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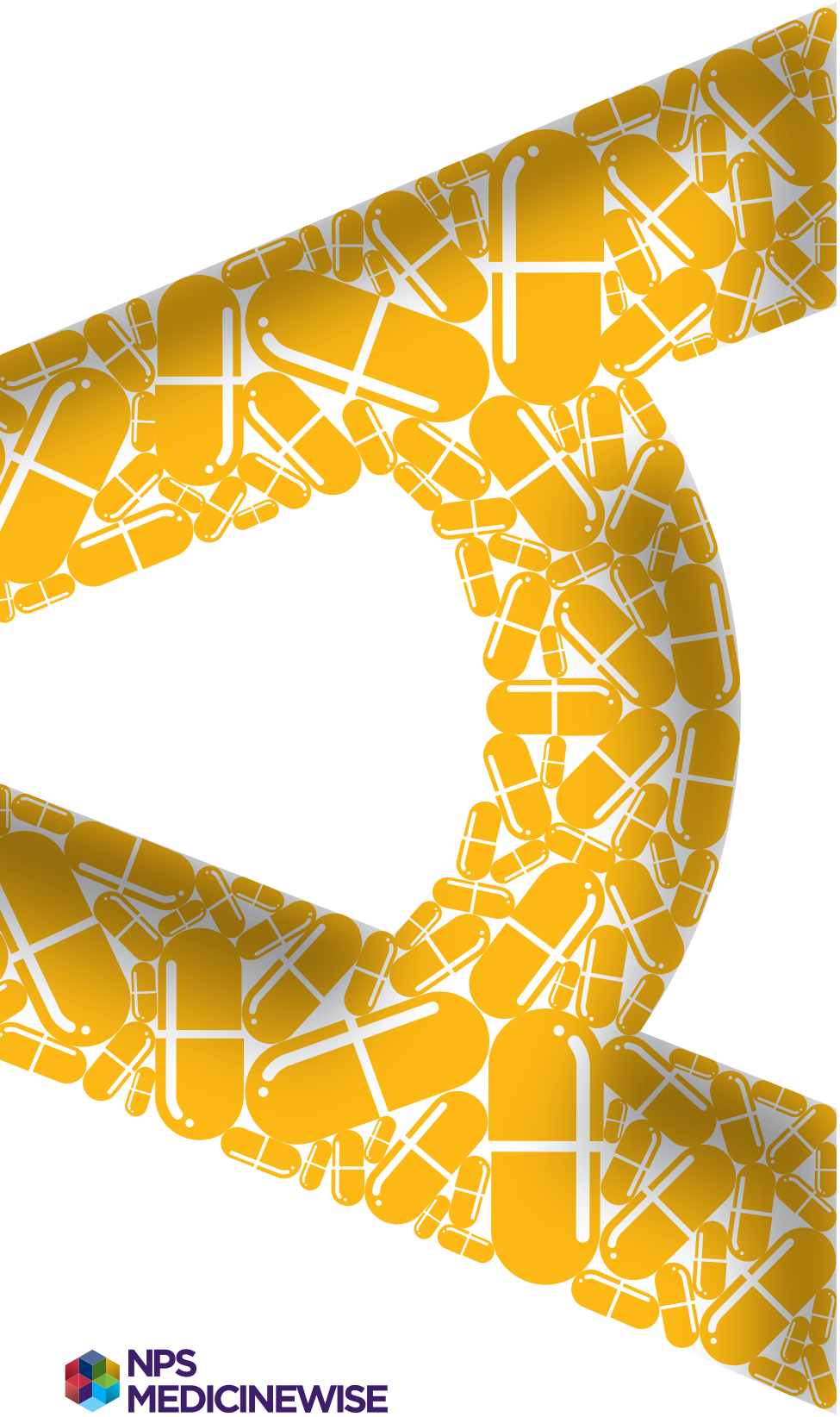

NPS MEDICINEWISE

CONTENTS

EDITORIAL

**Prescribing for refugees** 146
M Smith, W Lo, J Bindra

ARTICLES

**Asthma drugs in pregnancy and lactation** 150
A Lim, SY Hussainy, MJ Abramson

**Assessment and management of eating disorders: an update** PJ Hay 154

**Rational use of topical corticosteroids** 158
G Carlos, P Uribe, PF Fernández-Peñas

**Principles for managing attention deficit hyperactivity disorder** 162
B Tonge

**Making sense of equivalence and non-inferiority trials** B Ewald 170

LETTERS TO THE EDITOR 148

FEATURES

**Medicines Safety Update** 166

**Patient Support Organisation** 157
The Butterfly Foundation

**Book review**
Therapeutic Guidelines. Management guidelines: developmental disability 161

NEW DRUGS

Dapagliflozin for type 2 diabetes 174
Tafluprost for glaucoma and ocular hypertension
Vandetanib for medullary thyroid cancer
Vismodegib for basal cell carcinoma

EDITORIAL

# Prescribing for refugees

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**Key words**
migrants

*Aust Prescr 2013;36:146–7*

Australia has resettled over 750 000 refugees since Federation in 1901. In recent years the annual intake has been around 14 000, and this year around 20 000 refugees are settling in urban, regional and rural centres across Australia. A significant proportion of these individuals have had refugee status awarded overseas and are settled here under Australia's Humanitarian Migration Program, with full access to Medicare. A smaller number arrive by plane or boat as asylum seekers and their access to health services varies depending on their situation.

While most recent refugees tend to be young, some are older and those who settled here decades ago are now ageing. Disease profiles have changed as countries of origin change. Chronic medical conditions are just as relevant as communicable diseases.

Recently arrived refugees in particular should undergo a thorough health check. There are Medicare Benefits Schedule health assessment items for refugees and other humanitarian entrants.

While many issues relating to prescribing in this population are shared by other migrants, some factors are accentuated in refugees.

The first step in prescribing may be diagnosing an unfamiliar condition and having the knowledge to manage it. Despite a degree of screening conducted overseas or in detention centres, testing for conditions prevalent in the region of origin may be needed, for example chronic hepatitis B. Conditions such as schistosomiasis and strongyloidiasis are unfamiliar, but in fact uncomplicated cases of either require only two doses of treatment – praziquantel and ivermectin respectively, both of which are available on the Pharmaceutical Benefits Scheme. In contrast, vitamin D deficiency is extremely common. Guidelines are available for GPs who work with refugees.[1,2]

Psychological conditions are very common, as is psychosomatic pain – patient education may be needed regarding realistic expectations of analgesia. For post-traumatic stress disorder, trauma-focused psychological therapy is the preferred first-line intervention. Drug therapy, particularly selective serotonin reuptake inhibitors, can be useful if psychological intervention is insufficient, declined or unavailable.[3]

Clear communication is key to effective prescribing, be it lifestyle and dietary advice or a drug. Practitioners who share their patient's language are at an advantage. If they do not, professional interpreters are a very important resource. Failure to use interpreters can contribute to treatment non-adherence, adverse events or failure to follow instructions, with potential medicolegal implications.[4] The Australian Government funds the Translating and Interpreting Service Doctors Priority Line (1300 131 450) which provides free phone interpreters for doctors in private practice. This service is also available to community pharmacists. By booking in advance the service can arrange for an interpreter to attend a consultation.

If working with an interpreter in the room, ask them to write down the treatment dose and instructions in the patient's own language. You can also consider pictorial diagrams to explain dosing regimens.

Refugees are often mobile in the early months of settlement or may not understand the importance of a regular healthcare provider, leading to possible duplication of therapy. Providing your patient with a medicines list can improve understanding and minimise errors. Another useful strategy is to ask the patient to bring in all their medicine containers. These may reveal drugs that are duplicated, old or dispensed from overseas. You can also use the containers to assess adherence on the next visit. A Home Medicines

## From the Editor

*Australian Prescriber* is an international and independent medical journal. It is therefore appropriate that the journal has published two supplements, one on drug policies in the Asia Pacific region and the other on independence.

*Australian Prescriber* has quite a following in South America, so it is pleasing that we have a contribution from that continent to the article on topical corticosteroids.

Inhaled corticosteroids can cause concern for pregnant women with asthma. Angelina Lim, Safeera Hussainy and Michael Abramson provide reassurance about these drugs in pregnancy and lactation.

The new diagnostic manual for psychiatry DSM-5 was published earlier this year. Phillipa Hay provides an update on the management of eating disorders, and Bruce Tonge reviews the principles for managing attention deficit hyperactivity disorder in children.

Four new drugs are reviewed in this issue. Ben Ewald explains how some new drugs are assessed in 'non-inferiority' trials.

Review may be appropriate as one of the eligibility criteria is 'literacy or language difficulties'.[5]

It is important to ask whether the patient is using any traditional medicine, including products sent from overseas. These may interact with a prescribed drug, either reducing efficacy or increasing the risk of adverse reactions.[6]

Cultural beliefs and limited health literacy should also be considered. The concept of preventive care may not be well understood (for example taking an antihypertensive drug long term to prevent end-organ damage) and this could reduce adherence to treatment. Education of the patient and other family members is needed. This can be supported with translated information sheets for those literate in their own language.

Religious beliefs can impact on the acceptability of treatment, for example followers of certain religions avoid pork or beef products, leading to reluctance to take gelatin-containing capsules. However, a World Health Organization statement in 2001 made it clear that the transformation undergone in processing made it completely acceptable for Muslims to take such products. The same applies to vaccine additives.[7] Religions such as Islam that invoke fasting at certain times generally exempt people with medical conditions and pregnant women. However, many Muslim patients may still choose to omit their daytime drugs during Ramadan. Involving the patient and family members in discussion of these issues is likely to result in the best outcome.

A final but important issue is cost. Even for subsidised drugs, a large family with many members diagnosed with common conditions such as iron deficiency, vitamin D deficiency or *Helicobacter pylori* infection will face excessive costs that will hinder adherence. Additionally, a subset of asylum seekers live in the community without Medicare or Health Care Cards. While some may get assistance through organisations such as the Australian Red Cross, this is not the case for all. The cheapest effective treatment options should be offered, and asylum seeker health services and charitable organisations may be able to offer limited assistance with medications or funds.

In summary, prescribing problems in refugees can be minimised by taking the time necessary to undertake education and careful explanation, and to confirm the patient's understanding. Use a professional interpreter whenever required. Consideration of cultural and religious practices and the patient's socio-economic situation will also help promote adherence to treatment. ◁

*Conflict of interest: none declared*

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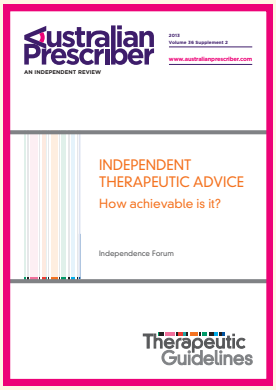
## FURTHER READING

Australian Government Department of Immigration and Citizenship. Free Services Through TIS National. www.immi.gov.au/living-in-australia/help-with-english/help_with_translating/free-services.htm#b [cited 2013 Sep 3]

## *Australian Prescriber* supplements

*Australian Prescriber* recently published two conference supplements.

Both are available on the website www.australianprescriber.com under Latest News, in HTML and PDF format.

LETTERS

# Letters to the Editor

## Calcium and cardiovascular risks

Editor, – I am writing in response to the recent article on calcium and cardiovascular risks by Mark Bolland, Andrew Grey and Ian Reid (Aust Prescr 2013;36:5-8).

I would like to address their statement that 'A more recent randomised controlled trial of sunlight exposure to raise vitamin D concentrations in Australian nursing home residents also found that the addition of calcium supplements to sunlight exposure was associated with increases in all-cause and cardiovascular mortality'.[1,2] The authors did not reveal that the assertion is based on comparisons between ultraviolet ray exposure only versus ultraviolet ray exposure plus calcium supplementation, and not to a control group. However, based on data analysis of death certificates within the study follow-up period, I do not see a significant difference between ultraviolet ray exposure plus calcium supplementation versus control group, hence it should be concluded that the former does not have increased cardiovascular mortality rates over the control population.

Shyan Goh
Locum orthopaedic registrar
Sydney

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*Mark Bolland, Andrew Grey and Ian Reid, the authors of the article, comment:*

The appropriate comparison to assess the effect of calcium is between the sunlight arm and the sunlight plus calcium arm, which only differ by use of calcium. This comparison showed increased all-cause and cardiovascular mortality in the sunlight plus calcium arm.

It is not surprising that our article challenges some readers because calcium has long been thought to be safe and effective. In 2005–06, five large randomised controlled trials were published on calcium with or without vitamin D in community-dwelling individuals with fracture as the primary end point.[1-5] The trials provide a strong evidence base to inform clinical practice. None of them reported statistically significant reductions in fracture, but individual studies reported that calcium increased the risk of hip fracture,[5] cardiovascular events,[5,6] kidney stones,[3] and hospitalisation from gastrointestinal symptoms.[4,7] Additionally, calcium was poorly tolerated (compliance approximately 50%). Meta-analyses confirmed these findings as discussed in our article.

Individually, concerns regarding the lack of efficacy, safety or poor tolerability of calcium supplements would provide a good reason for revisiting their role, but collectively these concerns provide a compelling argument against their widespread use. We think that dispassionate reviews of the evidence will lead to similar conclusions to ours, as shown by the US Preventive Services Task Force recently recommending against the use of calcium and vitamin D for primary fracture prevention.[8]

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The Editorial Executive Committee welcomes letters, which should be less than 250 words. Before a decision to publish is made, letters which refer to a published article may be sent to the author for a response. Any letter may be sent to an expert for comment. Letters are usually published together with their responses or comments in the same issue. The Committee screens out discourteous, inaccurate or libellous statements and sub-edits letters before publication. Authors are required to declare any conflicts of interest.The Committee's decision on publication is final.

## Sex, drugs and alcohol

Editor, – I found your recent article on 'Sex, drugs and alcohol: drug interactions of concern to consumers' (Aust Prescr 2013;36:46-8) informative. However, I believe there should be an addition to the box 'Drugs which can reduce the effectiveness of oral contraceptives'.

Sugammadex is a novel drug used in the reversal of neuromuscular blockade. At least anecdotally, use amongst anaesthetists in private practice is widespread. However, few anaesthetists are aware of its potential interactions with hormonal contraceptives.

