

# UPDATE

## Module 1674

### This module covers:

- The range of uses for steroids
- The pharmacology, pharmacokinetics and adverse effects of steroids
- How to advise your patients on their steroid treatment
- Treatment discontinuation

### OCTOBER >>

#### Endocrine system

- |                          |        |
|--------------------------|--------|
| ● Steroids               | Oct 5  |
| ● Type 1 diabetes        | Oct 12 |
| ● Diabetic complications | Oct 19 |
| ● Thyroid disease        | Oct 26 |

# Steroids: achieving balance

Steve Chaplin

Steroids are used to treat a remarkably wide range of disorders in which inflammation is fundamental. Common examples include asthma, eczema, psoriasis, inflammatory bowel disease and rheumatoid arthritis. Their versatility is reflected in the diversity of delivery systems and routes by which they are administered, but these measures have also been developed to limit potentially severe adverse effects.

## Pharmacology and pharmacokinetics

Corticosteroids are natural or synthetic steroid hormones. Glucocorticoids such as cortisone have marked metabolic activity (influencing carbohydrate, fat and protein metabolism and immune function) and anti-inflammatory activity. Mineralocorticoids such as aldosterone regulate sodium and water excretion.

There is a variable degree of overlap between these groups, such that some glucocorticoids have, in sufficient doses, enough mineralocorticoid activity to contribute to their adverse effects. Glucocorticoids are the corticosteroids most likely to be encountered in daily practice in primary care and from now on will be referred to as steroids.

Steroids act by crossing the cell membrane then binding to and activating the glucocorticoid receptor. The steroid-receptor complex relocates into the cell nucleus where, depending on the sites involved, it switches on or switches off transcription of different genes. The physiological effects include suppression of the many cytokines and pro-inflammatory cells that initiate and perpetuate the pathways contributing to inflammation.

They may also have other properties – for example, inhaled steroids increase expression of beta-2 receptors in the airways. This helps to explain the therapeutic value of combining a steroid and a beta agonist in the treatment of asthma.<sup>1</sup>

Steroids have, therefore, found a role in

Table 1. Principle adverse effects of long-term treatment with systemic steroids

Adrenal suppression	<ul style="list-style-type: none"> <li>● Adrenal atrophy may persist for years after discontinuation</li> <li>● Abrupt withdrawal of steroids may cause adrenal insufficiency</li> <li>● A temporary course or increased dose may be required to cover periods of stress, for example, surgery or illness</li> </ul>
Increased susceptibility to infections, which may be more severe	<ul style="list-style-type: none"> <li>● These include bacterial, mycobacterial and fungal infections, and helminth infestations</li> <li>● Increased risk of severe chickenpox and measles (prophylaxis required)</li> </ul>
Psychiatric effects	<ul style="list-style-type: none"> <li>● Euphoria, insomnia, irritability, depression, psychosis, behaviour disturbances</li> <li>● Risk of severe paranoia, depression and suicide in people with a history of mental illness</li> </ul>
Growth restriction	Delayed growth in children, though final height may not be affected
Other effects	Fluid retention, osteoporosis, diabetes, Cushing's syndrome, increased appetite, weight gain, glaucoma, cataract, skin atrophy, impaired healing, congestive heart failure, thromboembolism

Sources: BNF and summaries of product characteristics

the treatment of most disorders associated with inflammation or increased cell turnover. However, the mechanisms that account for their beneficial properties also cause the serious adverse effects associated with long-term use. It has, so far, proved impossible to separate their therapeutic from their toxic effects, prompting development of a range of synthetic steroids and formulations for non-oral routes of administration to minimise systemic exposure.

But systemic absorption of steroids occurs to some extent no matter which route of administration is used. The question faced by clinicians is, can this risk be minimised sufficiently to make it tolerable?

Inhaled steroids illustrate the complexity of this therapeutic challenge. Anything from 15 to 50 per cent of the inhaled dose is deposited in the lungs, depending on the inhaler design and the aerosol particle size.<sup>2,3</sup> The remainder is deposited in the oropharynx (causing local adverse effects) and swallowed.

