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CONTENTS

EDITORIAL

Changes for codeine

Darren M Roberts
Clinical pharmacologist
The Canberra Hospital

Associate professor
Australian National University Medical School
Canberra

Staff specialist
Alcohol and Drug Services
Clinical Pharmacology and Toxicology
St Vincent's Hospital
Sydney

Suzanne Nielsen
Senior research fellow
National Drug and Alcohol Research Centre
UNSW Sydney

Pharmacist
Drug and Alcohol Service
South Eastern Sydney Local Health District
Sydney

Keywords
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From 1 February 2018 codeine is being rescheduled to a prescription-only medicine.

Codeine is widely used in Australia, often in combination with other drugs. In 2013, more than 27 million packs of codeine-containing analgesic products were supplied by pharmacies, and 56% of these sales were over-the-counter without a prescription.[1] National sales data show that over-the-counter codeine-containing analgesics account for 37% of all opioid purchases in the community.[2]

Codeine is metabolised to morphine but there is marked interindividual variability in metabolism which contributes considerable differences in analgesic effects. Due to the opioid effects of codeine, people can become dependent with regular use.

The proportion of people seeking opioid substitution treatment for codeine dependence in Australia rose from 2.7% in 2014 to 4.6% in 2016. A study in Sydney reported that codeine was the sole substance used by 39% of patients with a pharmaceutical opioid dependence and 83% of these patients were using only over-the-counter codeine.[3] At a drug dependence unit in South Australia, the annual incidence of codeine dependence requiring intervention increased from 31 people in 2003 to 174 in 2014. The estimated cost of treating 30 patients with codeine-related admissions in one Adelaide hospital was over $1 million.[4] In 2013 the National Drug Strategy Household Survey reported that 33% of the people who had misused pharmaceuticals had used over-the-counter codeine-containing analgesics.[5] This increased to 75% in 2016.[6]

The long-term use of codeine-containing products, particularly in supra-therapeutic doses, risks complications from each of the co-formulated ingredients such as paracetamol and ibuprofen. Paracetamol can cause hepatotoxicity and ibuprofen has adverse cardiovascular, gastrointestinal and renal effects which can be life-threatening.

The Therapeutic Goods Administration (TGA) has reviewed the availability of codeine in response to reports of misuse and toxicity. In 2010 it removed the pharmacy-only (Schedule 2) listing for codeine-containing analgesics and restricted pack sizes to five days supply. In 2016 it proposed rescheduling all codeine-containing products to prescription only (Schedule 4).

Submissions to the TGA supporting rescheduling included addiction specialists reporting increasing numbers of patients with codeine dependence, pharmacists expressing frustration with the difficulty managing challenging patients, and members of the public speaking of families being destroyed by codeine addiction. Each group identified the ready availability of codeine over-the-counter as a contributor. In some cases it was being used non-medically or in excessive doses, in others it was being used to treat chronic pain with minimal oversight by a health professional.[7]

Those arguing against codeine rescheduling included patients using codeine regularly, people with limited access to GPs, and community pharmacists.[7] During the consultation period, the Pharmacy Guild of Australia introduced an opt-in database (MedsASSIST) to demonstrate the feasibility of pharmacists monitoring over-the-counter sales of codeine in real time.

After more than 18 months of consultation, the TGA announced that all codeine-containing products would become Schedule 4 from 1 February 2018. This decision was made because of the likelihood of significant public health benefits, based on the evidence of harm due to dependence on widely accessible, over-the-counter codeine-containing analgesics. This harm was contrasted with evidence that these products in recommended doses provided little additional benefit when compared to other analgesics without codeine.

Consumers and health professionals have questioned whether rescheduling codeine will reduce harm.[8] The TGA and professional societies have therefore issued guidance to health practitioners and the public.[9] It was hoped that individuals who had developed dependence would seek medical assistance before codeine was up-scheduled. However, due to stockpiling, shame, fear of stigma, and self-denial, it is possible that some people with codeine-use disorder will emerge after February 2018.

Australian data show that the typical codeine user is well-educated and employed, and that codeine-use disorder is a largely hidden problem.[3,10] People with substance use disorders are not always readily identified by stereotyped external features or behaviours, and such depictions can be detrimental in the context of substance use already being a highly stigmatised condition. They are often hesitant to disclose substance use, if indeed they acknowledge that their use is problematic.

It is anticipated that pain relief will be a key reason for people seeking prescriptions for codeine or other opioids. As always, the assessment of pain requires a careful history and examination rather than simply prescribing. A potential benefit of rescheduling codeine is that it will direct attention to the clinical

assessment and management of pain and the hazards of opioids. Clear messages for patients from health professionals about the relative efficacy of non-opioid analgesics available over-the-counter may also help address their concerns.[11]

The assessment of pain involves asking about the use of over-the-counter analgesics. The possibility that the patient is taking doses exceeding the usual daily maximum should be explored in a non-judgemental and patient-centred manner. The Government has proposed a national real-time prescription monitoring program, which in some jurisdictions may include the monitoring of Schedule 4 opioids. This may provide additional information to support the clinical assessment. In cases where the use of high doses is suspected, patients should be asked about symptoms of opioid withdrawal and symptoms due to co-formulated drugs, such as gastrointestinal toxicity due to ibuprofen.

When codeine dependence is identified, mental health and physical comorbidities that may have contributed to codeine use require careful assessment and treatment. This may include testing for anaemia, liver or renal dysfunction and electrolyte abnormalities. Patients with moderate–severe signs, symptoms or laboratory abnormalities may require specialist input to guide treatment. Presentations with any of these features provide a useful opportunity to review the current management plan and discuss treatment options, including consideration of referral if mental health symptoms have contributed to escalating codeine use.

The reduced availability of codeine can be anticipated to reduce harms for many who are codeine dependent. Opioid substitution treatment (methadone or buprenorphine/naloxone) offers the opportunity to promote physical, social and psychological stability for patients who are willing to receive it. Both methadone and buprenorphine are effective in treating pharmaceutical opioid dependence. An Australian case series found that buprenorphine/naloxone is commonly prescribed for people who are codeine dependent.[3] This treatment may have advantages over methadone in terms of reduced risk of respiratory depression, greater experience with its use in the treatment of codeine dependence, and more flexibility with unsupervised (take-home) dispensing. Expanding buprenorphine treatment in primary care may be an ideal way to help patients with codeine dependence. Anticipating and preparing for the changes to codeine availability in 2018 is as critical for patients as it is for health professionals. <

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EDITORIAL

Observations on the launch of new drugs for hepatitis C

Marianne Martinello
Postdoctoral research fellow[1]

Infectious diseases physician[2]

Behzad Hajarizadeh
Lecturer[1]

Gregory J Dore
Head[1]

Infectious diseases physician[3]

[1] Viral Hepatitis Clinical Research Program
Kirby Institute
UNSW Sydney

[2] Blacktown Mt Druitt Hospital
Blacktown
New South Wales

[3] St Vincent's Hospital
Sydney

Keywords
direct-acting antiviral drugs, hepatitis C

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Morbidity and mortality from hepatitis C virus infection have been increasing in Australia. This is partly due to the low uptake of treatment with interferon. The development of highly effective direct-acting antiviral therapy and the listing of these drugs on the Pharmaceutical Benefits Scheme (PBS) in March 2016 has revolutionised the clinical management of hepatitis C in Australia.

A goal of therapy is a sustained virologic response (SVR). This is defined as undetectable hepatitis C virus RNA in the patient's blood 12 weeks after treatment. An SVR is associated with favourable clinical outcomes, including reversal of liver fibrosis, improved quality of life and increased survival. The vast majority (>90%) of people treated with the new drugs will achieve an SVR after 8–12 weeks of therapy.[1,2] The availability of direct-acting antiviral therapy has therefore fostered optimism, providing the tools required to reverse the growing burden of hepatitis C virus-related liver disease in Australia.

In 2015, an estimated 227 300 Australians were living with chronic hepatitis C.[3] However, while the vast majority (82%) had been diagnosed, only a small proportion had ever received treatment (22%) and even fewer had been cured (14%). There was a persistently low uptake of treatment (1% per year),[3] due to the suboptimal efficacy and marked toxicity of interferon-based regimens. In contrast, direct-acting antiviral regimens have excellent efficacy and minimal toxicity, with shorter treatment durations and once-daily dosing,[1] which are potential enablers of treatment uptake.

Australia is currently unique in providing unrestricted government-subsidised direct-acting antiviral therapy to all adults living with chronic hepatitis C virus infection. 'Access for all' was achieved through strong advocacy, robust data, bipartisan political support and established partnerships between government, clinical, academic and community organisations. In the first 10 months of PBS listing (March–December 2016), an estimated 32 400 Australians started treatment. That is approximately 14% of the infected population.[4] Additionally, in 2014 and 2015, 4340 people had started direct-acting antiviral therapy via clinical trials, early access programs and personal importation.[5] In stark contrast, over the preceding two decades (1997–2015), only 46 310 people started interferon-based therapy.

Some key features of the PBS listing have enabled the rapid uptake of treatment. First, unlike most other countries, there are no restrictions based on the stage of an individual's liver disease or drug and alcohol use. This permits direct-acting antiviral uptake across the entire infected population. Encouragingly, significant (direct-acting antiviral) uptake has been reported among marginalised populations, including people who inject drugs[6] and people living with HIV,[7] with corresponding high rates of SVRs.[1,7]

Second, access to treatment has been enhanced with a wide range of health professionals (including authorised nurse practitioners and GPs) able to prescribe, with dispensing through public hospital and community pharmacies. In March 2016 only 8% of prescribers were GPs, but this had risen to 31% by December 2016.[4]

Additionally, the Australian Government has negotiated a five-year risk-sharing arrangement with the pharmaceutical companies. The Government has allocated $1 billion for hepatitis C treatment over five years (2016–20) with no cap on the number of people treated per year.

