The presence of either of these risk factors moves a person up one risk category from low risk for osteoporosis to moderate risk, or from moderate risk to high risk (20).

The guidelines for BMD reporting recommend that any patient that receives chronic OCS therapy should also be taking

concomitant bisphosphonate (eg, alendronate, etidronate) therapy to lower osteoporotic risk (20). It should be noted that bisphosphonates should be initiated regardless of baseline BMD results. Monitoring should include a BMD test every one to two years. For patients older than 65 years, measurement of height and weight, as well as thoracic and lumbar spine radiographs, should be obtained at baseline. Repeat x-rays should be obtained when there is a clinical suspicion of vertebral fracture (ie, prospective height loss of more than 2 cm).

The effect of OCS on fracture risk among children with asthma has also been evaluated. In a 2005 population-based retrospective study (21), the investigators analyzed data from 279 patients diagnosed with asthma in childhood and examined the impact of various risk factors on likelihood of fracture during a median follow-up of 24.3 years. They observed that the use of OCS was associated with a statistically significant doubling of fracture risk in this cohort compared with asthma patients who did not receive OCS. Importantly, however, OCS therapy was associated with limb fractures in this study, rather than osteoporotic fractures of the axial skeleton. The authors suggested that OCS use in children may impair development of a biomechanically competent skeleton. One potential confounder that was not addressed by the investigators was the possibility that OCS use allowed these asthmatic subjects to lead a more active lifestyle due to greater symptom control, thereby exposing them to a higher risk of fracture. However, this may be counterbalanced by the strengthening of bones associated with weight-bearing.

In addition to fracture risk, the use of OCS has also been associated with an increased risk of avascular necrosis. This adverse effect is most commonly associated with chronic OCS use but may also be associated with short-term 'bursts' of OCS (22). The presumed mechanism by which necrosis occurs is through intraosseous hypertension, which results in bone ischemia and necrosis. The clinical manifestations are joint pain and limitation of movement.

## Dermatological adverse effects

The possible adverse effects of OCS on the skin are well documented, and include a host of different problems, as shown in Table 4.

Subcutaneous fat redistribution is a very common effect, and one that may be particularly noticeable and undesirable for the patient. The most common presentations are facial ('moon face') and cervical ('buffalo hump'). A 2007 French

**TABLE 3**  
Relative risk (RR) of fracture in corticosteroid users

	General Practice Research Database RR (95% CI)	Other studies RR (95% CI)
Any fracture	1.33 (1.29–1.38)	1.91 (1.68–2.15)
Hip	1.61 (1.47–1.76)	2.01 (1.74–2.29)
Vertebral	2.60 (2.31–2.92)	2.86* (2.56–3.16)
Forearm	1.09 (1.01–1.17)	1.13 (0.66–1.59)

\*Test for heterogeneity statistically significant ( $P < 0.05$ ). Combined estimate may not be valid because individual studies had different results. Data from reference 19

study (23) prospectively evaluated the prevalence of these abnormalities in 88 patients starting long-term systemic corticosteroid therapy at an initial daily dosage of 20 mg or more. They found that the cumulative incidence rates (the total percentage of patients with this outcome from the start of the study to a given time point) of subcutaneous fat redistribution at months 3 and 12 were 61% and 69%, respectively. Risks were higher in younger patients, those with a higher initial body mass index and those with higher initial energy intake (greater than 30 kcal/kg/day). There was no relationship to carbohydrate, protein, fat or sodium intake.

To reduce the risk and/or magnitude of subcutaneous fat redistribution, one may consider recommending a lower caloric intake while on OCS, particularly for patients with higher body mass index or caloric intake at baseline.

Thinning of the skin is another common, potentially irreversible dermatological complication of OCS therapy. The mechanisms by which OCS induce atrophic changes in the skin include a decrease in size and suppression of keratinocyte proliferation; thinning of the stratum corneum; a decrease in synthesis of epidermal lipids (eg, ceramides, cholesterol, fatty acids); increased permeability of the epidermis and subsequent increased transepidermal water loss (24); and reduction in synthesis of type I and III collagen (25). The decreased tensile strength and elasticity resulting from dermal thinning and OCS-induced flattening of the dermal-epidermal junctions (26) make the skin more fragile and easier to shear off. OCS-induced purpura is in the same distribution as senile purpura (ie, extensor surface of arms, dorsum of hands, sides of neck, face, lower legs), and is usually irreversible.

OCS use may also lead to cutaneous red striae, particularly on the thighs, buttocks, shoulders and abdomen. Treatment is often disappointing, although striae distensae usually fade with time. Vitamin A 0.1% cream (27), the 585-nm flashlamp-pumped pulsed dye laser (28), and a combination of pulsed dye laser and Thermage (a nonablative radiofrequency device) (29) have been used with some success. One can decrease the risk of striae by recommending a low-caloric diet for patients initiating OCS.