A summary of the drug (Aust Prescr 2009;32:82-6) stated that 'Prescribers need to be aware that sugammadex may decrease progestogen concentrations, similar to the decrease observed after missing a daily dose of an oral contraceptive. Women on the pill should refer to the missed dose advice for their contraceptive. Likewise, women using non-oral hormonal contraceptives, such as depot formulations, should be advised to use additional contraception for the next seven days'.

Jennifer Dixon
Anaesthetist
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*Graeme Vernon, the author of the article, comments:*

Thank you for highlighting the warnings in the product information. It is not possible to assess the actual risk of this interaction as the warnings are based on chemical tests to determine the degree of binding and pharmacokinetic modelling, rather than evidence of contraceptive failure or reduced serum concentrations of oestrogens or progestogens.

Despite the low level of evidence to support this interaction, the recommended precautions should be taken. However, if sugammadex is being used routinely there should be scope for prospective studies of the actual effects on serum concentrations of contraceptive hormones. This could be an opportunity for regulators and sponsors to resolve an important clinical question and make the product information more clinically meaningful.

## Statins in older adults

Editor, – The article on statins in older adults (Aust Prescr 2013;36:79-82) has suggested that further information regarding effects of statins is important to inform clinical decision making in these patients.

There may be other patient groups where further information on the effects of statins is also important, for example indigenous Australians. A recent article described 15 cases of serious statin-associated myotoxicity in Aboriginal and Torres Strait Islander people.[1] Outcomes included death (three cases), and permanent severe disability (two cases) including effective quadraplegia. These patients were considerably younger (mean age 55 years) than the group generally considered at risk of statin myotoxicity.

Genevieve Gabb
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*Sarah Hilmer and Danijela Gnjidic, the authors of the article, comment:*

We thank Genevieve Gabb for her comments. We agree that it is important to study the effects of drugs in special populations. In the case of statins, older people differ from other special populations because they account for a large proportion of statin users in the community.

We also agree that adverse effects from statins are common across all age groups. In addition to muscle symptoms, younger patients may also experience statin-related adverse effects such as loss of energy and worsening fatigue with exertion.[1]

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ARTICLE

# Asthma drugs in pregnancy and lactation

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**Key words**
beta agonists, breastfeeding, corticosteroids

*Aust Prescr 2013;36:150–3*

## SUMMARY

Uncontrolled asthma during pregnancy poses many short and long-term risks to the mother and her baby. Maintaining optimal asthma control is important during pregnancy, but studies of drug safety are limited.

Inhaled short-acting beta agonists are safe to prescribe throughout pregnancy. Long-acting beta agonists need not be stopped in the first trimester and can be used in the second and third trimesters if needed to maintain adequate asthma control.

Inhaled corticosteroids, particularly budesonide, at recommended doses are safe to use during pregnancy and breastfeeding. Oral corticosteroids, at the doses used to treat asthma exacerbations, do not appear to pose a significant risk to the mother or child.

Pregnant women tend to overestimate the risk of using asthma drugs, but they are often unaware of the greater risks of uncontrolled asthma. They put themselves at unnecessary risk of acute exacerbations by discontinuing or reducing therapy.

Women with asthma should be advised to continue to take their treatment while breastfeeding. Spacing the dose and feed time may be necessary when using oral corticosteroids.

## Introduction

Approximately 8–13% of pregnant women have asthma.[1] Asthma control varies during pregnancy, but it can deteriorate in over one third of women.[2] Continuing therapy and monitoring is essential during pregnancy to maintain optimal control and prevent acute exacerbations. Pregnant women often accept frequent symptoms at the expense of less medication, but underestimate the harm an exacerbation may have on the pregnancy.

There are limited well-designed studies about asthma drugs during pregnancy and breastfeeding. The studies that assessed safety did not assess the drugs individually and rarely controlled for other drugs or medical conditions. Adverse events have also been attributed to worsening asthma, rather than its treatment.

In contrast, there is ample evidence of the risks associated with poorly controlled asthma during pregnancy.[3] These include an increased risk of preterm births, low birthweight, pre-eclampsia, malformations and poor fetal brain development.[3-5] Survivors of preterm birth and fetal growth restriction face an increased risk of cardiovascular complications in later life.[6] Optimal asthma control is therefore vital during pregnancy and a harm–benefit assessment should be done for each patient.

Women with asthma who smoke should be encouraged to quit as smoking can reduce their response to preventive therapy.[7]

## Non-adherence to asthma treatment

Almost a third of pregnant women discontinue or reduce their asthma preventing drugs during pregnancy and overcompensate with short-acting relieving drugs.[1] This jeopardises asthma control. The connotations of the word 'steroid' distress many women and they overestimate the harm steroids could have on their unborn child.[8] In addition, women who are unaware of the risks of poorly controlled asthma and not properly advised turn to unreliable resources, such as the internet, which often exaggerate the risks of treatment without highlighting its benefits.[8]

The uncertainty and anxiety surrounding the treatment of asthma during pregnancy emphasises the important roles of doctors, pharmacists, asthma educators and midwives in encouraging adherence to treatment. The first antenatal visit is an opportunity to discuss the benefits of continuing treatment and to review the patient's asthma management plan.[9] Any harmful effects from the drugs used to prevent asthma will be outweighed by maintaining good control and avoiding acute exacerbations.

## Inhaled beta agonists

Salbutamol and terbutaline are safe to use during pregnancy.[10] In the Australian categorisation of risk they are classified as category A (Table).[11]

Limited studies are available on long-acting beta agonists such as salmeterol and eformoterol,[12] which are thus categorised as B3 (Table). As the majority of these studies analysed long-acting beta agonists in

combination with other asthma drugs and have not shown any significant increase in harm, they are unlikely to pose a risk.[12] Furthermore, maternal plasma concentrations after inhaled salmeterol or eformoterol are very low or virtually undetectable.[13] The Asthma Management Handbook discourages starting treatment with long-acting beta agonists in the first trimester, but does not advocate withdrawing them if they are necessary to control the patient's symptoms.[14]

## Inhaled corticosteroids

Using inhaled corticosteroids during pregnancy has been associated with a decreased risk of low birthweight babies.[15] A study of women with asthma exacerbations found a 55% reduction in subsequent exacerbations and hospital admissions in those who used beclomethasone compared to those who did not.[16] Women should be advised to continue their preventive drugs during pregnancy.

Budesonide is a category A drug. The Asthma Management Handbook recommends switching to budesonide before pregnancy.[14] Ciclesonide, fluticasone and beclomethasone are category B3 (Table) with less evidence for safety during pregnancy.

Comparisons between different inhaled corticosteroids and doses are limited. In one study including beclomethasone, budesonide and fluticasone, women who used more than 1000 microgram daily in the first trimester were more likely to have a baby with congenital malformations (relative risk 1.63; 95% confidence interval 1.02–2.60).[17] However women on high-dose inhaled corticosteroids were likely to have more severe asthma, so adverse outcomes could have been associated with worsening asthma and oral corticosteroid use.[12] The negative outcomes reported should not discourage prescribers from increasing the dose of inhaled corticosteroids when necessary, as the risks of harm may be greater if the patient has uncontrolled asthma. Before increasing the dose it is important to check the patient's adherence and inhaler technique. The relationship between gestation and adverse events has not been explored in depth, but available studies suggest there is no greater risk with using inhaled corticosteroids in any particular trimester.[12]

*Table* **Australian categorisation of risk of asthma drugs in pregnancy** [11]

| Category | Definition | Drugs |
|---|---|---|
| A | Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed | budesonide<br>terbutaline<br>salbutamol<br>prednisolone |
| B1 | Drugs which have been taken by a limited number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage. | nedocromil<br>montelukast<br>sodium cromoglycate |
| B2 | Drugs which have been taken by a limited number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed. Studies in animals are inadequate or may be lacking, but available evidence show no evidence of an increased occurrence of fetal damage. | |
| B3 | Drugs which have been taken by a limited number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans. | beclomethasone<br>ciclesonide<br>fluticasone<br>eformoterol<br>salmeterol |
| C | Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Specialised texts should be consulted for further details. | |
| D | Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Specialised texts should be consulted for further details. | |
| X | Drugs which have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy | |

## Oral corticosteroids

Prednisolone, the oral corticosteroid mainly used in the treatment of exacerbations of asthma, has been shown to be under-prescribed in acute asthma exacerbations during pregnancy, leading to persistent and recurrent asthma symptoms two weeks later.[18] The risk of poorly-controlled asthma and the potential for another acute exacerbation during pregnancy is dangerous and acute asthma needs to be treated adequately.

There have been reports of an increased risk of cleft lip with or without cleft palate from first trimester use, however, the data were from studies with a small sample size that included corticosteroid use for other conditions that generally needed higher and more frequent doses.[19] It is also difficult to separate the potential effects of oral corticosteroids from the potential effects of poorly controlled maternal asthma as oral corticosteroids are generally indicated for severe asthma.

It is necessary to monitor blood glucose if oral corticosteroids are used in pregnancy, especially if there is gestational diabetes.

## Cromolyns and leukotriene receptor antagonists

Inhaled cromolyns are probably safe to use in pregnancy.[10] No well-designed studies have assessed the sole use of leukotriene receptor antagonists, such as montelukast, during pregnancy. Studies have shown an increase in adverse events with use, but these studies did not exclusively test montelukast during pregnancy.[12] Montelukast should be used in pregnancy only if clearly indicated and only after considering more effective and safer treatment, especially given its prescribing restrictions in the Pharmaceutical Benefits Scheme.[10]

## Anticholinergics

Currently there are no published controlled data on the use of inhaled anticholinergics during pregnancy and their use should be reserved as a last option. Nebulised ipratropium bromide with inhaled beta agonists and intravenous corticosteroids has been recommended for management of acute asthma during pregnancy.[20]

## Lactation

Asthma control in the postpartum period is important for the same reasons as it is in healthy, non-pregnant women, and the exacerbation risk is similar in the two groups of women. There are limited studies about the safety of asthma drugs during breastfeeding. Published studies in the postpartum period have been small case series with generally short follow-up.

Systemic absorption of inhaled drugs is generally minimal and causes little harm to the infant.[14] The infant's exposure is 10 to 1000 times less than during pregnancy.[21] The amount ingested through the mother's milk is far below the therapeutic level for an infant – mostly under 3% of a therapeutic dose per kilogram bodyweight.[22]

Short-acting beta agonists may be used at the usual doses.[10] Maintenance doses of inhaled budesonide (200 microgram or 400 microgram twice daily) result in negligible systemic exposure for the breastfed infant.[23] Once absorbed, inhaled budesonide is a weak systemic steroid and it is unlikely that clinically relevant concentrations would be transferred to the infant.[13] Similarly, only 30% of fluticasone is absorbed systemically and the majority is metabolised by first-pass metabolism.[24] No studies are available for the safety of ciclesonide and cromolyn (milk:plasma ratios unknown) in breastfeeding mothers, but in vitro studies show that the infant would be exposed to virtually undetectable concentrations so is unlikely to be at risk.[13]

There are no human studies of montelukast in breastfeeding, but animal studies have detected excretion into milk. Alternative treatment with short-acting beta agonists, long-acting beta agonists or inhaled corticosteroids should be considered during breastfeeding, particularly as montelukast is taken orally.[10]

Prednisolone at recommended doses is thought to be safe since the amount excreted in human milk is low with daily doses up to 80 mg. It is recommended to withhold feeds for four hours after each dose to reduce infant exposure. Prednisolone is preferred over prednisone, as prednisone is converted to prednisolone in vivo, causing a double peak of parent medicine and metabolite.[10]

## Conclusion and recommendations

Due to the limited evidence from large, well-designed prospective studies in pregnant and breastfeeding women, there is often a lack of confidence amongst health professionals when deciding the most appropriate asthma therapy. Optimal asthma control should always be the first priority.

Australian and international guidelines recommend that women continue with the same therapy they used before pregnancy, especially if this regimen adequately controlled their asthma, and that they monitor their asthma monthly.[14,25-27] A switch to budesonide could be considered if the patient is planning a pregnancy and is already taking another inhaled corticosteroid.[14]

Most of the asthma drugs are safe to use in breastfeeding. Women should be encouraged to continue their treatment during lactation.

Severe or difficult to treat asthma and asthma in women who continue to smoke may require a multidisciplinary approach with a respiratory specialist and more intensive monitoring.

Researchers are currently looking into markers of asthma control during pregnancy.[28] For now, spirometry is recommended for monitoring during pregnancy.[29] <

*Michael Abramson holds an investigator initiated grant from Pfizer for unrelated research.*

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Q:

## SELF-TEST QUESTIONS

*True or false?*

1. The risk of fetal malformations is increased by treating acute exacerbations of asthma with oral corticosteroids.
2. Inhaled budesonide can be used during lactation.

*Answers on page 179*

ARTICLE

# Assessment and management of eating disorders: an update

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**Key words**
anorexia nervosa, binge eating disorder, bulimia nervosa

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## SUMMARY

Eating disorders are common, but treatment is often delayed despite good outcomes with therapy.

Family-based treatment is recommended for children and adolescents with anorexia nervosa.

An extended form of cognitive behaviour therapy is effective for bulimia nervosa and binge eating disorder and can be used for adults with anorexia nervosa.

Selective serotonin reuptake inhibitors may help with bulimia nervosa and binge eating disorder.

Integrated primary and specialist care is recommended for optimal management.

## Introduction

Up to 1 in 10 Australians will experience an eating disorder in their lifetime with a general population point prevalence of around 5%.[1] Eating disorders, including anorexia nervosa, bulimia nervosa and binge eating, are characterised by disturbances in eating behaviour and psychological distress centred on food, eating and body image (Box 1).[1-3]

Diagnostic criteria for eating disorders are in a state of revision with new criteria introduced in 2013.[4] With less restrictive criteria, fewer patients fall into the residual category now termed 'other specified/unspecified' disorder, the most common category.

While there is a large unmet need, outcomes with treatment are good with most patients making a sustained recovery.[5,6] Even for anorexia nervosa, up to 40% of patients will make a good recovery within five years, a further 40% will make a partial recovery and those with persistent illness may yet benefit from supportive therapies. At least 50% of people with bulimia nervosa fully recover and the outcomes with treatment are also as good if not better for binge eating disorder.