In 2015, the United Nations and World Health Organization set ambitious hepatitis C elimination and control targets. Specific targets included an 80% reduction in hepatitis C virus incidence, a 65% reduction in hepatitis C virus-related mortality and an increase in hepatitis C treatment uptake to 80% of those eligible by 2030.

In order to reduce the incidence of hepatitis C, people at risk of hepatitis C virus transmission, including those who inject drugs, prisoners and HIV-positive homosexual-and-bisexual men, will require expedient treatment (and re-treatment for reinfection). To reduce hepatitis C virus-related mortality, patients with cirrhosis will require assessment, treatment and screening, particularly for hepatocellular carcinoma.

Very encouragingly, an estimated 70% of Australians with cirrhosis related to hepatitis C began direct-acting antiviral therapy between 2014 and 2016.[5] In addition to broad access to direct-acting antiviral therapy, effective hepatitis C virus elimination strategies will require high rates of testing, diagnosis linkage to care and treatment, along with education and prevention strategies, including harm reduction interventions such as opioid substitution therapy and needle exchange programs.[8]

The substantial uptake of therapy in the first 10 months after PBS listing has established a basis for the elimination of hepatitis C in Australia. Evaluating the progress towards elimination will require monitoring treatment uptake, adherence, adverse effects and outcomes,[1] particularly among populations at high risk of transmission. There will also need to be monitoring of hepatitis C virus prevalence and incidence (both primary infection and reinfection) and monitoring of the impact of therapy on hepatitis C virus-related morbidity and mortality on the Australian population. One of the keys to hepatitis C elimination in Australia will be a sustained high uptake of direct-acting antiviral treatment with equitable access to therapy.

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Gregory Dore is an advisory board member and has received honoraria from Roche, Merck, Janssen, Gilead, Bristol-Myers Squibb and Abbvie. He has received research grant funding from Roche, Merck, Janssen, Gilead, Bristol-Myers Squibb, Vertex, Boeringher Ingelheim and Abbvie, and travel sponsorship from Roche, Merck, Janssen, Gilead and Bristol-Myers Squibb.

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LETTERS

Letters to the Editor

Pharmacogenomics and drug therapy

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I thank Andrew Somogyi and Elizabeth Phillips for their article on the role of pharmacogenomics in drug therapy.[1] However, I am surprised and concerned that their discussion is limited to recently identified genes and will mislead the casual reader about the importance of genetic testing in daily practice.

For example, glucose 6-phosphate dehydrogenase (G6PD) deficiency has been acknowledged as 'the most common enzyme deficiency in the world'.[2] Its role in acute drug-induced haemolytic anaemia has been known for over half a century.[3] Medicines including primaquine and rasburicase are definite triggers for drug-induced haemolytic anaemia in patients with G6PD deficiency, but other commonly used drugs can also possibly cause it, including some sulphur-containing antibiotics, quinolones, high doses of aspirin and paracetamol.

Genetic testing also enables early diagnosis of other haemoglobinopathies such as sickle cell anaemia and beta-thalassemia. Many patients with these are also sensitive to drug-induced haemolytic anaemia via oxidative stress from medicines similar to the list above.[4]

Testing for G6PD deficiency is rebateable on the Medicare Benefits Schedule, but genetic testing for haemoglobinopathies are often not. More importantly, most direct-to-consumer genetic testing kits would include these conditions for investigation. In our increasingly multicultural society, awareness of these genetic conditions is ever so relevant to those of Asian, Mediterranean and African ethnicities.

Many recent review articles continue to list G6PD deficiency as an important exemplar when discussing advances in pharmacogenomics.[2,3,5,6] I fear that its conspicuous absence in this *Australian Prescriber* article will only reinforce the mistaken triviality of this common condition in the psyche of prescribing doctors.

Shyan Goh
Orthopaedic Surgeon
Meadowbrook Qld

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Andrew Somogyi and Elizabeth Phillips, the authors of the article, comment:

We thank Dr Goh for raising the relevance of G6PD deficiency and the indication for testing when prescribing primaquine and rasburicase. These drugs and others associated with haemolysis are invariably prescribed and monitored by specialists, and their use is infrequent. Indeed, for both drugs, G6PD deficiency has often been a contraindication in specific areas of the world where severe deficiency is common. As such, it is a subsidised test that should be performed before commencing treatment.

Like many of the genetically associated adverse drug reactions we draw attention to in our article, the prevalence of G6PD deficiency differs according to population and ethnicity, and is most prevalent in people of Mediterranean, African and Southeast Asian descent. This distribution of disease was likely driven by a protective effect of G6PD deficiency for falciparum malaria. In contrast to many of the adverse drug reactions that we discuss however, G6PD deficiency is inherited in a predicable X-linked recessive pattern – women are typically not affected as half of their red blood cells express the normal G6PD allele and are functionally normal – and infection or other illness precipitating oxidant injury rather than drugs is the most common precipitant of haemolysis.

Although haemolysis can be severe and prolong hospitalisation, it is easy to monitor through routine blood tests. It rapidly resolves either on discontinuation of the medicine or food, or resolution of the underlying acute illness, and is not a cause for significant ongoing morbidity or mortality.

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. When letters are published, they are usually accompanied in the same issue by any responses or comments. The Committee screens out discourteous, inaccurate or libellous statements. The letters are sub-edited before publication. Authors are required to declare any conflicts of interest. The Committee's decision on publication is final.

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ARTICLE

Drugs affecting milk supply during lactation

SUMMARY

There are morbidity and mortality benefits for infants who are breastfed for longer periods. Occasionally, drugs are used to improve the milk supply.

Maternal perception of an insufficient milk supply is the commonest reason for ceasing breastfeeding. Maternal stress or pain can also reduce milk supply.

Galactagogues to improve milk supply are more likely to be effective if commenced within three weeks of delivery. The adverse effects of metoclopramide and domperidone must be weighed against the benefits of breastfeeding.

Dopamine agonists have been used to suppress lactation. They have significant adverse effects and bromocriptine should not be used because of an association with maternal deaths.

Treasure M McGuire
Assistant director
Practice and Development
Mater Pharmacy Services
Mater Health Services
Brisbane

Conjoint senior lecturer
School of Pharmacy
University of Queensland

Associate professor
Pharmacology
Faculty of Health Sciences and Medicine
Bond University
Gold Coast

Keywords
breastfeeding, cabergoline, domperidone, galactagogues, lactation, metoclopramide, prolactin

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CPD FOR PHARMACISTS

This article has a continuing professional development activity for pharmacists available at https://learn.nps.org.au

Introduction

Breast milk is a complex, living nutritional fluid that contains antibodies, enzymes, nutrients and hormones. Breastfeeding has many benefits for babies such as fewer infections, increased intelligence, probable protection against overweight and diabetes and, for mothers, cancer prevention.[1] The World Health Organization recommends mothers breastfeed exclusively for six months postpartum.

Breastfeeding is influenced by many complex physiological and psychosocial factors. While most women have a desire to breastfeed, some do not. In high-income countries such as Australia the duration of breastfeeding is shorter than in low- and middle-income countries. A 2011 Australian Institute of Health and Welfare survey estimated that only 56% of infants younger than six months were exclusively breastfed, and by 12 months this dropped to 30%. While breastfeeding should be encouraged, a woman's right to choose not to breastfeed should be respected. By understanding the reasons for their decision, strategies can be offered to support their choice.

Physiology of lactation

Milk production begins between 10 and 22 weeks gestation. Within 48 hours of delivery, the mother produces a small amount of milk, mainly colostrum. However, it is not until serum progesterone decreases sufficiently, up to four days postpartum, that milk supply becomes more plentiful. Lactogenesis may be delayed if the baby is premature.

Milk production is controlled by a complex interplay of hormones and neurotransmitters. Prolactin is secreted by the anterior pituitary in response to nipple stimulation. Its release is inhibited by dopamine from the hypothalamus. Within a month of delivery, basal prolactin returns to pre-pregnant levels in non-breastfeeding mothers. It remains elevated in nursing mothers, with peaks in response to infant suckling. Drugs that act on dopamine can affect lactation.

In response to suckling, oxytocin is released from the posterior pituitary to enable the breast to let down milk. Oxytocin release is inhibited by catecholamines produced if the mother is stressed or experiencing pain.

The feedback inhibitor of lactation is a peptide found in breast milk. If the milk is not removed, the inhibitor will stop milk production. When the baby cannot suckle, expressing the milk will remove the inhibitor and encourage more production.

Milk supply

A maternal perception of insufficient milk is the commonest reason for ceasing breastfeeding. Some women have difficulty producing sufficient breast milk after a difficult labour, delayed initiation of breastfeeding, separation due to the baby being preterm, formula substitution, cracked nipples or maternal illness.

Support and reassurance are as important as determining the cause of the problem, before recommending infant formula. Simple strategies can restore confidence and assist in increasing milk supply. Encourage the mother to 'hang in a bit longer' as babies have adequate nutrient stores to cover the first postpartum week. Make sure she is well hydrated, has adequate nutrient intake and home support, and reassure her that a crying baby is not necessarily a hungry baby. Increase the frequency of feeding or

offer the baby both breasts at each feed. Check the baby's suckling patterns, ensure adequate but not excessive hydration and avoid the use of a dummy.

Where feeding problems persist, referral to a lactation consultant is an appropriate option.