Systemic absorption occurs from the lungs, but hepatic first-pass metabolism greatly reduces oral bioavailability, and absorption of the parent drug from the gastrointestinal tract is, therefore, small.

However, hepatic metabolism may convert the steroid to an active metabolite (as with beclometasone, but not fluticasone, whereas ciclesonide is converted to its active metabolite in the lung) and differences in systemic steroid potency mean that absorption from the lung can still result in significant adrenal suppression.<sup>3</sup> Add suboptimal adherence and poor inhaler technique to this picture, and it becomes clear that balancing the therapeutic and adverse effects of inhaled steroids can be difficult.

Difference in potency is another factor to take into account with topical steroids. Potency (defined according to a compound's potential to cause skin atrophy, vasoconstriction or suppress cell proliferation) is a product of the steroid and its formulation.

Its clinical impact is influenced by the site and manner of application. The BNF includes a list of generic and proprietary products classed as mild, moderate, potent or very potent. The potency of a topical steroid should be stated on the label, which should be attached to the tube (not the box).

The benefits of steroid therapy justify the effort. Regular use of an inhaled steroid, in addition to bronchodilator therapy for asthma, significantly improves lung function and symptoms, reduces bronchodilator use and allows people to stop taking an oral steroid.<sup>4</sup>

Topical steroids improve lesions on the skin and scalp and prolong remission in most people with plaque psoriasis.<sup>5</sup> Intranasal fluticasone improves the nasal and ocular symptoms of allergic rhinitis.<sup>6</sup> Oral steroids significantly slow progression of rheumatoid arthritis when added to disease-modifying therapy.<sup>7</sup>

But there is doubt about some long-established indications. For example, intra-articular injections offer only short-term pain relief in osteoarthritis of the knee.<sup>8</sup> Steroids are not effective for maintenance of remission in Crohn's disease<sup>9</sup> and the balance of risks and benefits remains uncertain for those with chronic obstructive pulmonary disease.<sup>10</sup>

### Adverse effects

The adverse effects of steroids may be local or systemic and depend on the route of administration and the formulation. The main effects of long-term systemic exposure to steroids are summarised in Table 1 (p13). The risk can be reduced by minimising the dose and duration of treatment and, where possible, choosing local over systemic administration.

Systemic effects may occur with prolonged use of high doses of inhaled steroids (beclometasone 800 to 2000mcg daily in adults, 400 to 800mcg daily in children). In the case of topical steroids, systemic effects are less likely with diminishing potency. Systemic absorption is increased by application to large areas of skin, to thin skin, to intertriginous areas (where two skin areas may touch or rub together) and by occlusion.

### Discontinuation of treatment

Some patients can stop abruptly; others should have their dosage gradually tapered off. The dose can be reduced rapidly to a physiological level (equivalent to prednisolone 7.5mg daily), then it should be lowered gradually. Gradual withdrawal should be carried out in patients in whom relapse is unlikely and who have:

- received more than 40mg/day prednisolone or equivalent for more than seven days
- taken repeat doses in the evening
- had more than three weeks of treatment
- recently received repeat courses
- taken a short course within one year of stopping long-term treatment
- other possible causes of adrenal suppression.

Table 2. Advice for patients using steroid preparations for selected disorders

Disorder	Route of delivery	Advice
Asthma prophylaxis	Inhalation	<ul style="list-style-type: none"> <li>● Inhaled steroids prevent symptoms, so regular use is essential</li> <li>● Take the prescribed dose (adherence is often poor)</li> <li>● Ensure good inhaler technique</li> <li>● Clean spacer as recommended by manufacturer</li> <li>● Carry steroid card if using high doses</li> </ul>
Eczema, psoriasis	Topical	<ul style="list-style-type: none"> <li>● Apply thinly and only apply to the affected area(s)</li> <li>● Once daily use should be enough. Maximum of twice daily</li> <li>● Use fingertip units to estimate dose (see BNF section 13.4)</li> <li>● Wash hands after application</li> <li>● Keep away from the eyes</li> <li>● Do not apply OTC formulations to the face, anogenital area, or broken or infected skin</li> </ul>
Rheumatoid arthritis	Oral	<ul style="list-style-type: none"> <li>● Take the dose in the morning to minimise impact on circadian cortisol secretion</li> <li>● Carry a steroid card</li> </ul>
Allergic rhinitis	Intranasal	<ul style="list-style-type: none"> <li>● Use regularly to prevent, not treat, symptoms</li> <li>● Avoid in the event of untreated nasal infection or nasal surgery. Smell and taste may be altered</li> </ul>