## Risk factors

Eating disorders are associated with heritable psychological and physical vulnerabilities, most notably:

- a predisposition for perfectionism and compulsivity
- mood intolerance and impulsivity
- obesity (more likely in bulimic and binge eating disorders).

Environmental factors such as adverse life experiences including trauma and abuse, often associated with ensuing low self-worth, can also play a role. Exposure to the western ideal of being thin and restrictive dieting appears to be a specific risk factor.

Comorbidity is common. Mood, anxiety (especially social phobia) and substance use disorders occur most frequently.[3]

### *Box 1* Definitions and features of eating disorders

**Anorexia nervosa**

- underweight for age and height
- self-starvation
- compulsive exercising is common
- with or without episodes of binge eating and extreme weight control behaviours
- self image that is unduly influenced by weight and shape
- often age of onset in early teens or younger[2]
- 10 times more likely in females

**Bulimia nervosa**

- uncontrollable overeating followed by extreme weight control behaviours such as vomiting or purging (laxative or diuretic abuse)
- self view that is unduly influenced by weight and shape
- 10 times more likely in females

**Binge eating disorder**

- recurrent regular binge eating
- patients often struggle with being overweight or obese
- often a midlife disorder with similar incidence in males and females[1,3]

**Other specified/unspecified feeding or eating disorder**

- patients who do not conform to the other categories – e.g. they have mixed or additional eating problems


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## Assessment

Most patients present late in the course of illness. Up to 50% of adults with anorexia nervosa may never seek treatment and people with bulimia nervosa present on average a decade or more after onset. When people do seek help, it is most often first from their family doctor and frequently for advice on weight loss, whether they are normal or overweight. People with anorexia nervosa, in particular, are ambivalent about treatment. A key task for health practitioners is motivating patients to commit to better nutrition and engaging them in psychological therapies to bring about sustained change.

All people presenting with an eating disorder need psychiatric and physical assessment. The history should include questions about:

- diet and attitudes to food
- weight, shape and body image
- common comorbidities, for example depression and/or an anxiety disorder
- risk of self-harm and suicide
- predisposing factors.

Physical examination should include cardiovascular status and a calculation of body mass index (BMI) based on weight and height (kg/m$^2$). Potential complications and important biochemistry tests are listed in Box 2.

In anorexia nervosa, physical complications of starvation are also present. While amenorrhoea may be removed from diagnostic criteria, it remains a useful indicator of starvation severity and the need for bone densitometry in women. Testing hormone levels will confirm hypogonadism, but is not essential. Women with eating disorders may present for infertility treatment. For those who become pregnant, it can be a stressful and challenging time.[7]

## Role of the general practitioner

GPs play a key role in early identification of eating disorders and the SCOFF questionnaire is a reliable and valid screening tool that can be used (Box 3).[8] They also have a valuable role in the management of these disorders (Box 2) and are the key link in access to specialist services and psychological therapies. They provide important support to families and carers, and doctors who have an interest in mental health may also provide psychotherapy. Cognitive behavioural guided self-help[9] is suitable for primary care.

## Anorexia nervosa

Although the evidence base for anorexia nervosa continues to be the least developed of the eating

### *Box 2* An overview of management of eating disorders in primary care

**Primary prevention**

Promotion of healthy attitudes towards body shape and weight

Promotion of good nutrition and exercise for health and social benefits

Identification and management (where appropriate) of risk factors (e.g. obesity)

**Detection and treatment**

Ask about symptoms of eating disorder

Education and family counselling

Supportive psychotherapy

Nutritional counselling

Cognitive behaviour therapy (with appropriate training)

Monitor for medical complications

Correct electrolytes and any deficiencies e.g. iron

Consider pharmacotherapy

Specialist referral (where appropriate) – with shared-care responsibility

**Usual investigations and associated complications**

Renal function and electrolytes (dehydration and hypokalaemia)

**Additional investigations in anorexia nervosa**

Full blood count (anaemia, leucopenia)

Magnesium and phosphate (low levels can precede re-feeding syndrome)

Liver function (raised liver enzymes)

Thyroid function ('sick euthyroid' syndrome)

Fasting glucose (hypoglycaemia)

Iron, vitamin $B_{12}$ and folate (may be deficient)

Electrocardiogram (risk of arrhythmia)

Bone densitometry (for osteopenia related to sustained hypogonadism)

### *Box 3* Screening questions for identifying eating disorders in primary care

**The SCOFF questionnaire** [8]

**S** – do you make yourself **S**ick because you feel uncomfortably full?

**C** – do you worry you have lost **C**ontrol over how much you have eaten?

**O** – have you recently lost more than 6.35 kilograms (**O**ne stone) in a three month period?

**F** – do you believe yourself to be **F**at when others say you are too thin?

**F** – would you say **F**ood dominates your life?

One point for every yes

A score of ≥2 indicates further questioning is warranted

A further two questions have been found to have a high sensitivity and specificity for bulimia (but are not diagnostic):

- Are you satisfied with your eating patterns? ('no')
- Do you ever eat in secret? ('yes')

disorders, a clearer understanding is emerging of what works and for whom. There is evidence from randomised controlled trials and prospective clinical studies that early and younger age at onset (under age 18 and within the first three years of illness) are together associated with good outcomes. The treatment of choice for this group is a family-based approach.[10] This therapy moves through three phases (Box 4) in which parental experience and expertise is engaged as a therapeutic tool.

In adults with anorexia nervosa and when family-based treatment is not possible or inappropriate, individual psychotherapy is the approach of choice. Cognitive behaviour therapy or other specialised individual psychotherapies (with the exception of interpersonal psychotherapy) have support from randomised controlled trials. An extended form of cognitive behaviour therapy[11] for bulimia nervosa has been developed and evaluated for use in all eating disorders (Box 4). It addresses the core eating behaviours and body image concerns and re-feeding. Complicating problems such as mood intolerance, low self-esteem, clinical perfectionism and interpersonal deficits are also considered.

In conjunction with psychotherapy, all patients need to be re-fed and monitored for medical complications. Re-feeding is the phase of gradual increase in food to promote weight regain and normalisation of eating behaviour. A dangerous reduction in serum electrolytes (phosphate, potassium and magnesium) can precipitate the re-feeding syndrome. This can cause arrhythmias, seizures and potentially death.

The majority of people are treated as outpatients with a collaborative approach. A dietitian provides essential expertise for meal planning and nutritional care in the re-feeding phase. Treatment goals include improved nutrition as one of the 'non-negotiables'.

When it is not possible to reverse weight loss or weight loss is rapid and severe and there may be medical and psychiatric complications, patients will require more intensive residential day or inpatient care. Children and adolescents (who may suffer growth retardation) and pregnant women are at particular risk. Compulsory treatment is now rare, but can be life saving. While a small number develop severe and enduring illness it is most important not to lose hope as improvements and even recovery can still occur.[12]

### *Pharmacotherapy* [13]

Antidepressants appear to offer little benefit for the dysphoria or depression associated with starvation. However, they are useful when there is comorbid major depression. There is insufficient evidence for the newer antipsychotics (for example quetiapine).[14] They are however used off-label in low doses in the re-feeding phase where it is thought they ameliorate psychological distress and anxiety. They should be withdrawn following weight regain and monitoring metabolic status is important as with any patient treated with antipsychotics.

*Box 4* **Psychological treatment approaches in eating disorders**

**Family-based treatment for anorexia nervosa** [10]

Parental empowerment to facilitate re-feeding the patient (including having a family meal)

Negotiating a new pattern of relationships

Establishing healthy relationships between the adolescent or young adult and the parents (with increased personal autonomy for the adolescent)

**Cognitive behaviour therapy**[11] **for anorexia nervosa, bulimia nervosa and binge eating**

Psycho-education and introduction to daily monitoring of relevant thoughts and behaviours

Prescribe 'normal' eating and prohibit dietary restriction

Gradual reintroduction of avoided foods into the diet

Cognitive restructuring of problematic beliefs

Problem solving

Relapse prevention strategies and addressing lapses

## Bulimia nervosa and binge eating disorder

Cognitive behavioural therapy[11] is the first-line treatment for bulimia nervosa (Box 4). It is also appropriate for binge eating disorder. In both disorders, it reduces binge eating and other eating symptoms and improves mood and general well-being. Additional modules, particularly the training in skills to regulate mood, improve outcomes in patients with additional psychological problems.[15]

When patients are overweight, increasing physical activity that is not compulsive but enjoyable and preferably sociable (for example tennis vs solitary gym exercises), and 'mindful' eating may be helpful in weight management. In treating comorbid obesity it is important to be cognisant that physical health and a healthy diet are not usually realised by any absolute weight, and may be found in people with a BMI range up to 30 (kg/m$^2$).

Inpatient admission is seldom required. Indications are pregnancy (as there is increased risk of spontaneous first trimester abortion in bulimia nervosa), severe symptoms (and failed outpatient care), and the presence of psychiatric complications such as suicidality.

ARTICLE

### *Pharmacotherapy* [13]

Selective serotonin reuptake inhibitors in high doses reduce binge eating and improve other symptoms in bulimia nervosa and binge eating disorder. The best evidence is for fluoxetine 60 mg daily.[16-18]

Antidepressants are also used to treat comorbid major depression when present. However, unlike extended cognitive behavioural therapy, maintenance of change is unclear and they are mostly used as an adjunct to psychotherapy. Effects on weight loss in binge eating disorder are mixed. In contrast topiramate may reduce binge eating and weight, but in randomised controlled trials the rate of adverse effects and discontinuation was high.[19]

## Conclusion

Eating disorders have moderate to high morbidity and increased mortality. However, many people with an eating disorder present late (if at all) for treatment. Early identification is associated with good outcomes, particularly for anorexia nervosa in children and adolescents and for bulimia nervosa and binge eating. Evidence-based treatments include family-based therapy for young people with anorexia nervosa, and a specific form of cognitive behavioural therapy with or without a selective serotonin reuptake inhibitor in bulimia nervosa and binge eating disorder. Optimal management should include coordinated care between primary and specialist care. ◀

*Professor Hay is deputy chair of the National Eating Disorders Collaboration. The views expressed in this article are entirely her own. There are no funding sources relevant to this article to declare.*

See also Eating disorders: the patient's perspective. www.australianprescriber.com/magazine/21/4/artid/277

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### SELF-TEST QUESTIONS

*True or false?*

3. Family-based therapy for adolescents with anorexia nervosa is the first-line treatment.
4. Fluoxetine can improve symptoms in bulimia nervosa.

*Answers on page 179*

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## The Butterfly Foundation

The Butterfly Foundation is a national organisation providing information and support for people with eating disorders. A phone line offers confidential counselling, as well as information on local support organisations across the country. Support is also available by email and one-on-one web chats.

The website contains useful factsheets about body image, anorexia and bulimia, and tips for recovery. The Butterfly Foundation's Twitter (@BFoundation) and Facebook sites are popular sources of information. Some financial relief is offered for those unable to afford treatment.

### Contact

| | |
|---|---|
| National Support Line | 1800 334 673 (Mon–Fri 9am–5pm AEST) |
| Website | www.thebutterflyfoundation.org.au |
| Email | support@thebutterflyfoundation.org.au |

### See also

| | |
|---|---|
| Eating Disorders Victoria | www.eatingdisorders.org.au |
| Eating Disorders Association Queensland | http://eda.org.au |

ARTICLE

# Rational use of topical corticosteroids

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**Key words**
atrophy, cream, ointment, pregnancy, vehicle

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## SUMMARY

Many dermatological conditions will respond to a topical corticosteroid. The clinical outcome will depend on making a correct clinical diagnosis and applying the right molecule in the most appropriate vehicle for the correct duration.

Topical corticosteroids are classified by their strength, but the same molecule will have different effects depending on the vehicle. The patient's age and the affected area of skin are other important factors.

If used correctly the adverse effects of topical corticosteroids are usually minimal. Systemic effects can occur with high doses.

## Introduction

Skin conditions represent 10% of the problems managed in general practice,[1] and many inflammatory skin diseases are treated with topical corticosteroids.[2]

Before prescribing a topical corticosteroid it is important to be certain of the diagnosis as the drugs exacerbate some conditions, such as tinea. Topical corticosteroids may be underused or overused, so it is important that the patient knows what the treatment is and how it should be applied.

## Molecules and vehicles

There are many topical corticosteroids which are available in a variety of strengths and in different vehicles. The classification of topical corticosteroids was based on how much vasoconstriction they cause and on some comparative clinical trials. The USA classification ranges from Class 1 (most potent) to Class 7 (least potent), whereas the UK classification has four different categories (Table). The Australian Medicines Handbook and Therapeutic Guidelines class topical steroids as mild, moderate, potent and very potent, while the Schedule of Pharmaceutical Benefits lists them as weak, moderately potent and potent.

Topical preparations may have the same or similar active compound but differ in their concentration or vehicle, which ultimately affects their potency, absorption and efficacy. As an example, betamethasone dipropionate 0.05% is found in a number of categories. By changing its vehicle from a cream to an ointment its potency increases from moderate to potent (UK category III to II), and when it is delivered in an optimised vehicle it becomes very potent (category I).

In general, ointments improve the drug's penetration as they occlude the skin and enhance hydration and absorption. However, ointments are greasy and difficult to spread. This is sometimes an important reason for a patient's poor adherence to treatment.

Creams are a combination of one or more non-mixable liquids and an emulsifying agent. They are less greasy than ointments, very easy to spread and are washable in water.

Lotions are insoluble preparations dispersed into a liquid. They may need shaking to get the mixture ready for use, but are easy to apply, can cover extensive areas and are preferred for children (due to their more permeable skin) and on hairy skin.[5]

## Mechanism of action

Topical corticosteroids act by binding to a specific receptor in the cellular cytoplasm and modulating the transcription of multiple genes. This leads to the suppression of the production of inflammatory substances such as prostaglandins and leukotrienes, and also inhibits the recruitment of inflammatory cells into the skin.