Maintaining the milk supply may also be problematic as the baby grows. An infant typically requires about 150 mL/kg/day. So, to feed a 9 kg versus 3 kg baby daily (1350 mL vs 450 mL) can be a physiological challenge for some women.

Galactagogues

Antipsychotic drugs can increase pituitary prolactin secretion and breast milk production through dopamine antagonism, but the gastrointestinal motility drugs metoclopramide and domperidone are most commonly used off label as galactagogues. Metoclopramide and domperidone block dopamine D_2 receptors in the anterior pituitary and, in a limited number of clinical trials, they have had modest efficacy over placebo in initiating and maintaining lactation.[2] The best chance for efficacy is if the galactagogue is started within three weeks of delivery.[3]

The safe duration of galactagogue therapy is controversial. Although increased prolactin can be detected within eight hours of the first dose, about two weeks is required for the breast changes required to sustain milk production. Current recommendations of 10–14 days are based on a limited number of controlled studies and the limited number of longer term controlled clinical trials.

Metoclopramide

Metoclopramide is a centrally acting drug. It can increase milk supply by 66–100% within 2–5 days in total daily doses of 30–45 mg. While the relative dose in milk ranges from 4.7–14.3%, adverse outcomes in infants have not been reported.[4] However:

- effects are dose dependent, with a threshold of 10 mg
- doses need to be administered regularly three times a day
- only 50–85% of women with low milk supply will respond
- maternal adverse effects include diarrhoea and depression
- there is a theoretical risk of extrapyramidal adverse effects in the baby
- if metoclopramide is discontinued rapidly, there can be a significant rebound decline in milk supply.

Domperidone

Domperidone is a peripheral dopamine antagonist. At doses of 10–20 mg three times daily it has comparable efficacy to metoclopramide.[4] Little domperidone passes into milk (relative infant dose 0.01–0.04%), so the risk of extrapyramidal effects in the baby is less than with metoclopramide.[4]

In 2004, the US Food and Drug Administration (FDA) issued an alert that domperidone could cause cardiac arrhythmias. This was in response to its illegal importation into the USA by breastfeeding mothers. The data related to historical cases of high-dose, intravenous use in sick patients receiving cancer chemotherapy. Two case control studies using oral domperidone in a general population supported this rare association. However, only three probable case reports in lactating women have been received by the FDA in postmarketing surveillance.[5] Concomitant use of moderate or strong inhibitors of cytochrome P450 3A4 such as ketoconazole can increase plasma concentrations of domperidone and therefore the risk of QT prolongation.

In 2013, the Pharmacovigilance Risk Assessment Committee of the European Medicines Agency recommended that the daily oral dose be restricted to a maximum of 30 mg and that domperidone not be used for longer than one week. It is therefore important that women being offered domperidone as a galactagogue have tried non-pharmacological strategies first. They need to be aware of the very low risk of QT prolongation and weigh this against the benefits of breastfeeding.

Complementary medicines

Herb-derived galactagogues have been used for centuries in folk medicine to augment lactation. These plants contain lipophilic, pharmacologically active constituents which, if taken in sufficient quantity, can pass into the breast milk. While there are generally few adverse effects (Table), there is limited evidence of efficacy. Most of the supporting evidence is based on case reports, or historical use.

Lactation suppression

Some women may require lactation suppression after miscarriage, stillbirth, maternal illness or when they do not wish to breastfeed. While breast stimulation should be avoided, there is a risk of engorgement if the breasts are not drained.

Pharmacological options all have significant adverse effects. The dopamine agonist bromocriptine was associated with maternal deaths from myocardial infarction and is no longer

recommended. It has been replaced by a single 1 mg dose of long-acting cabergoline, ideally taken on the first postpartum day. The common adverse effects are nausea, headache and dizziness. If the woman changes her mind, it can be difficult to restore milk production.

Other drugs no longer used include large doses of pyridoxine and diuretics. Oestrogen is avoided because of the risk of thromboembolism.

Conclusion

Breast feeding is a natural process with benefits for both mother and baby. Some women find it difficult to breastfeed, but many problems can be overcome with reassurance and support.

Occasionally, non-drug approaches may not increase the supply of milk. There is limited evidence for the off-label use of domperidone and metoclopramide. However, if a drug is considered for increasing milk supply, discuss with the mother a trial of an agreed dose, for a maximum agreed duration beginning as soon as feasible postpartum. Also discuss the potential for adverse effects.

There are few indications for using drugs to suppress lactation. Cabergoline has been used, but bromocriptine should be avoided because of maternal deaths. ≺

Conflict of interest: none declared

Table **Adverse effects of herbs used as galactagogues**

Herb	Adverse effects
Alfalfa *Medicago sativa*	Dose-related bleeding
Blessed thistle *Cnicus benedictus*	Gastric irritation and potential allergies, as it is part of the ragweed family
Chaste tree *Vitex agnus-castus*	Nausea, vomiting, irritation, pruritus, rash, headache, increased menstruation
Dill *Anethum graveolens*	Alterations in sodium balance
Fennel *Foeniculum vulgare*	Allergic reactions, dermatitis (photo and contact)
Fenugreek seed *Trigonella foenum-graecum*	Hypoglycaemia, hypertension, diarrhoea and maple syrup body odour in mother Allergy potential as part of the peanut family
Goat's rue *Galega officinalis*	Hypoglycaemia, hypotension, coughing, dose-related toxicity
Milk thistle (silymarin) *Silybum marianum*	Allergic reactions, diarrhoea
Malunggay *Moringa oleifera*	Hypoglycaemia, sedation
Raspberry leaf *Rubus idaeus*	Hypersensitivity reactions, changes in blood glucose
Shatavari *Asparagus racemosus*	Possible teratogenicity – avoid in pregnancy
Damiana *Turnera diffusa*	Hepatotoxicity, confusion and hallucinations with high-dose *Turnera*

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ARTICLE

Adverse effects of sports supplements in men

Sarah J Martin
Sexual health physician[1]
Senior lecturer[2]

Miranda Sherley
Sexual health registrar[1]
Lecturer[2]
General practitioner[3]

Malcolm McLeod
Associate professor
College of Physical and Mathematical Sciences[4]

[1] Canberra Sexual Health Centre
Canberra Hospital
[2] Australian National University Medical School
Canberra
[3] Bungendore Medical Centre
Bungendore
New South Wales
[4] Australian National University
Canberra

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SUMMARY

Sports supplements are widely available over-the-counter and online. They may contain undeclared substances including androgenic steroids.

According to the Australian Sports Anti-Doping Authority almost one in five sports supplements contain banned substances including stimulants and anabolic drugs. It warned that any supplement may not be safe to use.

Some supplements contain large amounts of protein or creatine. Their use may cause a raised blood urea or creatinine in an otherwise healthy individual.

Androgen deficiency with symptoms of hypogonadism may be due to use of androgenic steroids. This may be inadvertent as the labels on the sports supplements may not list steroids in the ingredients.

If a person admits to using sports supplements it is an opportunity to discuss their health and fitness. The Australian Sports Commission has advice on building muscle and the use of supplements.

Introduction

Legally obtained supplements marketed for performance enhancement are commonplace and include sports drinks, energy beverages, and a wide range of pills and powders for oral consumption. Multi-ingredient sports supplements containing taurine, creatine or other amino acids are readily available and appear to be increasingly popular.

In a 2011–12 survey, 2.9% of Australian adults of all ages reported using a special dietary product on the day before interview. Approximately 70% of these supplements were sport and protein beverages or powder. The rate of use was 7.8% in men aged 19–30.[1]

People take supplements to gain muscle mass, lose weight and improve their performance or general health. They may be unaware that long-term use of supplements can have adverse effects. Supplements could potentially worsen some health conditions or interact with drugs.

Some products are contaminated with substances that are prohibited in sport.[2-4] They may contain steroids that are not listed on the product label.[5,6] Australian research has found anabolic drugs or stimulants in 13 out of 67 supplements.[2] It was recognised over a decade ago that some 20% of nutritional supplements sold in Europe and the USA contained anabolic steroids.[7] Even products supplied by overseas pharmacies may contain prohibited substances.[8] The importation of prohibited substances may also breach customs regulations.

Energy drinks

Unlike sports drinks, which are generally used as hydration fluids, energy beverages are used for their supposed performance-enhancing properties.[9,10] Common energy beverages contain caffeine, taurine (an amino acid found naturally in meat and fish), B vitamins and sugars.[9]

Caffeine has stimulant effects on blood pressure and heart rate. It can cause nervousness, irritability and sleep disturbance.

Taurine is promoted for its ability to improve exercise capacity and performance, but most energy beverages do not contain enough of it for therapeutic or adverse effects.[9] Little is known about the effects of heavy or long-term taurine use.