Another common and potentially serious dermatological effect of OCS is impairment of wound healing. OCS interfere with many aspects of normal wound healing, including inhibition of leukocyte and macrophage infiltration, decrease in synthesis of type I and type III collagen in the dermis, decrease in tissue inhibitors of metalloproteinases and collagenase made by skin fibroblasts (25,30), and reduction of keratinocyte growth factor expression after skin injury and keratinocyte growth factor messenger RNA in cultured fibroblasts (31).

**TABLE 4**  
Possible skin changes with oral corticosteroids

Subcutaneous fat redistribution
Skin thinning
Skin fragility
Striae distensae
Purpura/easy bruising
Acneiform eruptions
Hypertrichosis
Impairment of wound healing
Increased risk of infection
Bacterial (eg, cellulitis)
Fungal (eg, tinea, Candida)
Allergic reactions
Maculopapular eruptions
Urticaria

Allergy to OCS may present as localized or generalized urticaria, angioedema, bronchospasm, anaphylaxis, widespread erythema, maculopapular exanthema or eczema (32–35). Patients who develop allergies to OCS usually have a pre-existing history of allergy to topical steroids. Patch testing and intradermal testing to the suspected compound may confirm the allergy (36,37). Corticosteroids have been grouped into four different classes (Table 5) (38). Individuals allergic to steroids in group A may also react to group D2 steroids and vice versa. Allergy to topical corticosteroids is not rare. Hydrocortisone allergy was noted in 4.8% of 497 patients at a contact dermatitis clinic (36). For patients with hydrocortisone allergy, prednisone should not be used; possible alternatives include betamethasone and dexamethasone (37).

#### Cardiovascular risk

Evidence has shown that OCS confer additional cardiovascular risk. An observational cohort study published in 2004 analyzed 68,781 corticosteroid users (inhaled, nasal and oral combined) and 82,202 controls, all without previous hospitalization for cardiovascular disease (39). In the control group, the rate of cardiovascular events was 17.0 per 1000 person-years in the comparator group, and 23.9 per 1000 person-years in the corticosteroid group (22.1, 27.2, and 76.5 in low-, medium-, and high-dose groups, respectively).

The relative risk for a cardiovascular event in patients receiving high-dose corticosteroids was therefore found to be 2.56 compared with controls who did not receive high-dose corticosteroids.

Other studies have also demonstrated a small increase in risk for the specific end point of acute myocardial infarction. A case-control study published in 2006 (40) showed that patients taking OCS at doses greater than 10 mg day had a relative risk of 2.15 compared with nonusers (40). Overall, among all users of OCS, there was also a statistically significant increase in relative risk of myocardial infarction (1.42) compared with nonusers.

The mechanisms behind these increases in risk are not completely understood, but increase in blood pressure, hyperglycemia and increased propensity for obesity are certainly contributing factors (39). OCS can cause hypertension by two distinct mechanisms: through increased renal sodium retention,

**TABLE 5**  
**Classes of corticosteroids**

Class	Examples	Notes
Group A	Tixocortol pivalate, hydrocortisone, prednisolone, methylprednisolone, prednisone	May cross react with group D2
Group B ('ides')	Budesonide, amcinonide, desonide, fluocinolone acetonide, fluciclonide, triamcinolone acetonide	
Group C	Betamethasone, dexamethasone, halomethasone	
Group D1 ('ates')	Betamethasone dipropionate, betamethasone 17-valerate, clobetasol propionate, fluticasone propionate, mometasone furoate	
Group D2	Hydrocortisone 17-butyrate, prednicarbate, methylprednisolone aceponate, hydrocortisone aceponate	May cross react with budesonide S-isomer and group A corticosteroids

Adapted from reference 38

and through potentiation of vasopressor responses to angiotensin II and catecholamines (1). There may also be other, more direct factors. A 2006 study (41), for example, showed that patients who take high-dose corticosteroids are at significantly increased risk of atrial fibrillation, which suggests an arrhythmogenic effect.

Patients taking chronic OCS therapy should therefore be monitored closely for changes in their cardiovascular risk profile. Abnormalities in blood pressure, lipids or other factors should be managed according to relevant clinical practice guidelines.

### Metabolic adverse effects

The use of OCS has long been associated with significant metabolic changes. Long-term use of these agents can lead to suppression of the HPA axis. The HPA axis, as its name suggests, refers to a complex set of homeostatic interactions among the hypothalamus, the pituitary gland and the adrenal gland. The role of these interactions is to control various body processes (eg, digestion, immunity, mood, sexuality, energy usage, stress management). Suppression of the HPA axis may lead to atrophy of the adrenal glands and, in turn, to unwanted effects in other organs – from mild nausea to overt adrenal crisis (42). The exact dosage and duration of use of OCS required to result in HPA axis suppression has not been reliably quantified. In theory, however, any dose greater than the equivalent of 5 mg of prednisone could cause suppression of the HPA axis (42). Short-term administration (ie, approximately one week) of relatively large doses of OCS, however, is not likely to cause clinically significant adverse effects (42).