## Adverse effects

Although topical corticosteroids are relatively safe, they can produce local (more frequent) and systemic (infrequent) adverse effects when used incorrectly.[6] High potency topical corticosteroids should not be used on areas of thin skin (for example face, flexural sites, scrotum, eyelids) as absorption is increased. They should not be used on denuded skin or for longer periods. Caution is needed if these drugs are used under occlusion, in children or in elderly patients.

### *Local effects*

Atrophy of the skin is one of the most common cutaneous adverse effects. There is an increase in skin transparency and brightness, telangiectasia, striae and easy bruising. Scars and ulceration may appear due to dermal atrophy. The use of topical corticosteroids on the face can induce eruptions such as steroidal rosacea, acne and perioral dermatitis.

Less frequent local adverse effects include hypopigmentation, delayed wound healing and

glaucoma when corticosteroids are applied around the eye. Contact sensitivity to preservatives in the product or the corticosteroid itself may occur and clinically it can be suspected by persistence or worsening of the skin disease.

Other adverse effects include:

- disease recurrence due to a rebound effect when treatment is stopped
- tachyphylaxis or loss of clinical improvement after a period of use (although frequently reported, it has not been observed in clinical trials)
- masking or stimulation of some cutaneous infections (for example tinea incognito).

### *Systemic effects*

Systemic adverse effects are uncommon and are mostly associated with the use of high potency topical steroids in large or denuded areas, under occlusion or in severe skin disease. Reversible suppression of the hypothalamic–pituitary–adrenal axis has been described in children with doses as little as 14 g per week. Moreover, stopping therapy may induce an Addisonian crisis. Other systemic effects include Cushing's syndrome, diabetes mellitus and hyperglycaemia.

## Recommendations for topical corticosteroid use

Establishing a diagnosis is essential to choosing the appropriate topical corticosteroid. Once a diagnosis has been made, several considerations influence the choice.[5,7] It is also important to ask if the patient has already been using an over-the-counter topical corticosteroid.

### *Disease responsiveness*

On thin skin, inflammatory skin conditions like intertriginous psoriasis, children's atopic dermatitis, seborrhoeic dermatitis and other intertrigos are highly responsive and will respond to a weak topical corticosteroid. Psoriasis, adult atopic dermatitis and nummular eczema are moderately responsive diseases so require a medium potency corticosteroid. Chronic, hyperkeratotic, lichenified or indurated lesions, such as palmo-plantar psoriasis, lichen planus and lichen simplex chronicus, are the least responsive diseases and require high potency topical corticosteroids.[5]

As a general rule, topical corticosteroids should not be used in patients with rosacea, perioral dermatitis or acne. Skin infections are also a contraindication.

### *Location*

The anatomical site, specific characteristics of the stratum corneum and skin lipid structure affect the penetration and absorption of topical corticosteroids. For example, absorption on the palms, soles (0.1–0.8%) and forearms (1%) is poor, compared to the face (10%), scalp and intertriginous areas (about 4%). Other areas such as the scrotum and eyelids will absorb up to 40%

*Table* **Classification system for commonly used topical corticosteroids** [3,4]

| | Presentations available | | |
|---|---|---|---|
| | **Ointment** | **Cream** | **Lotion** |
| **Superpotent – Class 1 USA, Class I UK** | | | |
| Betamethasone dipropionate 0.05% in optimised vehicle | X | | |
| Clobetasol propionate 0.05% | X | | |
| **High potency – Class 2/3 USA, Class II UK** | | | |
| Betamethasone dipropionate 0.05% | X | | |
| Betamethasone valerate 0.1% | X | | |
| Mometasone furoate 0.1% | X | X | |
| **Moderate potency – Class 4/5 USA, Class III UK** | | | |
| Betamethasone dipropionate 0.05% | | X | X |
| Betamethasone valerate 0.05% | X | X | |
| Triamcinolone acetonide 0.1% | | X | |
| Methylprednisolone aceponate 0.1% | X | X | X |
| Clobetasone 0.05% | | X | |
| **Low potency – Class 6/7 USA, Class IV UK** | | | |
| Hydrocortisone or hydrocortisone acetate 0.5%, 1% | X | X | X |
| Desonide 0.05% | X | X | X |

of applied drugs. Potent topical corticosteroids and prolonged use of lower strength topical corticosteroids should be avoided in these areas.

Dermatoses of the face and intertriginous areas are best treated with low-strength preparations. Lesions on the palms and soles frequently require treatment with high potency topical corticosteroids.

If the affected area is large, use low to medium potency corticosteroids to reduce the likelihood of systemic effects.

### *Vehicle*

Although ointments are generally the most effective vehicle for treating thick, fissured, lichenified skin lesions, patients may consider them cosmetically unappealing. Ointments should not be used in flexural or intertriginous areas due to high absorption. Creams are generally well accepted on most areas of the skin except the scalp.

Lotions are useful for extensive areas, while solutions, gels, sprays and foams are useful for the scalp and hairy skin. These products can produce irritation when applied to acute dermatoses.

### *Amount*

A single application to the whole body of an adult will require 30 to 40 g of product. An area of one hand (palm and digits) will require 0.3 g per application. No more than 45 g/week of potent or 100 g/week of a moderately potent topical steroid should be applied if systemic absorption is to be avoided. In children, the amounts should be smaller.

### *Frequency of application*

This depends on the selected topical corticosteroid and the site to be treated. Application once or twice daily is usually sufficient, but frequency may increase when treating areas where the preparation can easily be wiped off (for example palms and soles). Treatment under occlusion should be avoided and only prescribed by specialists familiar with the use of corticosteroids and the condition to be treated.

### *Treatment duration*

The shortest course of treatment is recommended for acute diseases, although small recalcitrant lesions may need to be treated for longer. Treatment should not be longer than two weeks on the face and 3–4 weeks on the rest of the body. For longer treatment periods, intermittent therapy such as every other day, weekend-only application or a resting period of 1–2 weeks between cycles may be an option. Very short treatments (1–3 days) will not provide enough improvement of some conditions and this may be wrongly interpreted as unresponsiveness.

### *Children*

Children, especially infants, are more susceptible to adverse effects. They have difficulty in metabolising potent corticosteroids and their skin surface area:body weight ratio increases systemic absorption. Topical treatment in children should be used with extreme caution. Prescribe a low potency corticosteroid and preferably for short periods. An application under occlusion in the nappy area or under plastic should be avoided.

### *Pregnancy and lactation*

All topical corticosteroids are classified category C by the US Food and Drug Administration, but some are classified category A by the Therapeutic Goods Administration (www.tga.gov.au/hp/medicines-pregnancy.htm). Studies in animals have shown that topical steroids are systemically absorbed and may cause fetal abnormalities. Limited and inconclusive data are available for humans, however there seems to be an association between very potent topical corticosteroids and fetal growth restriction.[8,9] Caution is needed, but topical corticosteroids have been frequently used in pregnancy.

Although the mechanism of topical corticosteroid excretion in breast milk is unknown, there are no reported adverse effects during lactation. These drugs should not be applied directly to the nipples before breastfeeding.

## Adjunctive treatments

Patients should be given advice about skin care. This includes the use of soap-free cleansers and moisturiser which will affect the skin's overall integrity and improve the clinical outcome.

## Conclusion

Topical corticosteroids are safe and effective drugs. Always establish a clinical diagnosis before prescribing. Choose an appropriate topical corticosteroid according to the affected area, patient's age, clinical presentation and predicted responsiveness to treatment.

Monitor the clinical response, even if symptoms have resolved. Consider changing or even stopping treatment according to the response. Also monitor for adverse effects and cease the drug straight away if there is skin damage.

Refer to a dermatologist if the disease does not respond to treatment or when the diagnosis is unclear. <

*Conflict of interest: none declared*

ARTICLE

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Q:

### SELF-TEST QUESTIONS

*True or false?*

5. The potency of a topical corticosteroid is likely to be increased if it is formulated as an ointment, rather than as a cream.

6. Topical corticosteroids are contraindicated during lactation.

*Answers on page 179*

# Book review

**Therapeutic Guidelines. Management guidelines: developmental disability.** Version 3.

Melbourne: Therapeutic Guidelines Limited; 2012. 303 pages

This book provides a practical approach to the management of developmental disability. Several chapters have been revised and this version offers new chapters on common presentations of developmental disability, oral health, dysphagia, nutrition, preventive health care and health promotion, men's health, fetal alcohol syndrome and neurofibromatosis type 1.

The book incorporates the International Classification of Functioning, Disability and Health used by the World Health Organization, refreshing the previous medical model and emphasising function, activity and participation. There are chapters focusing on the lifespan, including stages from birth, methods of delivery of information to new parents, adolescence, transition to adulthood, ageing and related medical health issues, and screening and preventive health. Issues of consent, legal framework and capacity and guardianship laws will assist with medical management.

Useful tables with checklists and highlighted boxes include differential diagnoses and appropriate referrals for developmental delay, health concerns for adolescents and adults with developmental disability, and useful questions and data sheets for monitoring challenging behaviour. These tables are clear and provide excellent summaries for a busy clinician. At the end of several chapters are clinical scenarios illustrating management points.

There are chapters devoted to the assessment, management and drug treatment of behaviour and psychiatric illnesses. Specific developmental disabilities are also covered and include Angelman syndrome, autism spectrum disorder, cerebral palsy, Down syndrome, fetal alcohol syndrome, fragile X syndrome, neurofibromatosis type 1, Noonan syndrome, Prader-Willi syndrome, Rett syndrome, tuberose sclerosis and Williams syndrome. References and lists of further reading allow for wider information to be sought.

The layout of the book and its size make it an easy read and excellent summary for the GP, paediatrician, adult physician and multidisciplinary team. A list of resources for each state and up-to-date telephone numbers and online resources are helpful for finding the myriad of organisations in disability.

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ARTICLE

# Principles for managing attention deficit hyperactivity disorder

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**Key words**
atomoxetine, dexamphetamine, methylphenidate, psychostimulant drugs

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## SUMMARY

Attention deficit hyperactivity disorder in children is characterised by developmentally excessive symptoms of inattention, impulsiveness and hyperactivity. This disrupts learning, socialisation and family life.

The cause is a complex interaction of biopsychosocial factors. Comorbid mental health problems are common.

General practitioners may detect the problem, but confirmation of the diagnosis requires a specialist psychiatrist or paediatrician. The child's general practitioner then has a vital role in ongoing care.

The children need psychosocial interventions, but if these are ineffective drug treatment can be added. Psychostimulants (dexamphetamine and methylphenidate) are effective first-line drugs.

## Introduction

Children and adolescents with attention deficit hyperactivity disorder (ADHD) have significant impairment in their daily life due to developmentally excessive and pervasive, hyperactive, impulsive and inattentive behaviour. Estimates of the prevalence of ADHD vary because of the diagnostic methods and criteria used (DSM-IV-TR[1] was more inclusive than ICD-10[2]), and because of cultural and demographic characteristics. The most recent Australian survey in 2000 found that 11% of 6–17 year-olds had symptoms.[3] The prevalence estimates vary from 1.5% in Europe to 5% in the USA for clinical cases of ADHD in primary school-aged children. In clinic populations ADHD is at least twice as common in boys, but is more likely to persist in girls.

The diagnostic criteria in DSM-IV-TR are essentially unchanged in the new DSM-5.[4] However, in DSM-5 symptoms must start before 12 years of age, not seven years, and only four instead of six symptoms of both inattentiveness and hyperactivity are required for the diagnosis in individuals older than 16 years.

## Aetiology

For some children the likely explanation for their symptoms is a condition such as fetal alcohol syndrome, a genetic disorder such as fragile X syndrome, an acquired brain injury, or parental abuse and neglect. For most the explanation is usually more complex and indeterminate.

ADHD results from an interaction of various biological, environmental and social factors.[5] Family heredity is common and is associated with gene variants for specific dopamine and noradrenaline neuroreceptors and structural differences in brain areas such as the frontostriatal cortex. These brain regions are critical for attention, working memory, executive function and the regulation of emotions and behaviour.

Environmental influences such as the effects of maternal alcohol consumption on the fetal brain, malnutrition, food colourings (tartrazine), exposure to lead and the impact of neglect and abuse during infancy have the capacity to adversely affect the developing brain and impair attention and behavioural control. The quality and consistency of formative social, parenting and educational experiences also act to either build resilience or contribute to inattention and hyperactivity.

## Comorbidity

The majority of children with ADHD have comorbid mental health problems. Hostile and argumentative behaviour (oppositional defiant disorder) is a challenge in about 30% of children. This is a risk for the subsequent emergence of offending and antisocial behaviour conduct disorder in approximately 3% of older children and adolescents with ADHD.

Around 75% of children with a tic disorder (for example Tourette's disorder) have ADHD symptoms. The emergence or worsening of tics may be an adverse effect of stimulant medication.

Anxiety (generalised, separation, school refusal, social, or obsessive compulsive) is common in about a third of children with ADHD. A similar proportion of older children and adolescents with ADHD also experience depression and irritability that is usually persistent (dysthymia). Suicidal behaviour can be a risk, perhaps exacerbated by impulsiveness.

Neurodevelopmental problems are common and adversely affect learning (spelling, writing, reading and numeracy), motor coordination, and speech and language skills. At least 20% of children with an autism spectrum disorder have problems with inattention, impulsiveness and hyperactivity. Unfortunately, these symptoms of ADHD may be less responsive to stimulant medication and adverse effects are more likely. In DSM-IV-TR, the diagnosis of autistic disorder precluded a diagnosis of ADHD, however in DSM-5 ADHD is recognised as a comorbid diagnosis.

## Assessment and diagnosis

General practitioners have a key role to play because they understand the family, community and cultural context. They can review the child again and assess if the difficult behaviour is developmentally excessive. Parents first contact their doctor because of concern about the child's behaviour and the stress this is causing the family. Referral also comes from other professionals such as a maternal and child health nurse, or school psychologist. In addition to a specialist referral and referral to a psychologist and speech pathologist, GPs can link the family with support services and provide information on child development.

General practitioners may suspect a child has ADHD, but the diagnosis should be confirmed by a specialist. It requires a comprehensive assessment of the:

- spectrum of symptoms of inattention, impulsiveness and hyperactivity
- developmental history
- cognitive and learning skills
- physical and mental health
- family and social environment
- cultural context.