Creatine

Creatine is derived from amino acids and produced by the liver and kidneys. It is primarily stored in skeletal muscle cells, where it serves as an energy source. Sports supplements may contain creatine alone or in combination. Creatine monohydrate has been popular for over a decade despite a lack of evidence of safety with long-term use. Supplementation may improve exercise performance in adults performing high-intensity short-duration exercises, although the extent of benefit is variable.[11] There is little evidence for the efficacy for creatine in combination products or of the safety of some of the newer forms of creatine such as creatine ethyl ester.[12]

Steroids

Some sports supplements also contain endocrine disruptors including anabolic drugs, or androgenic steroids.[5,6,13] When these synthetic drugs have been developed to evade regulatory control, they are referred to as 'designer steroids'.[6] In many cases these synthetic steroids have never been evaluated by regulatory bodies for purity, clinical efficacy or toxicity, so there are additional risks.[6] Designer steroids are often heavily marketed as prohormones, natural steroids and testosterone boosters on websites that promote supplement use for muscle bulk and strength.[6] The use of sports supplements containing steroids is a growing public health concern with evidence of increasing use among young gym attendees and men over 40 years old.[14,15]

Androgen deficiency and supplement cycling

Sports supplement users may engage in supplement cycles, with periods of intensive use followed by washout periods. If one or more products contain anabolic drugs, the exogenous androgens may promote muscle bulk, but will also suppress testicular testosterone production and exert negative feedback on the release of gonadotropins from the pituitary gland.[14,16] Excess circulating testosterone is converted into oestradiol, providing further negative feedback to the pituitary. High concentrations of oestrogen may lead to oestrogenic adverse effects including gynaecomastia.[14]

At the end of a supplement cycle, the body's own testosterone concentrations may be very low. Symptomatic individuals may then use post-cycle drugs such as aromatase inhibitors, to slow the conversion of endogenous androgens to oestrogen, or selective oestrogen receptor modulators such as clomiphene and tamoxifen, to reduce the effects of circulating oestrogen.[16] While these are prescription drugs in Australia, they are readily purchased online and may also be found in some supplements. There is little evidence that these approaches increase endogenous testosterone after supplement use.[16]

Clinical suspicions

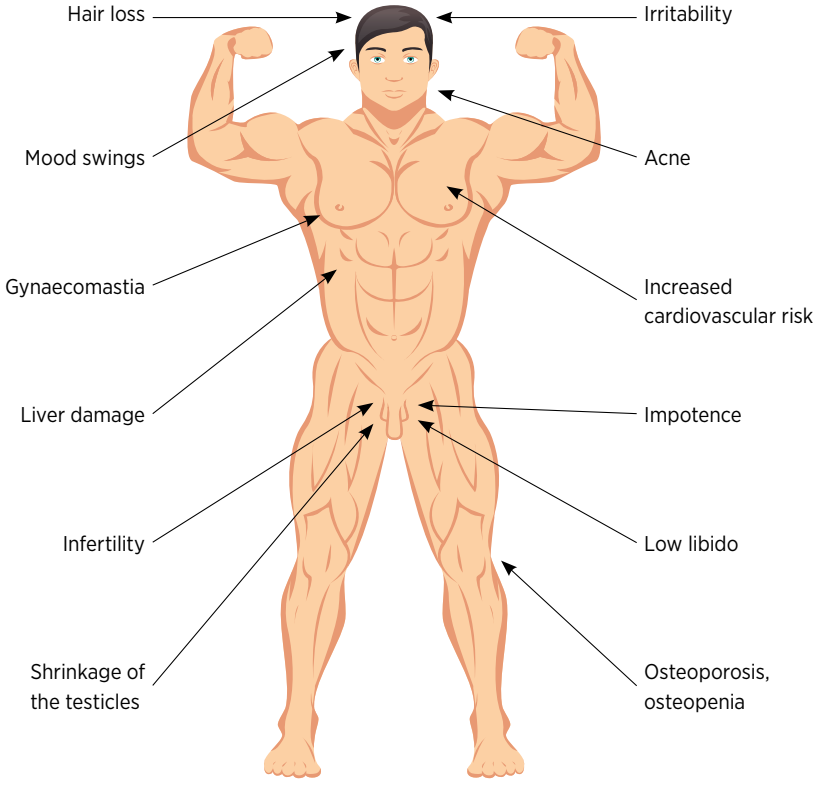
Some clinical presentations should prompt questioning about the use of energy beverages and sports supplements. Agitation, palpitations and insomnia, possibly in conjunction with high blood pressure, may be related to over-consumption of caffeine or energy beverages.[9]

Post-pubertal patients whose sports supplements contain androgenic steroids may present with features of androgen deficiency due to suppression of the hypothalamic-pituitary axis (see Fig.). Symptoms can be non-specific, such as lethargy, fatigue, low mood, irritability and poor concentration. More specific problems include male pattern hair loss, acne, liver injury, increased cardiovascular risk, osteopenia or osteoporosis, reduced muscle mass and strength, increased fat mass and gynaecomastia.[17] There may be reduced sexual and reproductive function, with low libido and erectile dysfunction.[14,18] Infertility may also occur.[19] Other causes of hypogonadism must also be considered when making the diagnosis.

Some patients may present requesting prescriptions for drugs such as selective oestrogen receptor modulators and aromatase inhibitors.[16] Consider whether this may be for the mitigation of adverse effects of androgen or anabolic steroid-induced hypogonadism.

Many users of high-protein sports supplements will be asymptomatic. However, renal function tests, done as part of an assessment for other clinical conditions, may find an incidental raised blood urea or creatinine. This should trigger an enquiry about supplement use. Supplements containing high quantities of protein may cause increased blood urea.[20] Those containing creatine may lead to increased creatinine concentrations.

Fig. **Androgenic adverse effects in men**



Obtaining a full history of supplement use can be complex. Multiple products are available online and may no longer be available for retrospective review of their contents. Even when details are available, the anabolic steroid content is unlikely to be listed.[5] Patients who are willing to provide a comprehensive history of their supplement use may deny taking androgens, but this does not exclude inadvertent oral ingestion.

Examination

The examination of a patient suspected of supplement use should include blood pressure, height, weight, body mass index and, if obese, waist circumference. Assess facial, head and body hair distribution for deviation from the normal male pattern. Check for gynaecomastia. Scrotal examination is essential and testicular volume should be assessed, preferably with an orchidometer (normal range 15–35 mL in men aged 21–35 years).[19]

Consider other explanations for any abnormal findings. For example, if there is a history of headache or changes in vision in the presence of hormonal changes, check the visual fields. Headache with a visual field defect should prompt further investigation for a pituitary mass.

Investigation

When an androgen deficiency is suspected the initial hormonal assessment should include serum testosterone. If the result is low the test should be repeated at least once and gonadotropins should be measured.[21] Serum testosterone is most accurately measured between 8 am and 10 am as concentrations may be lower later in the day (adjust timing for shift workers to shortly after waking).

In addition to sex hormone assays, a full blood count, liver and kidney function tests, and thyroid stimulating hormone may be considered as part of baseline assessment.

Secondary testicular failure (hypogonadotropic hypogonadism) due to sports supplement use is a diagnosis of exclusion and referral to an endocrinologist may be needed. Measure serum prolactin to help exclude prolactinoma or macroadenoma with pituitary stalk compression. Iron studies may exclude thalassemia and hemochromatosis. Imaging of the pituitary is indicated when there is suspicion of pituitary or hypothalamic disease.

Management

To the patient, problems resulting from sports supplements can be counterintuitive if the motivation for use is to 'get fit' and 'bulk up'. Guidance may be sought online, from blogs, peers or personal trainers rather than consultation with a GP, sports physician or nutritionist. Additionally, sports supplements are costly so are often a significant personal financial investment alongside gym equipment, gym membership and time spent working out.

Establish the patient's aims in taking supplements before reviewing and renegotiating use to reduce the risk of harm. Discussion of sleep patterns and sleep hygiene measures may be helpful for patients reliant on energy drinks. For oral protein supplement users, take a dietary history and encourage adequate but not excessive protein intake through food rather than supplements.

The Australian Sports Commission provides online advice on building muscle, protein and sports supplements.[22-24] Consider referral to a specialist in sports medicine or a nutritionist to optimise training and diet.

For supplement users with androgen deficiency, care can be more complex, especially when a patient is reluctant to cease use for fear of losing muscle bulk, strength and endurance. Discuss the impact on fertility as well as sexual function. Encourage them to stop the supplements and repeat hormone studies in three months to demonstrate improvement in endogenous hormones. If the patient agrees to stop using supplements, and hormone studies do not normalise over six to nine months, endocrinology referral is indicated.

Conclusion

Sports supplements are ubiquitous. Their ingredients may be obscure and reasons for their use can be complex. A history of use should be sought in patients presenting with concerns about agitation, sleep, libido and sexual function, as well as infertility.

The advice of the Australian Sports Anti-Doping Authority to competitive athletes in relation to sports supplements generalises well to the broader population. Think about whether supplements are safe, effective or necessary. Similar improvements in fitness may be gained through changes in nutrition, training or sleep programs. <

Conflict of interest: none declared

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ARTICLE

Prescribing for polymyalgia rheumatica

David F Liew
Rheumatologist and Clinical pharmacology fellow

Claire E Owen
Rheumatologist

Russell R Buchanan
Director of Rheumatology
Austin Health
Melbourne

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SUMMARY

Polymyalgia rheumatica is a common inflammatory condition but can be difficult to diagnose. Treatment is warranted in all cases to manage disabling symptoms.

Low–moderate doses of oral corticosteroids are highly effective. Once symptoms improve they can often be gradually reduced over months, but most patients require either prolonged or continuous treatment.

Despite their effectiveness, corticosteroids cause disproportionate damage in polymyalgia rheumatica compared to other rheumatic diseases. The therapeutic aim is to prescribe the minimum possible dose required for symptom control.

There is a lack of definitive evidence for steroid-sparing drugs in polymyalgia rheumatica. Methotrexate is typically used for relapsing disease. Leflunomide and tocilizumab are being investigated, but further research is needed.

Introduction

Polymyalgia rheumatica is the second most common autoimmune rheumatic disease after rheumatoid arthritis, with a lifetime risk of 2.4% for women, and 1.7% for men. It is the most common rheumatic disease in patients over 50 years old.[1]

Polymyalgia rheumatica and its treatment are often poorly understood by patients and healthcare professionals alike. The diagnosis can be difficult and there is a frequent dependence on corticosteroid therapy despite an increased propensity for long-term adverse effects.