Sources: BNF and summaries of product characteristics

Abrupt withdrawal is suitable for patients who have received treatment for three weeks or less, if relapse is unlikely and they do not meet the criteria for gradual withdrawal. Note that the recommended regimen of prednisolone for COPD exacerbation is 30mg per day for seven to 14 days, so there is no need for gradual discontinuation.

Stopping treatment of psoriasis with a potent or very potent topical steroid may cause a rebound of severe symptoms or provoke pustular psoriasis, and their use in this setting is limited to short-term treatment of specific sites. For management of asthma it is recommended that inhaled steroid doses should be reviewed every three months and dose reduction should be slow (25 to 50 per cent decrease each time), because patients' symptoms deteriorate at different rates.

### Drug interactions

Despite the problems associated with systemic absorption of topical steroids, the risk of clinically significant interactions with other drugs is largely confined to systemic administration.

Many interactions are associated with drugs more likely to be prescribed in secondary care but oral anticoagulants, vaccines and antiepileptic drugs are examples of interacting drugs commonly prescribed in primary care. These interactions include:

- rifamycins - induces steroid metabolism
- coumarins - steroids reduce or, in high doses, enhance their effects
- carbamazepine, phenytoin, phenobarbital - induce steroid metabolism
- amphotericin - increases risk of hyperkalaemia

- ciclosporin - high-dose methylprednisolone increases plasma concentration
- vaccines - high-dose steroids impair response
- live vaccines - avoid steroid use.

### Role of the pharmacist

Steroid phobia affects adherence and may be addressed by a clear explanation of the balance between the risks and benefits of treatment. It may be necessary to explain the difference between the therapeutic use of steroids and their abuse in sport and bodybuilding.

It is always helpful to ensure that first-time users and anyone who appears to be uncertain about using their medicine understands the product's patient information leaflet. This should include ensuring correct use of the product (especially inhaler technique, but also eye drop hygiene and precautions when using topical steroids) and its adverse effects.

Pharmacists should remind patients taking oral steroids and those using high-dose inhaled steroids to carry their steroid card. They should also be provided with written advice on steroid replacement during periods of stress.

Some patients have a supply of oral steroids at home to use when needed for exacerbation of asthma or COPD. They should be clear about the criteria for starting and stopping treatment, when to seek medical help and how to recognise and respond to adverse effects. They may also have a management plan (for example, for asthma) that includes further information. Patients should be reminded not to share their steroids with others. Table 2 (above left) summarises advice for patients using steroid preparations for selected disorders.

## References

1. Barnes PJ. *Glucocorticosteroids: current and future directions*. Br J Pharmacol 2011; 163:29-43.
2. Derendorf H. *Pharmacokinetic and pharmacodynamic properties of inhaled ciclesonide*. J Clin Pharmacol 2007; 47:782-9.
3. Jackson C, Lipworth B. *Optimizing inhaled drug delivery in patients with asthma*. Br J Gen Pract 1995; 45:683-7.
4. Adams NP, Bestall JC, Lasserson TJ, et al. *Fluticasone versus placebo for chronic asthma in adults and children*. Cochrane Database of Systematic Reviews 2008, Issue 4. Art. No.: CD003135. DOI: 10.1002/14651858.CD003135.pub4.
5. Castela E, Archier E, Devaux S, et al. *Topical corticosteroids in plaque psoriasis: a systematic review of efficacy and treatment modalities*. J Eur Acad Dermatol Venereol 2012; 26 (Suppl 3):36-46.
6. Rodrigo GJ, Neffen H. *Efficacy of fluticasone furoate nasal spray vs. placebo for the treatment of ocular and nasal symptoms of allergic rhinitis: a systematic review*. Clin Exp Allergy 2011; 41:160-70.
7. Kirwan JR, Bijlsma JWJ, Boers M, et al. *Effects of glucocorticoids on radiological progression in rheumatoid arthritis*. Cochrane Database of Systematic Reviews 2007, Issue 1. Art. No.: CD006356. DOI: 10.1002/14651858.CD006356.
8. Bellamy N, Campbell J, Welch V, et al. *Intra-articular corticosteroid for treatment of osteoarthritis of the knee*. Cochrane Database of Systematic Reviews 2006, Issue 2. Art. No.: CD005328. DOI: 10.1002/14651858.CD005328.pub2.
9. Steinhart AH, Ewe K, Griffiths AM, et al. *Corticosteroids for maintenance of remission in Crohn's disease*. Cochrane Database of Systematic Reviews 2003, Issue 4. Art. No.: CD000301. DOI: 10.1002/14651858.CD000301
10. Yang IA, Clarke MS, Sim EH, et al. *Inhaled corticosteroids for stable chronic obstructive pulmonary disease*. Cochrane Database of Systematic Reviews 2012 Jul 11; 7:CD002991. doi:10.1002/14651858.CD002991.pub3.