This requires the expertise of a child and adolescent psychiatrist or a paediatrician, supported when necessary by assessments from a clinical psychologist or neuropsychologist, a speech pathologist and perhaps an occupational therapist or physiotherapist. In rural areas GPs with training in child development and ADHD can be supported to undertake an assessment during a telemedicine consultation with a specialist.

The diagnosis is based on clinical judgement and the application of DSM-5 (previously DSM-IV TR) or ICD-10 criteria. These are met if the symptoms:

- started before the age of twelve years (seven years in DSM-IV)
- are excessive for the child's developmental level
- persist for at least six months
- are pervasive in more than one setting, and disabling
- are not due to another mental disorder such as an anxiety disorder.

A structured cognitive assessment is invaluable if available, as it defines associated attention and cognitive problems such as impaired short-term auditory memory, intellectual disability, and learning and motor coordination disorders. Information from a variety of settings, using structured parent and teacher questionnaires and perhaps direct observation, as well as a physical and neurological examination puts the symptoms into context.

## Treatment guidelines

In 2009 the Royal Australasian College of Physicians developed draft guidelines on ADHD. These were placed on the website of the National Health and Medical Research Council (NHMRC). However, these guidelines were not approved by the NHMRC because some unspecified work of overseas researchers, whose publications were often cited in the draft guidelines, was potentially open to bias due to conflicts of interest.

In the absence of a detailed Australian guideline the NHMRC established an expert working group to prepare clinical practice points as evidence-based, practical advice to Australian clinicians on the assessment and management of children and adolescents with ADHD. The NHMRC approved these clinical practice points in 2012.[6] They complement other more comprehensive clinical guidelines such as those by the National Institute of Clinical Excellence[7], the Scottish Intercollegiate Guidelines Network[8] and the American Academy of Pediatrics[9].

## Management

Given the complex interaction of biological, cognitive, family and social factors and comorbid conditions, treatment begins with a comprehensive assessment. This guides the management plan. The management is first focused on parent education and skills training, educational and behaviour management strategies, and treatment of comorbid problems, such as speech therapy for language disorder or cognitive behaviour therapy for anxiety. The GP has a key coordinating role especially if a mental health care plan, allied health care or psychological treatment is required. There is insufficient evidence on the benefits or harms of elimination and supplementary diets, naturopathic and physical activity to recommend their use.[6]

Parental involvement and consultation with others involved in the care of the child – such as teachers, an Aboriginal and Torres Strait Islander education worker or a disability case manager – is essential to facilitate

a consistent and sustained approach to management. If these psychosocial strategies fail, drug treatment is indicated.

## Drug treatment

This treatment is usually started by a specialist paediatrician, child psychiatrist or neurologist approved by the relevant Australian State or Territory to prescribe restricted stimulant drugs.

### *Psychostimulants*

Stimulant drugs are usually the first choice. There is consistent evidence that they reduce the symptoms of ADHD, improve cognitive and learning difficulties and improve family and social adjustment in the medium term of up to three years.[10] As yet there is no clear evidence for the longer-term (beyond three years) superiority of stimulant medication compared to behaviour management or to these treatments combined, but children with the best response to any of these treatments have the best long-term outcomes.[10]

Dexamphetamine sulfate and methylphenidate are short acting (2–6 hours) and therefore usually require 2–3 doses each day (see Table)[11]. Modified slow-release forms of methylphenidate are available which smooth out the drug concentration over a longer period of the day and are useful if there is a problem with compliance or stigma with taking a dose at school or adverse effects due to fluctuations in drug concentration. The equivalent dose of a modified form may be more than the combined daily dose of the short-acting form. In the short to medium term (up to three years), drug treatment alone or combined with behavioural treatment is more effective than psychosocial and behavioural treatment alone.

### *Precautions*

Before drug treatment begins, measure weight, height, pulse and blood pressure. An ECG or further cardiovascular investigations can be performed if there is a personal or family history of heart disease.

When treatment begins, weekly monitoring is required as it usually takes several weeks to find the

*Table* **Psychostimulant drug regimens** [11]

| | Action | Daily dose | Monitor |
|---|---|---|---|
| **Dexamphetamine sulfate** (immediate release) | onset 20–60 minutes<br>duration 3–6 hours | initially 2.5–5 mg after breakfast, titrated weekly<br>give in 2–3 divided doses when dose is above 5 mg (max 20 mg, occasionally 40 mg) | blood pressure<br>pulse<br>height and weight<br>sleep<br>appetite<br>tics<br>mood<br>risk of drug diversion<br>may have more adverse effects than methylphenidate[11] |
| **Methylphenidate** (immediate release) | onset 20–60 minutes<br>duration 2–4 hours | initially 5–10 mg after breakfast titrated weekly up to 2 mg/kg/day in 2–3 divided doses (max 40 mg) | blood pressure<br>pulse<br>height and weight<br>sleep<br>appetite<br>tics<br>mood |
| **Methylphenidate** (modified release) | onset 20–60 minutes<br>duration 8–12 hours | may require slightly more than the combined daily dose of the immediate form | as for the immediate form<br>discontinue if no benefit seen in one month, as the response may not always be equivalent or better than with the immediate release form |
| **Atomoxetine** | benefit develops over 4–6 weeks | children ≤70 kg start with 0.5 mg/kg/day increasing after 3 days to 1.2 mg/kg/day, then if indicated after 2–4 weeks to 1.4 mg/kg/day or 100 mg max, whichever is less<br>children/adults >70 kg start with 40 mg/day then increasing after 3 days to 80 mg/day to a max of 100 mg/day after 2–4 weeks if indicated | pulse<br>blood pressure<br>height and weight<br>mood<br>suicidal ideation*<br>liver function |

* See: Atomoxetine and suicidality in children and adolescents. Medicines Safety Update. Aust Prescr 2013;36:166.

optimum dose. Symptom checklists and standardised parent and school reports are robust methods for following the response. The GP is best placed to review the child weekly, then monthly. The specialist reassesses the child every six months and considers the justification for the continuation of treatment or a trial of withdrawal. Other family, school and social problems may require intervention and occasionally the illegal use of the drug by the child or parent (drug diversion) might emerge. If there is no benefit after titration to the maximum tolerable dose then alternative treatments should be considered.

### *Adverse effects*

Common adverse effects to stimulant medication are reduced appetite, nausea, headache and initial insomnia, although insomnia is also a symptom of ADHD. Anxiety, irritability, tics, growth retardation[12] and more rarely palpitations and minor increases in blood pressure and manic excitement might occur. Adverse effects may be more likely in children under seven years of age. For these young children drug treatment should be started at a low dose and frequently reviewed.

Currently there is no evidence of long-term adverse effects. Most of the known adverse effects are reversible and can usually be managed by clinical care and dose adjustment. Delay in growth is likely to attenuate after three years of treatment, but there is a risk of delayed pubertal maturation pointing to the need to use the lowest effective dose and regularly review the justification for stimulant therapy.[12]

### *Other drugs*

Atomoxetine, a selective inhibitor of noradrenaline reuptake, is a second-line treatment. It can be used when tics or anxiety are a problem or when a once-daily dose is necessary. Suicidal thinking and liver disease are potential adverse effects which require monitoring.

Clonidine is a third-line treatment which reduces hyperactivity and impulsiveness more than inattention. It is given at a low dose that avoids sedation and hypotension, usually as a single or twice-daily dose of 50–100 microgram.[13] Antipsychotic drugs such as risperidone do not have an evidence-based role in the treatment of ADHD. They are used to treat aggression and mood instability, particularly in young people with both ADHD and neurodevelopmental disorders such as autism.

## Prognosis

Given the developmental nature of ADHD symptoms, regular review by the GP supported by the specialist is required to help the child move through the transitions of childhood and adolescence into young adult life. The best outcomes occur when there is a working relationship with the child, the parents and others such as teachers, which takes account of the community and cultural context.

With brain maturation the prevalence of ADHD symptoms reduces through adolescence. However, young people with ADHD symptoms, particularly of inattention, and associated learning difficulties and problems with mental health are more likely to experience persistent difficulties with relationships and employment and offending behaviour in adult life.

*Bruce Tonge was the chair of the National Health and Medical Research Council Expert Working Group which produced the Clinical practice points on the diagnosis, assessment and management of attention deficit hyperactivity disorder.*[6]

Q:

### SELF-TEST QUESTIONS

*True or false?*

7. The symptoms of attention deficit hyperactivity disorder begin before the age of 12 years.

8. Risperidone is an effective treatment for attention deficit hyperactivity disorder.

*Answers on page 179*

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Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

# Medicines Safety Update

Volume 4, Number 5, October 2013

## In this issue


- Atomoxetine and suicidality in children and adolescents
- Rotavirus vaccination and the risk of intussusception
- Drug-induced liver injury


# Atomoxetine and suicidality in children and adolescents

Serious adverse events reported to the TGA, including one case involving the death of a child, reinforce the importance of health professionals adequately informing parents and caregivers of the risks of suicidal ideation and behaviour in children and adolescents being prescribed atomoxetine (Strattera).

Atomoxetine is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD), as defined by DSM-IV criteria, in children aged 6 years and over, adolescents and adults.

The risks of suicidal ideation and behaviour with atomoxetine are well known and are reinforced in the Product Information in the precautions section, as well as in a boxed warning.

## Clinical trials

A greater risk of suicidal ideation was observed in children and adolescents receiving treatment during clinical trials compared with placebo. A pooled analysis of 12 short-term (6–18 weeks) trials (11 in ADHD and one in enuresis) showed the average risk of suicidal ideation in patients treated with atomoxetine was 0.4% (5/1357) compared with 0% (0/851) in patients treated with placebo. One suicide attempt was reported in patients being treated with atomoxetine.

## Adverse event data

To July 2013, the TGA received 74 reports of psychiatric disorders associated with atomoxetine. In 65 of these cases, atomoxetine was the sole suspected medicine. Over half of the reported cases (42) were reports of suicidal ideation. Of the 38 reports of suicidal ideation in which the age of the patient was given, 28 reports were in children and adolescents aged 18 years and under. The TGA also received two reports of attempted suicide in children and adolescents and one report of completed suicide in a child being treated with atomoxetine.

## Information for health professionals

When considering prescribing atomoxetine in children and adolescents, health professionals should carefully weigh the risks of suicidality against the benefits of atomoxetine therapy.

Patients who are prescribed atomoxetine should be carefully monitored for suicidality, especially in the first few months of treatment and whenever there is a change in dose.

Parents and caregivers should be warned of the risks and alerted to the need to monitor for signs of unusual changes in behaviour or precursors of suicidality, such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania or mania. Parents and caregivers should also be advised of the importance of seeking immediate medical attention if such signs are identified.

Health professionals are encouraged to report all adverse events associated with atomoxetine to the TGA.

Medicines Safety Update is the medicines safety bulletin of the Therapeutic Goods Administration (TGA)

TGA Health Safety Regulation

MEDICINES SAFETY UPDATE

# Rotavirus vaccination and the risk of intussusception

Health professionals are advised that a recently completed study has confirmed that there is an elevated risk of intussusception following the first and second doses of rotavirus vaccines, Rotarix and RotaTeq.

The TGA, working in collaboration with state health authorities, has completed an investigation into this association. Interim results of the investigation were published on the TGA website in February 2011 and in Medicines Safety Update in April 2011.[1]

The final study included data from six jurisdictions (NSW, Victoria, Western Australia, South Australia, Queensland and the Northern Territory) for a three-year period from July 2007 to June 2010.[2] Validated cases of intussusception in children aged 1–12 months were identified from hospital admissions data and, in some states, through the Paediatric Active Enhanced Disease Surveillance System. Vaccination status for each case was obtained from the Australian Childhood Immunisation Register (ACIR). There were 306 cases of intussusception suitable for analysis, of which 260 were recorded to have received rotavirus vaccination.

The association between rotavirus vaccination and the risk of intussusception was examined using a self-controlled cases series (SCCS) method and was confirmed with a matched case-control analysis using matched controls from the ACIR.

Using the SCCS method, there was clear evidence of an elevated risk of intussusception following the first dose of both rotavirus vaccines. There was also some elevated risk of intussusception 1–7 days following the second dose of both vaccines (see Table). There was no evidence of increased risk of intussusception following a third dose of RotaTeq.

## Risk–benefit consideration

Prior to the introduction of rotavirus vaccination, there were an estimated 10 000 hospitalisations annually in children under five years due to rotavirus gastroenteritis. Since the introduction of Rotarix and RotaTeq onto the National Immunisation Program, emergency department visits for acute gastroenteritis in young children have declined and hospitalisations for rotavirus gastroenteritis in the under-five year age group have been reduced by over 70%.[3,4]

Based on the established benefits of rotavirus vaccination and the rare occurrence of intussusception, both the World Health Organization and the Australian Technical Advisory Group on Immunisation have recommended the continued use of rotavirus vaccine for infants.

## Information for health professionals

Health professionals are advised that information about the risk of intussusception following rotavirus vaccination has been added to the postmarketing adverse events sections of the Product Information of Rotarix and RotaTeq.

Health professionals should advise parents and caregivers of the risks and signs of intussusception, and the importance of seeking early medical attention if they suspect their child has intussusception.

Further information is available on the Immunise Australia website and in the Australian Immunisation Handbook.

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Table
**Relative risk of intussusception after first and second dose of Rotarix and RotaTeq**

| | Relative risk – dose 1 | | Relative risk – dose 2 |
|---|---|---|---|
| | Day 1–7 | Day 8–21 | Day 1–7 |
| **Rotarix** (95% CI) | 6.8 (2.4–19.0) p<0.001 | 3.5 (1.3–8.9) p=0.01 | 2.8 (1.1–7.3) p=0.03 |
| **RotaTeq** (95% CI) | 9.9 (3.7–26.4) p<0.001 | 6.3 (2.8–14.4) p<0.001 | 2.8 (1.2–6.8) p=0.02 |

CI confidence interval

MEDICINES SAFETY UPDATE

# Drug-induced liver injury

Drug-induced liver injury (DILI) has been associated with a wide variety of drugs, including prescription, over-the-counter and complementary medicines, and poses a diagnostic and management challenge for health professionals. Early recognition is important to minimise injury.