Clinical features

The onset of polymyalgia rheumatica can be abrupt, often seemingly occurring overnight. There is bilateral shoulder girdle pain and prolonged early morning stiffness (typically >45 minutes, but often lasting several hours). The hips are involved in the vast majority of patients,[2] with neck, back or buttock pain also commonly reported. Distal manifestations are less frequent and may include a peripheral arthritis of the wrists and knees which is typically more sensitive than rheumatoid arthritis to prednisolone.[3]

It is possible to confuse polymyalgia rheumatica with other conditions including rheumatoid arthritis, spondyloarthritis, mechanical tendinopathies and fibromyalgia. To further complicate matters, elderly-onset rheumatoid arthritis may have an initial 'polymyalgic' presentation before overt arthritis emerges.

Diagnosis

The difficulty with diagnosis is accentuated by the absence of a gold standard investigation. Patients typically have a raised erythrocyte sedimentation rate or C-reactive protein, but infrequently the inflammatory markers are normal. Although interleukin-6 is typically elevated in untreated patients, no specific biomarker exists. Alternative diagnoses such as myositis, infection, malignancy and endocrinopathies should be excluded (Box).[2,4]

A rapid resolution of symptoms in response to prednisolone 15 mg daily was previously thought to represent a diagnostic surrogate for polymyalgia rheumatica. However, a small proportion of patients do not respond to three weeks of this therapy[5] so it cannot be used to make the diagnosis. Classification criteria therefore combine clinical features and serology with the optional incorporation of ultrasound (Table 1).[6] Ultrasound may show bursitis or tenosynovitis. In practice, the diagnosis is a clinical one and may require specialist involvement.

Giant cell arteritis

The most feared complication of polymyalgia rheumatica is giant cell arteritis. These conditions are closely related, and 16–21% of patients with polymyalgia rheumatica either have or will go on to develop giant cell arteritis.[7] All patients with polymyalgia rheumatica should be educated about this complication and the need to seek urgent medical attention if they develop suggestive symptoms. Giant cell arteritis may present with

headache, localised scalp tenderness, jaw claudication and, more concerningly, sudden visual loss or stroke. A small rise in erythrocyte sedimentation rate does not exclude giant cell arteritis.[7] Giant cell arteritis requires high-dose corticosteroids, which should never be delayed while a diagnostic temporal artery biopsy is obtained.

Extracranial giant cell arteritis is under-recognised and most commonly presents with constitutional features and persistently elevated inflammatory markers. Untreated it can eventually lead to formation of aortic aneurysms or stenoses of other large arteries.[8] Imaging is being increasingly used to detect extracranial giant cell arteritis. CT angiography or magnetic resonance angiography may be useful. Nuclear medicine studies such as positron emission tomography (PET) with fluorodeoxyglucose (FDG) have been used.[9] Although cost and radiation limit its use in routine practice, PET can identify important differential diagnoses such as infection and malignancy, and characteristic features of polymyalgia rheumatica may also be seen.[10]

Corticosteroids

Typically, untreated disease is markedly disabling due to the combination of pain, extensive stiffness and accompanying constitutional features. Corticosteroid therapy is therefore indicated and can result in a dramatic improvement for many patients. However, there is no evidence to suggest that it alters the likelihood of developing giant cell arteritis.

Prednisolone 15 mg daily is highly effective in most patients, although a few may need up to 25 mg daily.[11-13] Moderate-dose corticosteroids have been the first-line treatment for over 50 years, but were introduced before the widespread use of placebo-controlled trials to confirm effectiveness.[12]

After several weeks of treatment, approximately one-third of patients are able to gradually reduce their prednisolone over many months and can eventually stop.[14] Different weaning protocols have been devised, although the ideal approach remains controversial and individual tailoring may be necessary.

The British Society of Rheumatology has proposed a regimen[15] which is globally accepted[2] and reflected in local guidelines.[16] This recommends prednisolone 15 mg daily for three weeks, then tapering to 12.5 mg daily for an additional three weeks, 10 mg daily for 4–6 weeks and then a reduction of 1 mg daily every 4–8 weeks thereafter. Disease relapse, defined by a recurrence of symptoms accompanied by a rise in inflammatory markers, warrants an escalation of prednisolone to the last effective dose before recommencing the weaning schedule from that dose.

Box **Important differential diagnoses of polymyalgia rheumatica**

Inflammatory musculoskeletal diseases:

- rheumatoid arthritis
- spondyloarthritis
- ANCA-associated vasculitis and other connective tissue disorders
- inflammatory myositis
- crystal arthropathies

Non-inflammatory musculoskeletal disorders:

- osteoarthritis
- mechanical tendinopathies including rotator cuff syndrome
- pain syndromes including fibromyalgia
- other myopathies including drug-induced myopathies

Endocrinopathies:

- thyroid and parathyroid disease
- vitamin D deficiency

Infection

Cancer including paraneoplastic syndromes

Parkinson's disease

ANCA antineutrophil cytoplasmic antibody

Table 1 **Scoring algorithm for classifying polymyalgia rheumatica**

Required criteria: age 50 years or older, bilateral shoulder aching and abnormal C-reactive protein or erythrocyte sedimentation rate*

Criteria	Points without ultrasound (0–6)	Points with ultrasound (0–8)
Morning stiffness duration >45 min	2	2
Hip pain or limited range of motion	1	1
Absence of rheumatoid factor or anticitrullinated protein antibody	2	2
Absence of other joint involvement	1	1
At least one shoulder with subdeltoid bursitis, or biceps tenosynovitis, or glenohumeral synovitis (either posterior or axillary), and at least one hip with synovitis or trochanteric bursitis	Not applicable	1
Both shoulders with subdeltoid bursitis, biceps tenosynovitis or glenohumeral synovitis	Not applicable	1

* A patient is categorised as having polymyalgia rheumatica if the total score without ultrasound is 4 points, or is 5 or more points with ultrasound.

Source: Reference 6

The British weaning schedule is more rapid than most others, but involves at least 46 weeks of prednisolone therapy. This is a much longer period of exposure compared to most other inflammatory diseases. In practice the majority of patients will need corticosteroids for at least two years and a large proportion will require ongoing low-dose prednisolone to control their symptoms.[17] There are currently few data to help predict which patients will require ongoing therapy. Extended exposure to prednisolone is inevitable for these patients.

Adverse effects

Corticosteroids cause dose-dependent adverse effects. While the doses of prednisolone used in polymyalgia rheumatica might be lower than what was historically considered acceptable in many inflammatory conditions, they still confer a burden of morbidity.

The damage from prolonged use of low–moderate doses of corticosteroids is multimodal and has been better appreciated in recent years with more sophisticated investigative methods (Table 2).[18-20] Screening for these complications and treating them is important in mitigating their impact, although prevention is preferable.

In polymyalgia rheumatica the morbidity from similar doses of corticosteroids is both greater and occurs more frequently than in other rheumatic diseases.[21] It is not clear why, and this area warrants further research as it may have therapeutic implications. The cumulative effect, however, is that up to 81% of patients develop adverse events in the first year.[5] Furthermore polymyalgia rheumatica is a disease of older people who are at risk of complications as a consequence of these adverse events.

Uncontrolled inflammation itself can also cause problems, therefore corticosteroid therapy in polymyalgia rheumatica is a balance. Aim to achieve the minimum total exposure to prednisolone while maintaining control of the disease.[4]

Steroid-sparing drugs

There is great impetus to develop treatment alternatives to corticosteroids. However, there is currently no alternative drug in polymyalgia rheumatica which is supported by good evidence and is affordable. Steroid-sparing drugs, such as methotrexate, are therefore not currently recommended to be started soon after diagnosis, as is the case in rheumatoid arthritis. The decision to commence a steroid-sparing drug is a personalised one based on perceived ongoing need for prednisolone. It is not possible to predict who will benefit. One approach is to consider a steroid-sparing drug in patients who flare at least twice while following the British weaning schedule[15] or who develop overt inflammatory arthritis.

Methotrexate is currently recommended by both international[4] and local guidelines[16] as the first-line steroid-sparing drug to consider in polymyalgia rheumatica. These recommendations acknowledge that the evidence to support this advice is of poor quality. Leflunomide might have promise,[22,23] and it is currently the subject of a trial in Europe, but there may be problems with individualising the dosing.[24] Both of these drugs are used in rheumatoid arthritis, but there is no role for most other antirheumatic drugs in polymyalgia rheumatica.[4] This emphasises the fact that polymyalgia rheumatica is not merely an extension of rheumatoid arthritis. The use of either leflunomide or methotrexate in polymyalgia rheumatica is off label so specialist oversight is recommended.

Tocilizumab, an interleukin-6 receptor antagonist, has become of increasing interest as interleukin-6 is elevated in polymyalgia rheumatica.[25] The drug has also had recent success in treating giant cell arteritis,[26] but there are important immunological differences between the two diseases[27] so the results are not necessarily transferrable. Dedicated studies in polymyalgia rheumatica are therefore required. Two phase II trials have supported the use of tocilizumab[28,29] and a phase III trial is currently underway.[30] Even if this trial is successful, the cost of tocilizumab is likely to be prohibitive for routine use, and there is a risk of serious infection, myelosuppression, hypertension and dyslipidaemia.[31]

Conclusion

Polymyalgia rheumatica can be hard to diagnose and to treat optimally. While corticosteroids are effective and necessary to prevent disease-related morbidity, they have a burden of morbidity themselves and no steroid-sparing drug has yet emerged as ideal for routine use. Close clinical monitoring is important to detect the evolution of giant cell arteritis and to minimise and manage the adverse effects of therapy.