## 5 minute test

■ Sign up to take the 5 Minute Test and get your answers marked online: [chemistanddruggist.co.uk/update](http://chemistanddruggist.co.uk/update)

# Take the 5 Minute Test

1. Steroids act by crossing the cell membrane and activating the glucocorticoid receptor.

**True or false?**

2. Steroids are not effective maintenance of remission in Crohn's disease.

**True or false?**

3. Psychiatric side effects of steroids include euphoria, insomnia, irritability and depression.

**True or false?**

4. COPD patients taking a short course of prednisolone 30mg daily should gradually reduce the dose when stopping.

**True or false?**

5. Abrupt withdrawal is suitable for patients who have been taking steroids for six weeks.

**True or false?**

6. Stopping treatment of psoriasis with a potent or very potent topical steroid may cause a rebound of severe symptoms.

**True or false?**

7. Steroids can induce the metabolism of rifamycins.

**True or false?**

8. High doses of steroids significantly reduce the effects of coumarins.

**True or false?**

9. Rheumatoid arthritis patients should be advised to take their oral steroid dose in the evening.

**True or false?**

10. Intranasal steroid sprays may alter smell and taste.

**True or false?**

## SIGN UP TO UPDATEPLUS

Sign up for Update Plus, C+D's premium CPD package for pharmacists and pharmacy technicians. Go to the website at [chemistanddruggist.co.uk/update-plus](http://chemistanddruggist.co.uk/update-plus) and sign up for £52+VAT today.

## Tips for your CPD entry on steroids

**Reflect** How do steroids work and why do they have such a wide range of uses? What are the main side effects of long-term systemic treatment with steroids? Which commonly prescribed drugs interact with steroids?

**Plan** This article discusses steroids and includes information about their pharmacology, pharmacokinetics, adverse effects, drug interactions and the factors to consider when discontinuing treatment. Advice that pharmacists can give to patients who are being treated with steroids is also included.

**Act** Read the Update article and the suggested reading (below), then take the 5 Minute Test (above). Update and Update Plus subscribers can then access their answers and a pre-filled CPD logsheet at [chemistanddruggist.co.uk/mycpd](http://chemistanddruggist.co.uk/mycpd).

Find out more about corticosteroids and advice that you could give to patients about them on the NHS Choices website [tinyurl.com/steroids11](http://tinyurl.com/steroids11)

Read more about topical steroids in the BNF – section 13.4 – Topical corticosteroids, and on the Patient.co.uk website for information about quantities to apply and fingertip units [tinyurl.com/steroids13](http://tinyurl.com/steroids13)

Read the article about steroid phobia on the National Eczema Society website for information about the benefits of topical steroids and how to explain this to patients [tinyurl.com/steroids14](http://tinyurl.com/steroids14)

**Evaluate** Are you now confident in your knowledge of the use, side effects and interactions of steroids? Could you give advice to patients about how to take or use steroids?

## ASK THE EXPERT

October is endocrine system month and our expert is on hand to answer your queries. From diabetes to thyroid disease submit your questions by email: [steve.titmarsh@ubm.com](mailto:steve.titmarsh@ubm.com)