Because there is no pathognomonic injury type associated with DILI, the diagnosis is often one of exclusion. However, it should be included in the list of differential diagnoses in any patient with new-onset liver disease and in any patient with deterioration of existing liver disease after the recent addition of a new drug.[1]

Important differential diagnoses include viral hepatitis, alcoholic liver disease, autoimmune disorders, liver congestion from cardiac failure, liver injury from shock or septicaemia, and biliary tree disorders. Rarer infiltrative liver diseases, such as haemochromatosis and Wilson's disease, may also require exclusion.

Table
**Some drugs commonly known to cause elevated liver enzymes** *

| Pattern of abnormality | Examples of drugs associated |
|---|---|
| Hepatocellular | Antibiotics: isoniazid, rifampicin |
| | Antifungals: ketoconazole, itraconazole, fluconazole |
| | Antivirals: zidovudine, didanosine, nevirapine, ritonavir, indinavir |
| | Anticonvulsants: phenytoin, carbamazepine, sodium valproate, phenobarbitone |
| | Antihypertensives: captopril, enalapril, lisinopril, losartan |
| | Antidepressants: amitriptyline, imipramine, trazodone, venlafaxine, fluoxetine, paroxetine, duloxetine, sertraline, bupropion |
| | Anti-inflammatories: ibuprofen, indomethacin, diclofenac, sulindac |
| | Statins |
| Mixed hepatitis/ cholestasis | Antibiotics: amoxycillin/clavulanic acid, trimethoprim/ sulfamethoxazole, clindamycin |
| | Immunosuppressive: azathioprine |
| Cholestatic | Antibiotics: erythromycin, nitrofurantoin, rifampicin, amoxycillin/clavulanic acid |
| | Antidepressants: duloxetine, mirtazapine, tricyclic antidepressants |
| | Antiplatelets: clopidogrel |

* Note: this list is not comprehensive

## Causes

Determining the cause of liver injury is often complex, as initial symptoms may be non-specific, the date of commencement of drugs may not be clearly recalled, and the picture may be confounded by underlying disease processes.

There is a wide spectrum of presentations of DILI, ranging from mild asymptomatic elevation of liver function tests to serious DILI with acute fulminant hepatic failure.

Liver injury associated with medicines occurs via two mechanisms. The pathogenesis involves either direct biochemical effects or the stimulation of an immune response by the toxic drug or metabolite.[1]

## Hepatotoxins

Most significant hepatotoxins cause a hepatocellular pattern of injury, but cholestasis and mixed-pictures can also be drug-induced.[2] However, individual drugs that cause liver injury tend to cause patterns of injury and latency periods characteristic of that drug. Exceptions include amoxycillin/clavulanic acid, which can produce more than one pattern of injury.[3]

Examples of drugs known to cause elevated liver enzymes are in the Table. These drugs are also included in a list of substances most implicated in DILI-Acute Liver Failure (ALF).[4] Caution should be exercised and more regular liver monitoring undertaken when combining two or more drugs known to cause ALF in vulnerable patients, such as the elderly, those on polypharmacy, those with potential liver ischaemia, or those with existing liver disease.

Latency periods can be short (hours to days), intermediate (1–8 weeks) or long (1–12 months or more). In rare cases, the reaction can occur after the drug is ceased.

## Diagnosis

Alanine transferase (ALT) and alkaline phosphatase are considered the most useful of the liver function tests to determine the type of hepatic injury but, despite a high sensitivity, they carry a low specificity for predicting serious hepatotoxicity. ALT values that are within the reference range at baseline and rise two- to threefold should lead to enhanced vigilance in terms of more frequent monitoring. ALT values 4–5 times higher than the reference range should lead to prompt discontinuation of the drug.[3]

Bilirubin levels twofold greater than baseline, when accompanied by a rise of ALT of more than threefold, indicate a more severe liver injury has already occurred and must prompt investigation. If a drug is suspected to be the causative agent, it should be promptly discontinued.

Because the diagnosis and prediction of a serious DILI is difficult, recent research has focused on the role of biomarkers, such as micro-RNAs.

### Treatment

Treatment of DILI is largely supportive. Most events resolve with the withdrawal of the causative agent. While the time to recovery can take a few days to a week, more commonly there is improvement on cessation of the drug with slower resolution over several weeks to months. In very rare cases, liver injury is permanent and a liver transplant is required.

It is advised that a drug suspected of causing liver injury should not be re-introduced, as the subsequent reaction may be more severe than the initial one, especially if the reaction was hypersensitivity related. In cases where a number of possible medicines could have been involved, careful consideration should be given to recommencement of the medicines, together with careful monitoring.

Health professionals are encouraged to report all cases of liver injury associated with prescription, over-the-counter and complementary medicines to the TGA.

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## What to report? You don't need to be certain, just suspicious!

The TGA encourages the reporting of all **suspected** adverse reactions to medicines, including vaccines, over-the-counter medicines, and herbal, traditional or alternative remedies. We particularly request reports of:

- all suspected reactions to new medicines
- all suspected medicines interactions
- suspected reactions causing death, admission to hospital or prolongation of hospitalisation, increased investigations or treatment, or birth defects.

Reports may be submitted:

- **using the 'blue card'** available from the TGA website and with the October issue of *Australian Prescriber*
- **online** at www.tga.gov.au
- **by fax** to (02) 6232 8392
- **by email** to ADR.Reports@tga.gov.au

For more information about reporting, visit www.tga.gov.au or contact the TGA's Office of Product Review on 1800 044 114.

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ARTICLE

# Making sense of equivalence and non-inferiority trials

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**Key words**
clinical trials, statistics, treatment efficacy

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## SUMMARY

New drugs are usually compared to a placebo. Sometimes it may be unethical to give patients a placebo, so the new drug is compared with standard treatment.

Trials which compare treatments may not be designed to show that one treatment is superior. These are known as non-inferiority or equivalence trials.

Non-inferiority trials aim to show that the new drug is no worse than standard treatment. Equivalence trials aim to show the new treatment is no better and no worse.

An equivalence boundary should be set before the trial. This is the definition of what would be the minimum important difference between the treatments.

There are several traps in the interpretation of trials of non-inferiority or equivalence. The results can be influenced by many factors including the size of the equivalence boundary and whether an intention-to-treat or 'per protocol' analysis is used.

## Introduction

Many clinical trials compare new drugs to placebo. Once there are proven effective treatments for a disease, the clinically important question is whether a new treatment is better than the old one. We would like new treatments to be progressively better than old treatments, but it becomes increasingly difficult to demonstrate the superiority of new treatments if the current treatment achieves most of the possible clinical benefit. New treatments may still be desirable, even when they do not have a superior treatment effect, if they are safer, cheaper, or more convenient. It is also good to have new options for patients who are intolerant of current drugs. This has led to some new drugs coming into use after trials that show they are as good as the old drug, without ever being compared to placebo. These 'active control' trials include equivalence and non-inferiority trials (see Box).

### Definition of equivalence and non-inferiority trials

**Equivalence trials** aim to show that there is no significant difference between treatments

**Non-inferiority trials** aim to show that one treatment is not significantly worse than another treatment

## Confidence intervals

Every experimental trial is subject to the play of random factors that could add a few more successes or failures to the particular group of patients given the experimental or control treatment. While the observed point estimate of effect is the most probable true result, there is a range of values in which we can be confident that the true result will lie. By convention the 95% confidence interval is examined. If this interval does not include the relative risk of 1.0 we accept that there is a difference between treatments. Failing to prove a difference is, however, not the same thing as proving there is no difference.

In Fig. 1 the results of several hypothetical trials are displayed in the same format as a forest plot used in meta-analysis. The line of no difference is when the relative risk is 1.0. A value below 1.0 favours the experimental treatment and a value above 1.0 favours the control. In Fig. 1 all the trials give the same point estimate suggesting that the treatments are equal. In trial 1 there is a wide confidence interval (due to small sample size or poor measurement) so the new treatment could be 10 times better or 10 times worse. This is of no use to a clinician trying to decide whether to use the new treatment. Trial 2 also has a point estimate of no difference, but the 95% confidence interval is smaller due to a larger sample size, and the interval in the larger trial 3 is smaller still. To shrink the 95% confidence interval to zero would take an infinite sample size which is impossible. It is necessary to make a judgement about a boundary that is close enough to 1.0 that we will accept that the result shows equivalence.

## Equivalence or non-inferiority?

From a clinician's perspective, if a new drug is not better we at least want to know it is not worse than the old drug. Statisticians use different methods if they are testing only one end of the equivalence boundary. In effect clinicians do not care how far the

'good' end of the 95% confidence interval goes, just as long as the 'bad' end is within an acceptable limit. For this reason most trials will use a non-inferiority analysis, and although it sounds weaker it is just as good as an equivalence analysis.

In an equivalence trial the statisticians look at both ends of the boundary. Is the new drug no better or no worse? (see Fig. 2).

## Setting the equivalence boundary

The two main methods for setting the equivalence boundary are clinical and statistical. The statistical method is more widely used.

### *Clinical method*

A group of clinicians give their opinion on the 'minimum clinically important difference' which is the smallest difference that they or their patients would think was important. This might be a change of 5 mmHg of blood pressure or 10 mm on a pain scale. The basis for these arbitrary judgements is rarely explained, such as why it is 10 mm rather than 8 mm or 13 mm. Small differences like this might make all the difference in statistical testing. There is also the problem that although 5 mmHg is a small change in blood pressure it still makes a difference to stroke risk, and 10 mm on a pain scale still affects the patient's comfort.

### *Statistical method*

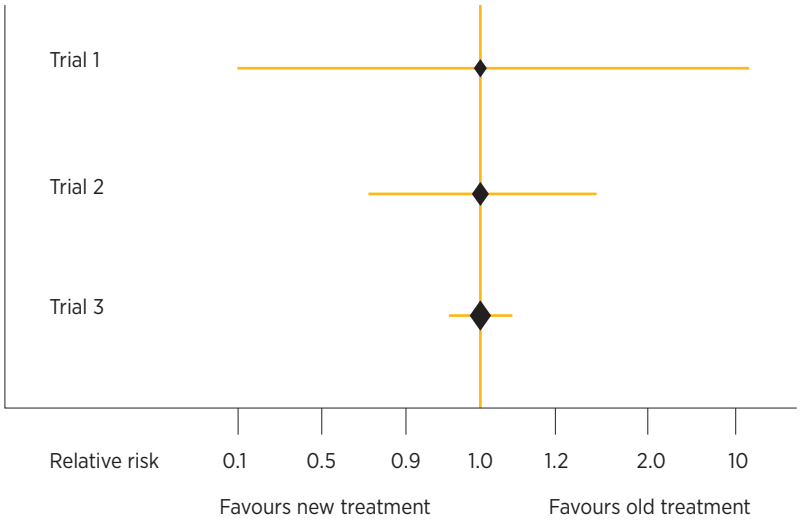
The statistical method relies on examining the difference between the standard treatment and placebo. This is derived from the original placebo-controlled studies of efficacy. The equivalence boundary could be set to prove that the new treatment is no worse than the outcome for placebo in the original trials, although sometimes it is set to be 50% better than placebo.

As the minimum clinically important difference between active treatments is usually smaller than the treatment benefit found in placebo-controlled trials, the sample size required for non-inferiority trials is generally bigger than for superiority trials.

## Differences in analysis

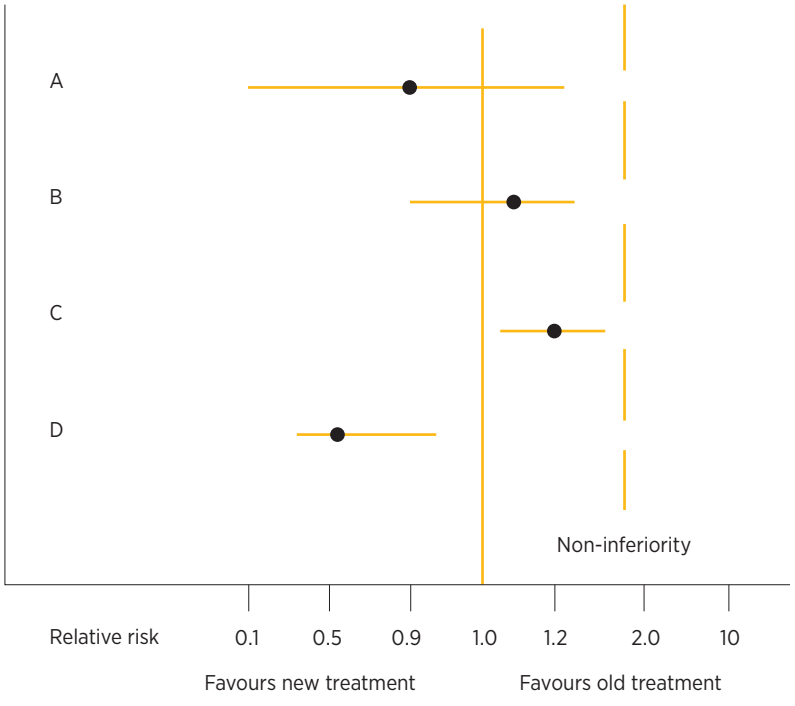
The analysis of a superiority trial should be by 'intention to treat'. This means that the outcomes are measured in patients who were randomised even if they did not take the treatment or complete the trial. This analysis is conservative, because if anything it biases the result towards a null effect. In a non-inferiority trial an intention-to-treat analysis with its bias toward a null effect could be misleading. It is good practice to also perform a 'per protocol' analysis, in which groups are defined by who took the drug rather than just by randomisation.

*Fig. 1* **Effect of trial size on the 95% confidence interval**




Confidence intervals reduce with larger trial sizes (represented by the size of the diamonds). A narrow confidence interval increases the chance that the observed result is close to the true value.

*Fig. 2* **Spectrum of outcomes included in non-inferiority trials**




All of A B C D are 'non-inferior' to old drug
A + B are not statistically superior or inferior
C is statistically inferior
D is statistically superior

## Interpretation

In assessing non-inferiority trials the issues of trial design, such as randomisation, blinding and follow-up, are considered in the same way as they are in trials looking for superiority. However, there are other considerations when assessing non-inferiority trials. It can be difficult to judge if the statistical equivalence boundary has been appropriately set. There is scope for pharmaceutical companies to set the equivalence boundary too wide, making it easy to claim equivalence when it may not exist.