More research is required into the mechanisms behind corticosteroid-related damage in polymyalgia rheumatica. There is also a need to find ways to predict which patients are likely to require prolonged corticosteroids, and to devise a pragmatic therapeutic approach for them. <

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Table 2 **Long-term toxicity of prednisolone (≤15 mg daily)**

Toxicity	Details	Implications for screening and management*
Musculoskeletal		
Osteoporosis	Reduced bone density Altered microarchitecture Increased fracture risk	Optimise vitamin D and calcium intake Consider DEXA screening Order plain-film X-rays for new back pain Consider bisphosphonates or denosumab
Osteonecrosis	Possible increased risk	Investigate new hip pain
Myopathy	Risk of painless proximal muscle weakness and atrophy†	Take history, including difficulty with activities above shoulder height or rising from chairs without use of arms
Metabolic		
Diabetes and glucose intolerance	Increased risk of developing type 2 diabetes† Increased fasting glucose	Measure fasting glucose or HbA1c Encourage lifestyle modification Optimise diabetic therapy in patients with diabetes
Body morphology	Increased body weight Altered fat distribution (cushingoid appearance)	Measure height and weight Encourage lifestyle modification
Interference with sex hormone secretion	Increased risk of loss of libido† Hirsutism†	Take appropriate history, including patterns of body hair growth
Adrenal suppression	Increased dosage-dependent risk	Educate regarding staged withdrawal Check biochemical tests if rapid withdrawal required Consider an increased dose of prednisolone on sick days
Cardiovascular		
Dyslipidaemia	Increased dyslipidaemia†	Measure fasting lipids† Encourage lifestyle modification and provide pharmacotherapy
Hypertension	Increased blood pressure†	Monitor blood pressure† Encourage lifestyle modification and pharmacotherapy
Atherosclerosis and ischaemic heart disease	Increased risk of cardiovascular events and subclinical atherosclerosis† Possible increased risk of cardiovascular events	Encourage lifestyle modification
Infections		
Infections	Possible increased risk of general infection† Possible increased risk of opportunistic infection and herpes zoster	Give scheduled vaccinations (inactivated) including influenza vaccination Educate regarding late presentation of symptoms
Dermatological		
Skin atrophy	Increased risk	Educate
Acne, alopecia, bruisability	Increased risk	Educate

Table 2 **Long-term toxicity of prednisolone (≤15 mg daily) (continued)**

Toxicity	Details	Implications for screening and management*
Ophthalmological		
Cataract	Increased risk	Consider ophthalmologic evaluation if symptomatic
Glaucoma	Increased risk in individuals already at risk†	Consider ophthalmologic evaluation with tonometry in at-risk patients
Psychological		
Mood disturbance and psychosis	Increased risk†	Educate, screen and provide therapy as appropriate
Insomnia	Increased risk	Educate, take dose in morning
Gastrointestinal		
Peptic ulcer disease	Possible increased risk	Consider proton pump inhibitor only in patients at risk of ulcers

* Management of all of these adverse events includes minimisation of the corticosteroid dose.
† Applies to moderate doses (prednisolone ≥7.5 mg daily) only, based on References 18–20.
DEXA dual-energy x-ray absorptiometry
HbA1c glycated haemoglobin

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ARTICLE

An update on the treatment of rosacea

Alexis Lara Rivero
Clinical research fellow
St George Specialist Centre
Sydney

Margot Whitfeld
Visiting dermatologist
St Vincent's Hospital
Sydney

Senior lecturer
UNSW Sydney

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SUMMARY

Rosacea is a common inflammatory skin disorder that can seriously impair quality of life.

Treatment starts with general measures which include gentle skin cleansing, photoprotection and avoidance of exacerbating factors such as changes in temperature, ultraviolet light, stress, alcohol and some foods.

For patients with the erythematotelangiectatic form, specific topical treatments include metronidazole, azelaic acid, and brimonidine as monotherapy or in combination. Laser therapies may also be beneficial.

For the papulopustular form, consider a combination of topical therapies and oral antibiotics. Antibiotics are primarily used for their anti-inflammatory effects.

For severe or refractory forms, referral to a dermatologist should be considered. Additional treatment options may include oral isotretinoin, laser therapies or surgery.

Patients should be checked after the first 6–8 weeks of treatment to assess effectiveness and potential adverse effects.

Introduction

Rosacea is a common chronic relapsing inflammatory skin condition which mostly affects the central face, with women being more affected than men.[1] The pathophysiology is not completely understood, but dysregulation of the immune system, as well as changes in the nervous and the vascular system have been identified. Microbes that are part of the normal skin flora, and specifically in the pilo-sebaceous unit – including *Demodex* mites and *Staphylococcus epidermidis* – may also play a role as triggers of rosacea.[2,3]

Symptoms are initially transient. This is followed by persistent erythema due to repeated vasodilation, then telangiectasia and skin inflammation in the form of papules, pustules, lymphoedema and fibrosis.[2,4]

Rosacea can seriously affect a patient's quality of life. This should prompt clinicians to diagnose it early and start treatment.[1]

Diagnosis

The diagnosis of rosacea is usually made on history and clinical features. If it is not clear, differential diagnoses must be considered and ruled out (see Box).[1,5,6]

Clinical manifestations

The presence of at least one of the following primary features indicates rosacea:

- flushing (transient redness)
- non-transient redness
- papules
- pustules
- telangiectases.

In addition, at least one of the secondary features of burning or stinging, a dry appearance, plaque formation, oedema, central facial location, ocular manifestations and phymatous changes are considered enough to make the diagnosis accurately in most cases. Rosacea usually follows a pre-rosacea stage that involves flushing only.

Box Differential diagnoses of rosacea

Common

Acne vulgaris
Seborrhoeic dermatitis
Tinea faciei
Periorificial dermatitis
Contact dermatitis (irritant or allergic)
Steroid-induced acneiform eruption
Folliculitis

Uncommon

Lupus erythematosus
Dermatomyositis
Drug reaction, e.g. isoniazid
Sarcoidosis
Demodicosis (mange)

Source: References 1, 4, 6

Rosacea can be classified into four subtypes: erythematotelangiectatic, papulopustular, phymatous and ocular.[1,5]

Erythematotelangiectatic rosacea

Erythematotelangiectatic rosacea is characterised by flushing and persistent central facial erythema. Redness may also involve the peripheral face, ears, neck and upper chest, but periocular skin is typically spared. Telangiectases are also common, but are not required for the diagnosis (Fig. 1).

Papulopustular rosacea

Papulopustular rosacea subtype includes patients who develop papules or pustules in a central facial distribution. In severe cases, these episodes of inflammation can lead to chronic facial oedema (Figs 2 and 3).

Phymatous rosacea

Phymatous rosacea is characterised by thickened skin with enlarged pores and irregular surface nodularities. These changes are most commonly found on the nose (rhinophyma), but can occur on the ears, chin and forehead. This subtype is more common in men than women (Fig. 4).

Ocular rosacea

Ocular rosacea is characterised by a watery or bloodshot appearance of the eyes, foreign body sensation, burning or stinging. Blepharitis, conjunctivitis, dryness, itching, light sensitivity, blurred vision and telangiectasia of the conjunctiva or eyelids also occur. Chalazia and styes are more common in ocular rosacea than other forms. Because there is no specific test, the diagnosis relies on the physician's

Fig. 1 **Erythematotelangiectatic rosacea**

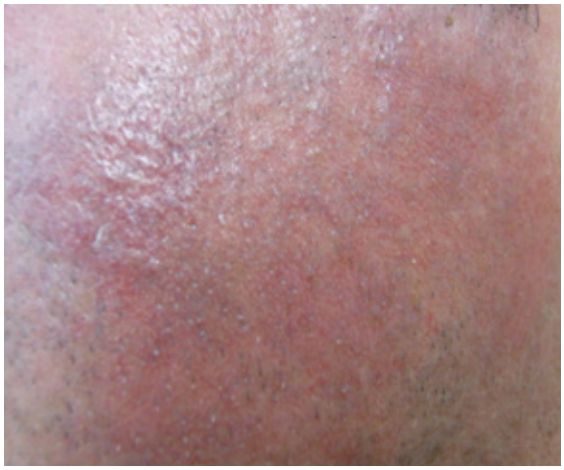


Fig. 2 **Papulopustular rosacea**

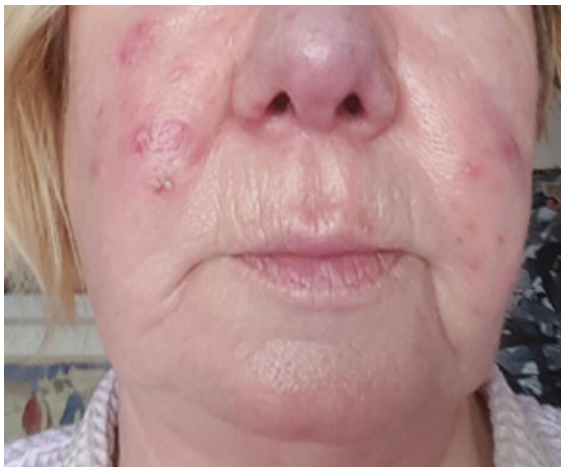


Fig. 3 **Papules and pustules – close-up**

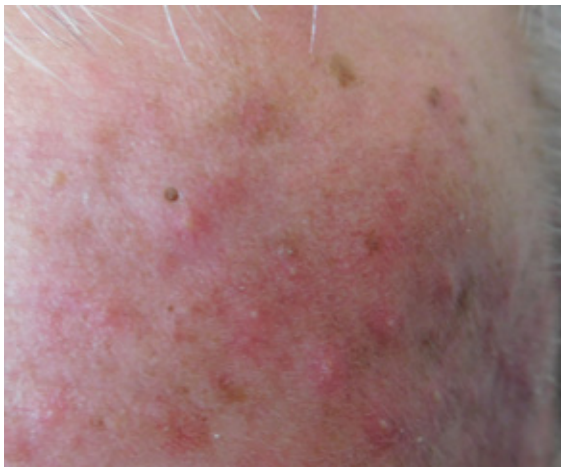
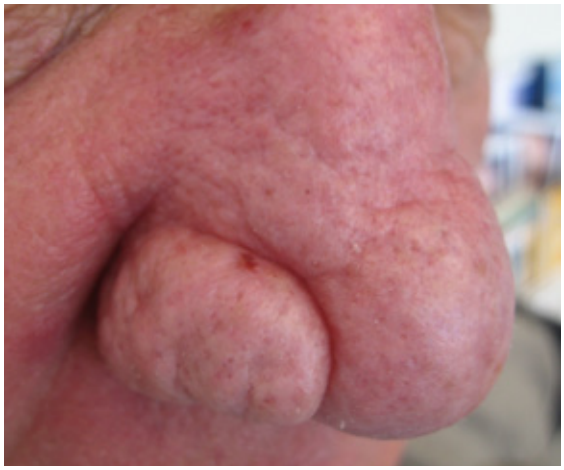