One of the more common features that arises from HPA suppression is weight gain (43), which may or may not be associated with OCS-induced Cushing's syndrome. In addition to weight gain, Cushing's syndrome can include the 'moon face' Cushingoid features as described above, hirsutism, sexual dysfunction, muscle atrophy, fatigue and bone pain. Patients with Cushing's syndrome are at significantly increased risk for adverse cardiometabolic events. Those patients diagnosed with Cushing's syndrome should be referred to an endocrinologist for a full work-up (44).

OCS use can also cause hyperglycemia. Some of the mechanisms by which this may occur include the inhibition of glucose uptake and utilization by peripheral tissues, direct inhibition of glucose transport, decrease in glucose transporters in adipose tissue and inhibition of insulin-stimulated glucose transport in muscles.

A study published in 1997 (45) quantified the risk of the occurrence of hyperglycemia (defined as requiring initiation of antihyperglycemic agents) in patients treated with OCS. The investigators found that among patients using OCS, the relative risk for development of hyperglycemia requiring treatment was 2.23 (95% CI 1.92 to 2.59) as compared with nonusers. The relative risk increased with increasing dose (Figure 3).

This substantial increase in risk for hyperglycemia with OCS should not be overlooked. Patients starting chronic OCS should first be screened for pre-existing blood sugar abnormalities and should be monitored thereafter. If hyperglycemia develops, it should be actively treated with antihyperglycemic agents.

Dyslipidemia can also arise secondary to OCS therapy. The mechanisms by which this may occur include: as a secondary result of increased visceral adiposity and insulin resistance, or through more direct mechanisms, such as increased cholesterol esterification and increased free fatty acids. It would, therefore, be wise to monitor lipid levels in patients on OCS. Studies in patients with lupus have identified steroid duration as a risk factor for hyperlipidemia and atherosclerosis. Therefore, it is wise to monitor lipids including low-density lipoprotein, high-density lipoprotein and triglycerides every six months, as well as other traditional risk factors for cardiovascular disease. It is unclear what low-density lipoprotein targets should be aimed for in patients on long-term corticosteroid therapy but other risk factors should be taken into account when determining this.

### Ophthalmological adverse effects

There are two major potential ophthalmological adverse effects associated with OCS use: posterior subcapsular cataracts (PSC) and glaucoma.

PSC are a very common consequence of OCS therapy, particularly at higher doses. While patients treated with lower doses (eg, prednisone less than 10 mg/day) are not at substantially increased risk, as many as three-quarters of patients receiving greater than 15 mg/day for longer than one year may develop PSC (46). Overall, the reported incidence of steroid-induced cataracts in clinical trials has ranged from 6.4% to 38.7% (47). The risk of steroid-induced cataracts increases with increasing steroid potency, duration and dose (49). It is also accepted that OCS therapy can have a more pronounced effect on cataract risk among children compared with adults (50).

The mechanism(s) behind steroid-induced PSC are not well understood. One hypothesis is that OCS create an imbalance in ocular growth factors, which results in abnormal cell behaviour (48).

On a positive note, steroid-induced PSC responds very well to modern cataract surgery.

Glaucoma, however, is a more serious, irreversible complication. Use of OCS can painlessly increase intraocular pressure, which leads to irreversible optic nerve cupping /atrophy within approximately two to six weeks (although it can happen even faster than this). This pressure increase leads to irreversible optic nerve cupping/atrophy and blindness. This is classified as secondary open angle glaucoma (OAG).

As is the case with cataracts, the precise mechanism(s) by which OCS elevate risk of glaucoma is not fully understood. However, there are several suggested contributing factors; for example, OCS inhibit fluid outflow from the trabecular meshwork, leading to increased intraocular pressure (49).

While all OCS patients are at risk for OAG, there are certain groups that are at even higher risk, especially those with a history of primary OAG. Most patients with primary OAG respond with a rise in intraocular pressure when using topical or systemic steroids. Those with a family history, connective tissue disorders, high myopia and diabetes are also at risk of steroid-induced glaucoma (47).

It is important to stress that the increase in eye pressure happens painlessly. A shrinking field of vision is usually not appreciated by the patient until very severe damage has occurred.

Once OCS therapy is discontinued, the elevation in intraocular pressure often resolves in a matter of weeks, but the negative pressure effects on the optic nerve are permanent.