### *Traps*

Proving that two drugs are equivalent could mean that they are both ineffective or even harmful. The evidence for the old drug must be considered when relying on an equivalence trial to show evidence for the efficacy of a new drug. If drug A is superior to placebo and drug B is proved non-inferior to drug A (and becomes the drug of choice because it is cheaper and easier to administer) but later drug C is proved to be non-inferior to drug B, can we be certain drug C is superior to placebo? This problem has been called 'biocreep' and could lead to the acceptance of progressively worse treatments if non-inferiority is blindly accepted. It can be avoided by selecting the most effective drug in the class as the control for non-inferiority trials, even if this is not the drug in most common use.

Can the data from a failed superiority trial be used to demonstrate non-inferiority (Fig. 2 – Trial A, B, C)? Can the data from a non-inferiority trial that goes particularly well be used to demonstrate superiority (Fig. 2 – Trial D)? These are controversial questions, however there is a view that if the non-inferiority boundary is selected a priori a failed superiority trial can be taken as evidence of non-inferiority, although the test for statistical significance should be adjusted for multiple comparisons.

### *Example 1*

The RE-LY trial set out to demonstrate non-inferiority of dabigatran versus warfarin for preventing stroke in patients with atrial fibrillation.[1]

#### *Choice of boundary*

The non-inferiority boundary was chosen as a relative risk of 1.46 for stroke or systemic embolism. This boundary was derived on statistical grounds from a meta-analysis of trials of warfarin versus placebo and chosen as 50% of the proven benefit of warfarin. Although this may have satisfied the statisticians it is clearly not acceptable to clinicians that a new drug could allow 46% more strokes and still be regarded as non-inferior. As it turned out, dabigatran 110 mg dose reduced the relative risk to 0.91 (95% confidence interval 0.74–1.11). The upper boundary of an 11% increase in strokes is probably acceptable to clinicians and patients.

#### *Analysis*

An intention-to-treat analysis was performed. As 99.9% of the patients were followed up, loss to follow-up did not introduce bias. The proportions discontinuing treatment were 14.5% for the low dose and 15.5% for the high dose of dabigatran and 10.2% for warfarin, possibly biasing the relative risk towards 1.0. This could have given a spurious non-inferiority result if the point estimate had been a relative risk greater than 1.0, but would not have had this effect on a point estimate less than 1.0. A per protocol analysis was not done.

The trial set out to demonstrate non-inferiority, but ended up showing superiority of the 150 mg dose over warfarin with a relative risk of 0.66 (95% confidence interval 0.53–0.82) so the intention to treat analysis is appropriate for a claim of superiority (see Fig. 3). If the trial had claimed non-inferiority by showing the relative risk for stroke had a 95% confidence interval extending just short of the boundary (for example to 1.45), it should not have been accepted. To me the possibility that the new drug could lead to a 45% increased risk of stroke would be unacceptable.

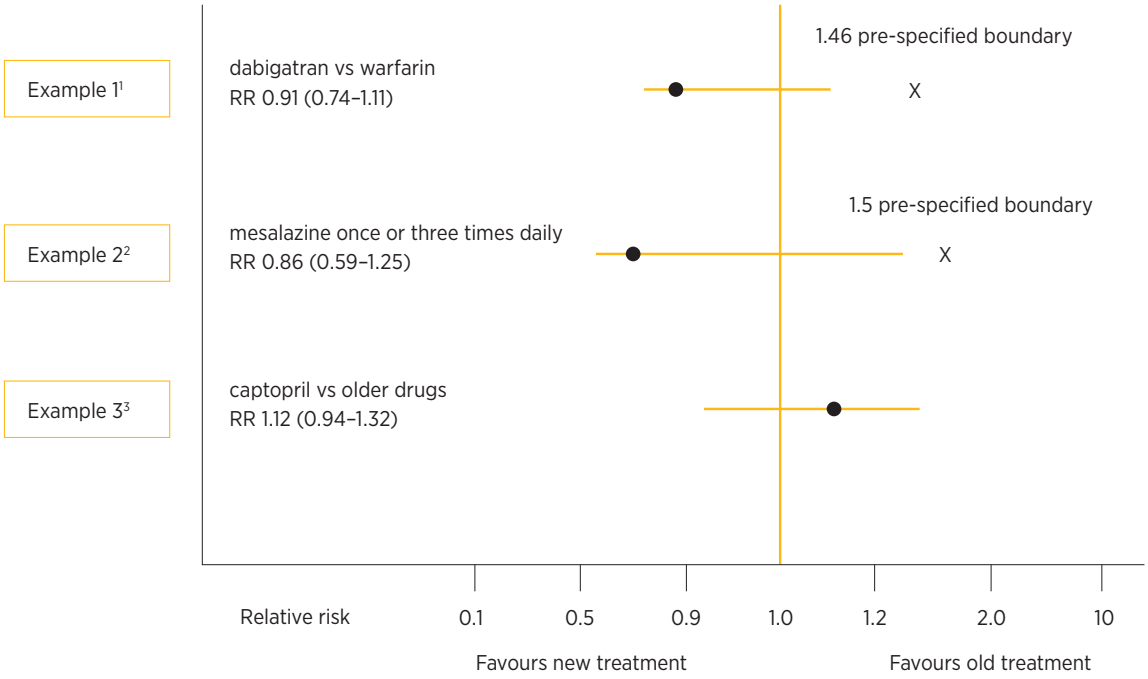
### *Example 2*

A study set out to show that once-daily dosing with mesalazine granules was as good as three-times-daily dosing at inducing remission during first episodes of ulcerative colitis. The rate of non-remission at eight weeks was 24.3% in the three-times-daily group, but only 20.9% in the once-daily group. The relative risk was 0.86 (95% confidence interval 0.59–1.25). The non-inferiority boundary was set at relative risk of 1.6, and as the upper limit of the confidence interval is clear of this, non-inferiority is accepted (see Fig. 3).[2]

### *Example 3*

The Captopril Prevention Project compared the efficacy of the drug to older antihypertensives in the prevention of stroke, myocardial infarction and cardiovascular death. The authors presented both intention to treat and per protocol analyses, showing somewhat worse outcomes for captopril. The adjusted relative risk was 1.12 (95% confidence interval 0.94–1.32). The authors claimed equivalence, but did not pre-specify an equivalence boundary. Patients may not view the possible 32% increase in serious outcomes as equivalent (see Fig. 3).[3]

*Fig. 3* **Examples of equivalence and non-inferiority trials**




RR relative risk (confidence interval)

## Conclusion

Equivalence and non-inferiority trials are becoming more frequent as use of a placebo control group is no longer justified in many diseases. As well as all the usual issues of trial quality, interpretation of these trials is complicated by the need to establish and justify a minimal clinically important difference. The minimum difference established by statistical means may include values that are not acceptable to clinicians, so this is an issue that warrants close attention. ≺

*Conflict of interest: none declared*

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NEW DRUGS

# New drugs

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may be limited published data and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

## Dapagliflozin

**Approved indication: type 2 diabetes**
**Forxiga (Bristol-Myers)**
**10 mg film-coated tablets**
**Australian Medicines Handbook section 10.1**

In diabetes, changes in insulin resistance and secretion result in hyperglycaemia. The glucose in the blood enters the glomerular filtrate, but most of it is reabsorbed. This reabsorption involves the sodium-glucose co-transporter in the proximal tubules. Inhibiting this co-transporter should therefore increase glucose excretion and reduce hyperglycaemia. Dapagliflozin is the first sodium-glucose co-transporter inhibitor to be marketed for diabetes.

The drug is taken once a day. Although fat decreases absorption, the dose can be taken with or without food. Most of the dose is metabolised and most of the metabolites are excreted in the urine. Dapagliflozin is contraindicated if renal function is moderately or severely impaired (creatinine clearance below 60 mL/min). The effect of the drug on the developing kidney also precludes its use in pregnancy and lactation. Dapagliflozin should not be used by patients with severe hepatic impairment. No clinically significant interactions in the metabolism of dapagliflozin and other drugs have been identified.

Dapagliflozin has been studied as monotherapy in previously untreated patients whose type 2 diabetes was inadequately controlled by diet and exercise. The 559 patients were randomised to take one of six different dose regimens of dapagliflozin or a placebo. After 24 weeks the glycated haemoglobin (HbA1c) had fallen by 0.58–0.89% (units from baseline) in the dapagliflozin groups and by 0.23% in the placebo group. This difference was statistically significant for the 5 mg and 10 mg doses of dapagliflozin.[1] The 10 mg dose has been recommended for use in Australia.

The Australian approval for dapagliflozin allows it to be used as monotherapy only in patients who cannot tolerate metformin, but it can be used as initial therapy in combination with metformin. Dapagliflozin was compared with extended-release metformin in two trials involving a total of 1244 previously untreated patients who had HbA1c concentrations of 7.5–12% despite diet and exercise. They were randomised to take dapagliflozin, metformin or both. One trial studied dapagliflozin 5 mg and the other studied 10 mg. Over 24 weeks HbA1c reduced in all treatment groups with the combined regimen having the greatest effect. The effect of dapagliflozin 10 mg on HbA1c was not inferior to the effect of metformin. On average, patients taking dapagliflozin lost more weight than those taking metformin (Table 1).[2]

Dapagliflozin has also been studied in patients whose type 2 diabetes was not well controlled with metformin alone (HbA1c 7–10%). The 546 patients were randomised to add a daily dose of dapagliflozin 2.5 mg, 5 mg, 10 mg or a placebo. After 24 weeks HbA1c concentrations had fallen significantly more, in the patients taking dapagliflozin, than the 0.3% reduction in the placebo group. The reductions were 0.67% with 2.5 mg, 0.7% with 5 mg and 0.84% with 10 mg. Significantly more of the patients taking

*Table 1* **Dapagliflozin and extended-release metformin for untreated type 2 diabetes** [2]

| | Study 1 | | | Study 2 | | |
|---|---|---|---|---|---|---|
| | **Dapagliflozin 5 mg** | **Metformin** | **Dapagliflozin 5 mg with metformin** | **Dapagliflozin 10 mg** | **Metformin** | **Dapagliflozin 10 mg with metformin** |
| Number of patients | 203 | 201 | 194 | 219 | 208 | 211 |
| Baseline mean HbA1c | 9.14% | 9.14% | 9.21% | 9.03% | 9.03% | 9.10% |
| Mean HbA1c at 24 weeks | 7.96% | 7.79% | 7.13% | 7.59% | 7.6% | 7.10% |
| Mean decrease in HbA1c | 1.19% | 1.35% | 2.05% | 1.45% | 1.44% | 1.98% |
| Baseline mean weight | 86.2 kg | 85.6 kg | 84.1 kg | 88.5 kg | 87.2 kg | 88.4 kg |
| Mean weight reduction at 24 weeks | 2.61 kg | 1.29 kg | 2.66 kg | 2.73 kg | 1.36 kg | 3.33 kg |

dapagliflozin 10 mg reached an HbA1c of 7% or less than in the placebo group (40.6% vs 25.9%).[3]

Another option when metformin alone is ineffective is to add a sulfonylurea. This strategy has been compared with adding dapagliflozin in a 52-week trial of 814 patients with HbA1c concentrations of 6.5–10%. At the end of the year the addition of either glipizide or dapagliflozin had reduced HbA1c by a mean of 0.52%. While this outcome was equivalent, patients taking glipizide gained an average of 1.44 kg, but those taking dapagliflozin lost 3.22 kg.[4]

Dapagliflozin has also been assessed as an add-on treatment in patients whose diabetes was not controlled (HbA1c 7–10%) by a sulfonylurea. A total of 597 patients taking glimepiride were randomised to add dapagliflozin 2.5 mg, 5 mg, 10 mg or a placebo. After 24 weeks HbA1c had fallen by 0.13% in the placebo group, and in the dapagliflozin groups by 0.58% with 2.5 mg, 0.63% with 5 mg and 0.82% with 10 mg. All the patients lost weight. Those taking dapagliflozin 10 mg lost an average of 2.26 kg compared with a loss of 0.72 kg in the placebo group.[5]

Some patients with type 2 diabetes use insulin as well as oral antidiabetic drugs. The effect of adding dapagliflozin to such regimens was studied in a placebo-controlled trial of 71 patients. In this trial dapagliflozin 10 mg and 20 mg were used and the patients had their doses of insulin halved. After 12 weeks, HbA1c concentrations had increased by 0.09% in the placebo group, but decreased by 0.61% with 10 mg dapagliflozin and by 0.69% with 20 mg.[6]

Increasing glucose excretion causes an osmotic diuresis. This can be a problem in patients who are volume depleted or are taking loop diuretics. Glycosuria also increases the risk of urinary tract infections. In the clinical trials 4.8% of patients taking dapagliflozin 10 mg developed genital infections, such as vulvovaginitis or balanitis, compared with 0.9% of the placebo group. When used alone dapagliflozin does not appear to cause significant hypoglycaemia,[1] however the risk increases in combination with a sulfonylurea.[5]

Dapagliflozin is the first of a new class of drugs. In addition to reducing HbA1c and weight, it also lowers systolic blood pressure by 1–5 mmHg. These effects could be beneficial, but longer-term studies will be needed to see if dapagliflozin improves the outcomes for patients with type 2 diabetes. These studies will also need to assess the safety of dapagliflozin. In the trials the relative risk of bladder, breast and prostate cancer was slightly increased. Until long-term data are available, dapagliflozin should probably only be used as an adjunct to treatment with drugs, such as metformin, which have more evidence to support them.

T T manufacturer provided additional useful information

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*First published online 9 August 2013*

## Tafluprost

**Approved indication: glaucoma, ocular hypertension**
**Saflutan (Merck Sharp & Dohme)**
**single-dose eye drops containing 15 microgram/mL**
**Australian Medicines Handbook section 11.2.2**

The topical prostaglandin analogues, bimatoprost, latanoprost and travoprost, are replacing beta blockers as the first-line treatment for reducing intraocular pressure in open-angle glaucoma. They are thought to work by increasing uveoscleral outflow.