Fig. 4 **Rhinophyma**



clinical judgment. Ocular involvement is estimated to occur in 6–50% of patients with cutaneous rosacea, and can occur with or without a diagnosis of cutaneous rosacea.[7]

Additional tests

If the diagnosis cannot be made clinically, other tests may be necessary. These include skin swabs and scrapings for microbiology studies primarily to exclude staphylococcal infection. An antinuclear antibody test can be useful if photosensitivity is prominent. A skin biopsy is useful when other diagnoses such as lupus or chronic folliculitis are being considered.[1,8]

Approach to the patient with rosacea

Educating the patient about rosacea as a chronic relapsing skin condition which can be controlled but does not have a traditional 'cure' is important. Warning them that flare-ups can occur even when treated properly is also useful and plays a key role in the patient's expectations and the role of therapy.

General measures

The treatment plan will be adapted to the subtype of rosacea and then realistic expectations are set and potential adverse effects discussed. This enables the patient to participate in the choice of therapy appropriate for them and consider the balance between the disease and the treatment.[9]

Skin care

Sun avoidance and photoprotection are an important part of management.[10] Reducing skin irritability is also key. Skin care should include a gentle facial cleanser and a moisturiser or barrier repair product, as this can adjunctively improve therapeutic outcomes and reduce skin irritation in patients undergoing medical therapy. Cosmetic products, especially those with a green tinge, may help to cover erythema and may improve the patient's self-perception.[11]

Avoiding triggers

Avoiding triggers such as extreme temperatures (hot or cold), ultraviolet radiation exposure, spicy foods, hot or alcoholic beverages, wind, exercise and stress, should be recommended to all patients. Hormonal replacement therapy can be used for menopausal flushing.[12]

It is important to ask the patient what medicines they are taking as some over-the-counter or prescription drugs may worsen rosacea or trigger flushing episodes. These include calcium channel blockers, sildenafil, nitrates, nicotinic acid and some vitamin B-related medications including niacin.[2]

Specific treatments

Treatment can be optimised according to the dominant features.[9,13] Topical therapies are recommended for at least six weeks to effectively review the response.[5,9] Topical corticosteroids should be avoided.[14]

Treatment for flushing and erythema may involve oral drugs with vasoconstriction properties including adrenergic antagonists including mirtazapine (alpha blocker), propranolol (beta blocker) or carvedilol (both alpha and beta blocker).[2] These are used at low doses to avoid adverse effects such as hypotension, somnolence, fatigue and bronchospasm. They should be prescribed under specialist supervision, and careful monitoring is required.

Clonidine is an oral alpha$_2$ agonist that has been used for flushing. However, topical alpha$_2$ agonists are preferred because they target the skin and carry less risk of systemic adverse effects. Brimonidine is a topical alpha$_2$ agonist which can reduce erythema for up to 12 hours through direct cutaneous vasoconstriction. Brimonidine 0.33% gel is very useful for some people when not used on a daily basis.[6,9] Post-treatment rebound erythema may occur, and in general telangiectases will not clear.

Erythematotelangiectatic rosacea

Topical treatments for this form of rosacea include metronidazole, azelaic acid and brimonidine. They can be used alone or in combination. Metronidazole works as an anti-inflammatory drug by altering neutrophil chemotaxis and inactivating reactive oxygen species. Metronidazole 0.75% has been shown to reduce erythema, papules and pustules in multiple trials of patients with moderate to severe rosacea. It is usually well tolerated with minor local adverse effects such as skin irritation.[9,15]

Topical azelaic acid is an over-the-counter preparation which has anti-inflammatory, anti-keratinising and antibacterial effects. A 15% gel and 20% lotion are available and can be applied once or twice daily. Adverse effects may include skin irritation, but azelaic acid is usually well tolerated and can be used for long periods of time.[8,16]

Laser therapy, including vascular lasers or intense pulse light, may help to reduce refractory background erythema and clinically significant telangiectases, but will not reduce the frequency of flushing episodes. Different laser therapies that target the vessels have been used such as 595 nm pulsed dye laser, Nd:YAG and other vascular lasers, or intense pulsed light therapy. These should be administered by an experienced and trained laser therapist and the number of sessions and length of treatment varies for each individual.[11,17]

Papulopustular rosacea

Combining topical treatments with oral antibiotics may be needed for papulopustular rosacea. Topical treatments include metronidazole, azelaic acid, ivermectin and dapsone.

Ivermectin (1% cream) is useful for mild to moderate rosacea. It has an anti-inflammatory effect as well as having an effect on *Demodex* mites, which may activate the local immune response to produce the pustules. It is applied once daily for up to four months, and the course may be repeated if needed.[5,15]

Topical dapsone is a sulfone antibacterial with anti-inflammatory actions. It was recently approved for acne in Australia, but in the USA it is approved for rosacea. Dapsone 7.5% gel is applied once daily for up to 12 weeks. It should be avoided in those with known glucose-6-phosphate dehydrogenase deficiency.[18]

Oral antibiotics used in papulopustular rosacea include minocycline, doxycycline, erythromycin, clarithromycin and clindamycin. Their effectiveness at sub-antimicrobial doses is mostly due to their anti-inflammatory properties rather than a direct antimicrobial mechanism. Although bacteria may contribute to this form of rosacea, evidence for this is scant.[3]

Doxycycline 40 mg per day is commonly given in the USA as a sub-antimicrobial dose. The risk of resistance at this dose is less than with higher doses. In Australia 50 mg daily is used (range 25–100 mg). Photosensitivity is the main adverse effect, and sun avoidance or sunscreens may be required, especially during the summer months. Minocycline is probably a more effective agent but the increased risk of pigmentation, liver disorders and lupus-like syndrome limits its long-term use.

The goal of oral therapy is to improve the rosacea to a point where control is achieved by topical therapies. Treatment duration varies from four weeks to supress flares to many months for long-term disease suppression. With lower doses, adverse effects like headache, photosensitivity, diarrhoea and mucosal candidiasis are relatively uncommon. The antibiotics should be taken with food.[9,10,13]

Erythromycin and clarithromycin are generally used in patients who are intolerant or have refractory disease to tetracyclines (e.g. doxycycline, minocycline). Topical or oral erythromycin is sometimes used in pregnant women with papulopustular rosacea.

Oral isotretinoin is usually reserved for patients who are intolerant to oral or systemic therapies. Its effect is thought to be secondary to the downregulation of the local cutaneous immunity, although an alteration in the lipid environment of the skin cannot be excluded. Low-dose isotretinoin (10 mg daily) may be effective and have less adverse effects. The teratogenicity and adverse effects of isotretinoin requires routine clinical and laboratory monitoring for safety. Referral to a dermatologist is therefore recommended.[9,19]

Phymatous rosacea

Oral isotretinoin is also used in phymatous rosacea as with papulopustular rosacea.

The hypertrophied tissue in patients with phymatous rosacea can be reshaped and contoured with ablative lasers including carbon dioxide or electrosurgery devices. Treatment is aimed at debulking the excess tissue and then sculpting the disfigured area. Lasers produce less bleeding when compared to traditional surgery. Patients may be referred to a dermatologist or plastic surgeon for these therapies.[11,17] Traditional surgery involving scalpel and loop electrosurgical excision are also used to debulk and sculpt the nose, but experience in this is required as precision may be more difficult compared to laser treatments.[10]

Ocular rosacea

Lid care and artificial tears are used for ocular rosacea, as are oral tetracyclines. Ciclosporin drops are reserved for moderate to severe cases and are prescribed by a consultant ophthalmologist.[7]

Patient monitoring

If there is an important clinical improvement in the first six weeks, the patient may need to stay on therapy for at least six months. Patients receiving oral antibiotics for six months with stable or improving rosacea should have the dose tapered as tolerated.

If the response is inadequate, therapy is completed for another six weeks and compliance should be assessed. Consider the differential diagnosis at this stage. If the diagnosis of rosacea remains, alternative regimens of oral antibiotics or switching of topical treatment may be considered. If this is not successful, consider oral isotretinoin or laser/light therapies.[5,9]

Conclusion

Rosacea can be a challenging condition to treat. Tailoring therapies to the type of rosacea is an important part of management.