To reduce the risk of OCS-induced glaucoma blindness, each patient should be asked whether they or a close family member suffers from glaucoma. If a patient does have glaucoma and still needs to use OCS, he or she should have eye pressure measurements with full ocular assessment, including disc and field examination, every one to three months to detect steroid-induced glaucoma. Regardless of whether a patient has additional risk factors, it is imperative that all patients have regular examinations by an eye specialist (optometrist or ophthalmologist) if they are on long-term OCS therapy.

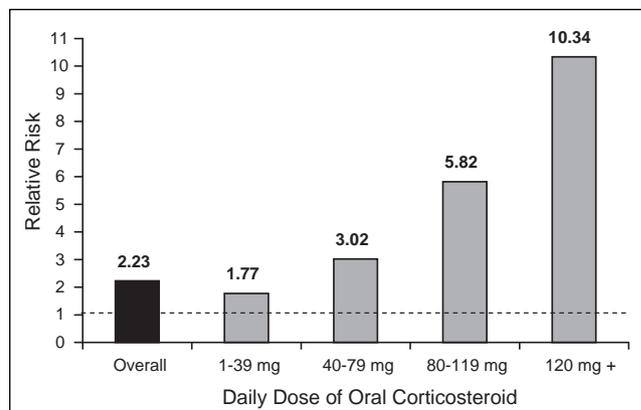
### STRATEGIES TO LIMIT USE OF OCS IN ASTHMA

The potent anti-inflammatory activity of OCS may be required in certain asthma patients, but steps should be taken to ensure they are not used inappropriately.

When faced with a patient with refractory asthma, in whom OCS are considered, one should first ensure the correct diagnosis. For asthma, the differential diagnosis is extensive: cystic fibrosis, bronchiectasis, chronic obstructive pulmonary disease, obstructive bronchiolitis, alpha<sub>1</sub>-antitrypsin deficiency, congestive heart failure, pulmonary embolism, reflux esophagitis, vocal cord dysfunction syndrome, tracheobronchomalacia, tumours in or impinging on central airways, inhaled foreign body and bronchial amyloidosis are among the potential confounders.

Before adding OCS, one should also assess the patient's adherence to the therapeutic regimen to ensure that the current therapy is optimized, both in terms of compliance and proper inhaler technique. Optimal therapy includes environmental avoidance (eg, pets, dust, etc) if appropriate, including possible occupational inducers and irritants. A search for other aggravating factors or diseases (eg, use of angiotensin-converting enzyme inhibitors, beta-blockers [including eye drops], reflux esophagitis, rhinitis, etc) should be carried out.

Other agents may also be considered in an uncontrolled patient before adding chronic OCS for control. The anti-immunoglobulin E agent omalizumab has been shown to be effective in approximately two-thirds of severely asthmatic patients (50). There have also been variable reports of benefit with immunosuppressants (eg, methotrexate, cyclophosphamide, cyclosporine) (51). However, the efficacy results



**Figure 3)** Relative risk of hyperglycemia by oral corticosteroid dose. Broken line denotes reference point (no oral corticosteroid use). Adapted from reference 47

have been less than overwhelming and these agents are not without their own toxicity concerns.

Preliminary studies using tumour necrosis factor-alpha antagonists have been equivocal. An open-label study (52) using etanercept was positive, but a randomized study (53) using infliximab produced underwhelming results.

Another possible approach for patients with refractory asthma is bronchial thermoplasty, which has also demonstrated significant benefits in patients with moderate to severe asthma (54). This approach is, however, still experimental and requires additional research to confirm its efficacy and safety.

### DISCUSSION AND RECOMMENDATIONS

OCS are, currently, indispensable agents for the treatment of asthma. As the most potent anti-inflammatory agents in the therapeutic armamentarium, they are useful for controlling acute exacerbations, and for control of patients who remain symptomatic despite optimal controller therapy.

As detailed above, chronic OCS therapy is associated with a number of significant adverse effects. Strategies to reduce their use can be employed, but they remain necessary for some patients. In these cases, there are a number of important measures that can be used to help reduce the potential deleterious impact of OCS. All patients taking chronic OCS should:

1. have a baseline BMD test before initiating therapy (as well as radiographs and height and weight measurements for older patients);
2. be administered concomitant antiosteoporotic therapy (eg, bisphosphonate with calcium, vitamin D);
3. be counselled on the importance of diet with respect to weight change and subcutaneous fat redistribution;
4. be screened for cardiometabolic risk factors (eg, blood pressure, lipids, blood sugar, glycosylated hemoglobin) before initiation;
5. be monitored for cardiometabolic risk factors during therapy;
6. be treated for abnormalities in cardiometabolic risk factors that emerge during therapy; and
7. be seen regularly by an ophthalmologist for screening for cataracts and glaucoma.



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