Tafluprost is a new prostaglandin analogue. After being instilled in the eye, it is absorbed through the cornea and hydrolysed to the active metabolite – tafluprost acid. Intraocular pressure begins to decrease 2–4 hours later and the maximum effect is reached after 12 hours.

In a phase III trial, once-daily tafluprost was found to be non-inferior to the beta blocker timolol in 643 randomised patients with open-angle glaucoma or ocular hypertension. These patients had an intraocular pressure of 23–26 mmHg in at least one eye at baseline. After 12 weeks, mean intraocular pressures had reduced to 17.4–18.6 mmHg with tafluprost and 17.9–18.5 mmHg with timolol.[1]

In another phase III trial, tafluprost was compared to latanoprost in 533 patients who had intraocular

pressures of 22–34 mmHg at baseline. Mean intraocular pressures were decreased by 7.1 mmHg with tafluprost and 7.7 mmHg with latanoprost. These reductions were sustained over the 24 months of treatment.[2]

Tafluprost can be added to timolol as adjunctive treatment. Timolol acts by reducing the production of aqueous humour so these drugs have potentially additive effects on intraocular pressure. In a trial of 185 patients who had uncontrolled disease with timolol alone, tafluprost reduced intraocular pressure more than placebo when added to therapy. After a four-week run-in period with timolol, adding tafluprost for six weeks reduced pressures by a further 5.49–5.82 mmHg compared to placebo which reduced pressures by 3.99–4.15 mmHg.[3]

The adverse effects of tafluprost are similar to other prostaglandin analogues and mainly relate to the eye. The most common adverse event was ocular hyperaemia which affected 14.2% of patients. Other common events (1–10% patients) in the eye included pruritus, pain, irritation, dryness, increased lacrimation, blurred vision and erythema of the eyelid.

Patients should be warned that long-term use of tafluprost can darken pigmentation of the iris, eyelid and eyelashes. This can be permanent and may become more noticeable if drops are only used in one eye. Eyelashes can also become longer and thicker and increase in number. This is usually reversible.

This product does not contain a preservative so adverse effects from this are not a problem. One drop of tafluprost in the conjunctival sac is recommended each evening. If more than one ophthalmic drug is used, they should be given five minutes apart.

Tafluprost, alone or in combination with timolol, lowers intraocular pressure in patients with open-angle glaucoma or ocular hypertension. In a comparative study, it was slightly less effective than latanoprost. It is unclear how tafluprost will compare to the other prostaglandin analogues.

T manufacturer provided the AusPAR

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*First published online 2 September 2013*

## Vandetanib

**Approved indication: medullary thyroid cancer**
**Caprelsa (AstraZeneca)**
**100 mg and 300 mg film-coated tablets**
**Australian Medicines Handbook section 14.2.3**

Medullary thyroid cancer is a rare malignancy stemming from parafollicular C cells which produce calcitonin in the thyroid gland. Treatment is mainly by thyroidectomy and over three-quarters of patients survive for more than 10 years if treated early. However, options are limited for patients with distant metastases as these do not respond well to radiation or chemotherapy.

Vandetanib, an orphan drug, is a tyrosine kinase inhibitor. It is thought to work by blocking signalling via growth factors VEGFR (vascular endothelial growth factor receptor), EGFR (epidermal growth factor receptor) and the oncogenic RET (rearranged during transfection) kinase.

Following oral administration, peak plasma concentrations are reached after 4–10 hours. Excretion of the dose is slow, with a half-life of approximately 19 days, and 44% of the drug is recovered in the faeces and 25% in the urine.

The efficacy of daily vandetanib 300 mg has been assessed in one phase III placebo-controlled trial in 331 patients with advanced inoperable or metastatic disease.[1] Most of these patients (90%) had had their thyroid removed. The median follow-up of two years was too short to detect significant differences in overall survival (see Table). The estimated median progression-free survival was 11 months longer in the vandetanib group than in the placebo group. This was an estimate due to the lack of events at data cut-off.

In the trial, diarrhoea (56%), rash (45%), nausea (33%), hypertension (32%), fatigue (24%), headache (26%),

*Table* **Efficacy of vandetanib 300 mg/day in advanced or metastatic medullary thyroid cancer** [1]

| | vandetanib 300 mg/day | placebo |
|---|---|---|
| Number of patients | 231 | 100 |
| Median progression-free survival | 30.5 months (estimated‡) | 19.3 months |
| Deaths | 32/231 (13.9%) | 16/100 (16%) |

‡ this value was estimated using the Weibull model of probability

decreased appetite (21%) and acne (20%) were the most common adverse events with vandetanib. Just over a third of patients needed to have their dose reduced and 12% stopped treatment because of an adverse event or QTc prolongation. Asthenia and rash led to treatment discontinuation in 1.7% and 1.3% of patients. There were five deaths relating to adverse events in the vandetanib arm. The causes were aspiration pneumonia, respiratory arrest, respiratory failure and sepsis in single patients, and arrhythmia and acute cardiac failure in one patient.

Vandetanib 300 mg was associated with substantial QTc prolongation in the trial. Torsades de pointes, ventricular tachycardia and sudden death have been reported with vandetanib, and the drug is contraindicated in those with congenital long QTc syndrome or a long QTc interval (>480 milliseconds). Vandetanib is also not recommended in patients with a history of ventricular arrhythmias or those taking concomitant drugs that prolong the QTc interval.

ECG monitoring is recommended before and during treatment. If a patient develops a prolonged QTc interval, treatment should be interrupted. It can be resumed at a lower dose only if ECG findings improve. Electrolytes should also be monitored, especially if the patient has diarrhoea. Hypocalcaemia, hypomagnesaemia and hypokalaemia should be corrected if they occur. As vandetanib has a long half-life, patient monitoring should be continued for at least three weeks after the dose is stopped.

Vandetanib is not recommended in severe renal impairment and a reduced starting dose is recommended in moderate impairment. As with other VEGF inhibitors, proteinuria can occur with vandetanib. Elevations in alanine aminotransferase are also common and treatment may need to be interrupted. Pancreatitis has been reported with vandetanib.

Thyroid-stimulating hormone should be measured before and during treatment as almost half of patients taking vandetanib in the trial needed an increase in their thyroid replacement therapy.

Bleeding is an adverse event and has been fatal in some cases. Treatment should be stopped in severe haemorrhage and vandetanib should not be given to patients with a recent history of haemoptysis. As photosensitivity is increased with vandetanib, prescribers should advise their patients to wear sunscreen or avoid sun exposure during and for four months after treatment.

Vandetanib caused fetal abnormalities in animal studies and is classified as a pregnancy category D drug. It may be excreted in breast milk and should be avoided during lactation.

Vandetanib is a substrate of cytochrome P450 (CYP) 3A4, so co-administration of potent CYP3A4 inhibitors (itraconazole, ketoconazole, clarithromycin) or inducers (rifampicin, carbamazepine, St John's wort) could affect vandetanib exposure. Avoidance or dose adjustment is recommended. Vandetanib is also a moderate inducer of CYP3A4 so caution is urged with concomitant CYP3A4 substrates such as cyclosporin and docetaxel.

Because vandetanib is a weak inhibitor of P-glycoprotein, it may increase plasma concentrations of drugs excreted by this transporter such as dabigatran and digoxin. Vandetanib also inhibits the organic cation transporter 2 (OCT2) and may increase concentrations of substrates such as metformin. In both instances, careful monitoring is recommended and dose adjustments may be needed.

Co-administration with proton pump inhibitors could potentially decrease exposure to vandetanib and is not recommended. Increased INR monitoring may be necessary in patients receiving vitamin K antagonists.

Although vandetanib may prolong the onset of progressive disease in some patients with advanced inoperable or metastatic medullary thyroid cancer, benefits to overall survival have not yet been shown. Patients and doctors need to balance this against the drug's potentially life-threatening adverse effects.

T T T manufacturer provided clinical evaluation

**REFERENCE** *†

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*First published online 2 September 2013*

## Vismodegib

**Approved indication: basal cell carcinoma**
**Erivedge (Roche)**
**150 mg capsules**
**Australian Medicines Handbook section 14.2.4**

Basal cell carcinomas are generally caused by exposure to ultraviolet radiation. They are very common, with half of all Caucasian Australians developing a lesion before the age of 70 (Aust Prescr 2011;34:6-7). However, metastatic disease is rare. Vismodegib is a new oral treatment for patients with metastatic or locally advanced basal cell carcinoma.

Most basal cell carcinomas have mutations in the hedgehog signalling pathway. These alterations up-regulate the pathway and cause unrestrained proliferation of basal cells. Vismodegib is a small

NEW DRUGS

molecule which inhibits the hedgehog pathway by blocking the expression of one of its signalling molecules.

After showing anticancer activity in a small trial,[1] vismodegib 150 mg given once a day was assessed in an open-label trial which included Australian patients. After a median of 10 months treatment, a third of patients with metastatic disease and 43% of patients with locally advanced disease had responded (Table). While almost half of the responders with locally advanced disease had a complete response, patients with metastatic disease had only partial responses. The median duration of response was 7.6 months in both groups of patients.[2]

Another study compared vismodegib to placebo in 41 patients with the rare basal cell naevus (Gorlin) syndrome. Because of a defect in a gene encoding an inhibitor of the hedgehog signalling pathway, patients can develop numerous basal cell carcinomas. Patients took vismodegib 150 mg once a day and were followed for a mean of eight months. Vismodegib significantly reduced the number of new lesions compared to placebo (2 vs 29 per patient per year). It also reduced the mean diameter of existing lesions compared to placebo (by 65% vs 11%).[3]

In a safety cohort of 138 patients, the most common adverse events with vismodegib were muscle spasms (71.7%), alopecia (63.8%), dysgeusia (55.1%), decreased appetite (25.4%), weight loss (44.9%), fatigue (39.9%), nausea (30.4%), vomiting (13.8%), diarrhoea (29%) and constipation (21%). In the basal cell naevus syndrome trial, 54% of patients discontinued treatment because of an adverse event.[3] There were seven deaths in the open-label trial – three of unknown cause, one each from hypovolaemic shock, acute myocardial infarction, ischaemic stroke and meningeal disease.[2]

Vismodegib may affect fertility as amenorrhoea has been observed. It is not known if this effect is reversible.

The hedgehog pathway is involved in embryonic development so it is not surprising that vismodegib causes birth defects and fetal death in animals. It is contraindicated in pregnancy (category X) and barrier contraception with spermicide is recommended for men and women during treatment and for seven months after stopping it. As exposure via seminal fluid can occur, this also applies to men who have had a vasectomy. A second form of contraception is recommended in women. Vismodegib is also contraindicated during breastfeeding because of the risk of irreversible effects on an infant's development.

Steady-state plasma concentrations of vismodegib are reached seven days after a daily oral dose. Its half-life is approximately four days and most of the dose is excreted in the faeces. Vismodegib is a substrate of P-glycoprotein in vitro, so co-administration with a P-glycoprotein inhibitor may increase vismodegib concentrations and consequently adverse events. Drugs that reduce gastric pH such as proton pump inhibitors, H2-receptor antagonists and antacids may reduce vismodegib's solubility and therefore bioavailability.

Vismodegib is the first systemic treatment for patients with advanced basal cell carcinoma who cannot have surgery or radiation. It is modestly effective in metastatic or locally advanced basal cell carcinoma and very effective in basal cell naevus syndrome. However, adverse effects such as muscle spasms, dysgeusia and gastrointestinal problems are very common and more than half of patients with basal cell naevus syndrome could not tolerate ongoing treatment. Rapid rebound of lesions after stopping vismodegib has been reported in a patient with basal cell naevus syndrome.[4]

*Table* **The efficacy of vismodegib in patients with advanced basal cell carcinoma in an open-label trial** [2]

| | Patients with metastatic basal cell carcinoma | Patients with locally advanced basal cell carcinoma |
|---|---|---|
| | **33 patients** | **63 patients** |
| Complete‡ or partial§ response | 10 (30%) | 27 (43%) |
| Stable disease¶ | 21 (64%) | 24 (38%) |
| Progressive disease# | 1 (3%) | 8 (13%) |

‡ disappearance of all target lesions
§ at least 30% decrease in size of target lesions
¶ no change in size of target lesions
# at least 20% increase in size of target lesions

T manufacturer provided the product information

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The Transparency score (T) is explained in 'New drugs: T-score for transparency', Aust Prescr 2011;34:26–7.

* At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov).

† At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Medicines Agency (www.ema.europa.eu).

A At the time the comment was prepared, information about this drug was available on the website of the Therapeutic Goods Administration (www.tga.gov.au/industry/pm-auspar.htm)

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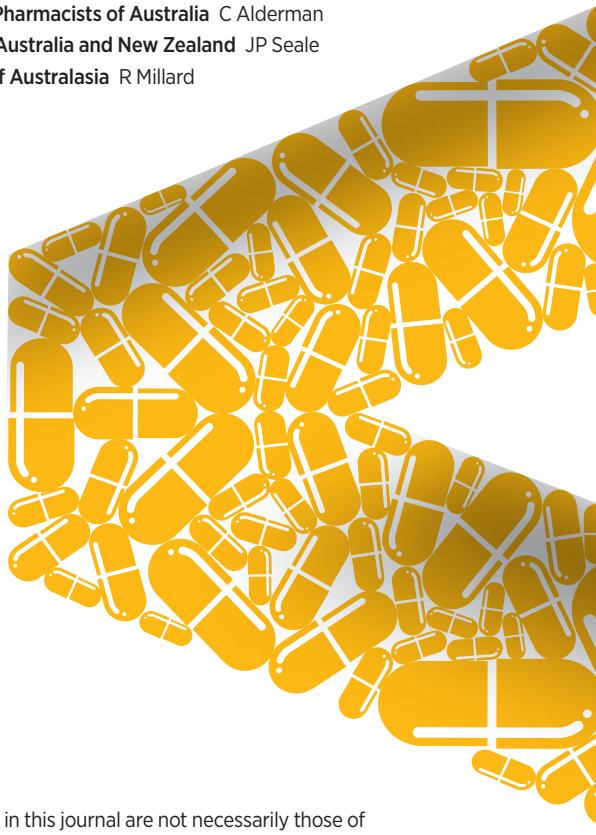


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