Information about possible triggers of flushing can allow the patient to decide which are important for them. One goal should be to reduce treatment from oral to topical when possible, advise on physical therapies including laser treatment if appropriate, and to be able to explain both physical and medical management of rosacea. Asking about ocular rosacea should be considered to ensure eye health is maintained where possible. For those with severe disease or with refractory cutaneous or ocular rosacea, referral to a specialist may be required. <

Conflict of interest: none declared

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New drugs

Alectinib

Aust Prescr 2018;41:25-6
https://doi.org/10.18773/austprescr.2017.081
First published 21 December 2017

Approved indication: non-small cell lung cancer

Alcensa (Roche)
150 mg capsules
Australian Medicines Handbook section 14.2.4

Lung cancer is usually associated with heavy smoking, however some non-small cell lung cancers occur in patients who are light smokers or have never smoked. These patients may have a genetic rearrangement. In about 5% of non-small cell lung cancers there is an abnormality involving the anaplastic lymphoma kinase (ALK) gene which results in the growth of cancer cells. These cancers can be treated with tyrosine kinase inhibitors such as crizotinib, but often spread to the brain. Alectinib hydrochloride is a tyrosine kinase inhibitor which can be used for patients who have ALK-positive, locally advanced or metastatic non-small cell lung cancer, which has progressed despite treatment with crizotinib. It can also be used in patients who cannot tolerate crizotinib.

Alectinib is taken twice a day with food. The drug is highly protein bound and the concentration in the cerebrospinal fluid is similar to the unbound fraction in plasma. Alectinib is metabolised by cytochrome P450 3A4, but no dose adjustments are recommended if alectinib is taken with inducers or inhibitors of this enzyme system. As alectinib may inhibit the P-glycoprotein transporter additional monitoring is recommended for drugs such as digoxin and dabigatran. Most of the dose of alectinib is excreted unchanged in the faeces, so renal impairment is unlikely to affect clearance. There are no pharmacokinetic studies in patients with moderate or severe liver impairment.

The initial approval of alectinib appears to have been based on two open-label, phase II studies. All the patients had ALK-positive cancers (mostly adenocarcinomas) which had progressed during treatment with crizotinib. The efficacy of alectinib was assessed using the standard Response Evaluation Criteria in Solid Tumours (RECIST).

A North American trial enrolled 87 patients, including 52 with metastases in the central nervous system. After a median follow-up of 43 weeks there was a response in 51% of the patients. The median progression-free survival was 8.1 months. The response rate for patients with central nervous system disease was 40% with 25% having a complete response.[1]

An international study enrolled 138 patients, including 84 with metastases in the central nervous system. The median follow-up was 30 weeks. There was an objective response in 50% of the 122 evaluable patients and the median progression-free survival was 8.9 months. In the patients with metastases, the disease was controlled in 83% and 27% had a complete response.[2]

Tyrosine kinase inhibitors can have serious adverse effects. Two patients died of adverse events in the American trial[1] and four died in the international trial.[2] Alectinib has been associated with pneumonitis, bradycardia and hepatotoxicity. Liver function should be checked regularly. In both trials the most frequent adverse effects included constipation, fatigue, peripheral oedema and myalgia.[1,2] Creatine kinase should be checked in the first month of therapy and in patients with muscle symptoms. Patients should minimise sun exposure as alectinib may cause photosensitivity. Dose reductions or interruptions may be needed in response to adverse reactions.

Alectinib is likely to be harmful in pregnancy and lactation. Women with a male sexual partner who is taking alectinib should use highly effective contraception.

While the response rates in the uncontrolled studies suggest a benefit for alectinib, its effect on survival still needs to be established. The response to treatment can vary, for example in the international trial the objective response rate did not reach statistical significance in patients who had previously received chemotherapy.[2] An advantage over crizotinib is that alectinib can enter the central nervous system.

A phase III trial in untreated patients has recently reported that progression-free survival with alectinib is significantly longer than with crizotinib.[3] The indications for alectinib will therefore probably evolve as more data become available.

T manufacturer provided the product information

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Some of the views expressed in the following notes on newly approved products should be regarded as preliminary, as there may be limited published data at the time of publication, 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. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

NEW DRUGS

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The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, the European Medicines Agency and the Therapeutic Goods Administration.

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Ixekizumab

Aust Prescr 2017;41:27-8
https://doi.org/10.18773/austprescr.2017.080
First published 21 December 2017

Approved indication: psoriasis

Taltz (Eli Lilly)
1 mL single-dose prefilled pen
Australian Medicines Handbook section 8.2.1

Ixekizumab is indicated for moderate–severe plaque psoriasis. Like secukinumab,[1] it is a monoclonal antibody that targets interleukin 17A. This cytokine is involved in the activation and proliferation of keratinocytes so blocking its action aims to reduce the severity of psoriasis.

This drug has been investigated in three main trials – UNCOVER-1, -2 and -3.[2,3] In total, 3866 people requiring systemic treatment or phototherapy for their psoriasis were enrolled in the studies. Subcutaneous ixekizumab 80 mg (every 2 or 4 weeks) was compared to placebo in the UNCOVER-1 trial[2] and to placebo and subcutaneous etanercept 50 mg (twice a week) in the UNCOVER-2 and -3 trials.[3] The primary outcome of the trials was at least a 75% reduction in patients' Psoriasis Area and Severity Index (PASI75) score and a score of 0 (clear) or 1 (minimal psoriasis) on the six-point static Physician Global Assessment (sPGA) after 12 weeks of treatment.

At baseline, the patients had psoriasis on 25–29% of their skin. After 12 weeks, over 80% of the people who received fortnightly ixekizumab responded and reached the primary endpoint (see Table).[2,3] Both 2- and 4-week regimens of the drug were significantly better than placebo and etanercept. Differences in the efficacy of ixekizumab over etanercept were apparent within the first two weeks of treatment. In the UNCOVER-2 and -3 trials, around 30–40% of patients given ixekizumab had a complete resolution of their psoriatic plaques compared with 0.6% (1 of 168 patients) and 0% in the placebo groups and 5.3% and 7.3% in the etanercept groups.[3]

In two of the trials (UNCOVER-1 and -2), patients who had responded to ixekizumab treatment in the first 12 weeks (sPGA 0, 1) were randomised to ixekizumab or placebo for a further 48 weeks. At the end of these extension studies, 74.6% of the 181 patients who had originally responded to fortnightly ixekizumab injections continued to respond to ixekizumab given every four weeks. This compared with only 7.4% of the 203 patients who were switched to placebo.

The most common adverse events with ixekizumab were mild–moderate injection-site reactions which occurred in 16.8% of those receiving fortnightly treatment. This was followed by upper respiratory

Table **Efficacy of ixekizumab in moderate–severe plaque psoriasis**

Trial	No. of patients	Treatment arm*	Efficacy endpoints†	
			PASI75	sPGA (0, 1)
UNCOVER-1	433	ixekizumab every 2 weeks	89.1%	81.8%
	432	ixekizumab every 4 weeks	82.6%	76.4%
	431	placebo	3.9%	3.2%
UNCOVER-2	351	ixekizumab every 2 weeks	89.7%	83.2%
	347	ixekizumab every 4 weeks	77.5%	72.9%
	168	placebo	2.4%	2.4%
	358	etanercept	41.6%	36%
UNCOVER-3	385	ixekizumab every 2 weeks	87.3%	80.5%
	386	ixekizumab every 4 weeks	84.2%	75.4%
	193	placebo	7.3%	6.7%
	382	etanercept	53.4%	41.6%

* Patients were given subcutaneous injections of an active treatment or placebo for 12 weeks. Those in the ixekizumab arm received a 160 mg loading dose followed by 80 mg doses every 2 or 4 weeks. Etanercept 50 mg was given twice weekly.

† Proportion of patients who had at least a 75% reduction in their Psoriasis Area and Severity Index score (PASI75) from baseline to week 12 and a score of 0 (clear) or 1 (minimal psoriasis) on the static Physician Global Assessment (sPGA) after 12 weeks of treatment. sPGA is a 6 category scale from 0 (clear) to 5 (very severe) of plaque thickness, erythema and scaling.

Source: References 2, 3

NEW DRUGS

tract infection (14%), nausea (2%), oropharyngeal pain (1.4%) and tinea infection (1.5%). Oral and vaginal candidiasis were also reported, as was neutropenia. As there is an increased risk of infection, caution is urged if ixekizumab is given to people with chronic or active infection. Patients should be tested for tuberculosis before treatment and live vaccines are not recommended.

Patients can have hypersensitivity reactions to ixekizumab, and 9–17% of patients developed antibodies to treatment. However, most of these cases were not associated with reduced efficacy.

Crohn's disease and ulcerative colitis, including exacerbations, were more common with ixekizumab than with placebo (0.1–0.2% vs 0%). People with inflammatory bowel disease should therefore be monitored closely.

There have been no drug interaction studies with ixekizumab and it has not been assessed in pregnant or breastfeeding women. In studies on monkeys, the drug crossed the placenta but did not appear to be toxic to the fetus. It was also excreted at low levels in the breastmilk of lactating monkeys. It is not known if ixekizumab affects fertility.

The recommended regimen for ixekizumab is a 160 mg loading dose as two subcutaneous injections. This should be followed by a single 80 mg injection every two weeks until week 12, then every four weeks.

Ixekizumab seems to be very effective for people with moderate–severe plaque psoriasis in the short term. It also appeared to be relatively safe but, because of its effects on the immune system, patients need to be monitored for infections. As ixekizumab probably needs to be continued indefinitely, it will be important to find out what the long-term safety of this drug is and how it compares to other biological drugs for psoriasis such as secukinumab, ustekinumab, adalimumab and infliximab. Ixekizumab has also shown efficacy in psoriatic arthritis.[4]

[X] manufacturer did not respond to request for data

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Australian Prescriber
PO Box 104
DEAKIN WEST 2600

Telephone (02) 6202 3100

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